

Immunotec®

Scientific and Medical Publications Featuring Immunocal®

A collection of journal articles following the research and development of a patented cysteine-rich undenatured whey protein isolate: Immunocal

Edited and compiled by:

Jimmy Gutman MD – Chairman, Scientific Advisory Board, Immunotec

45+ Years of Scientific Research



History of Immunocal

A specially prepared cysteine-rich whey protein isolate

In the 1960s, Dr. Gustavo Bounous, originally a surgeon in Italy, initiated research studies in the United States examining the course of recovery in post-surgical patients. He noted that seemingly similar patients could have vastly different outcomes and recovery from their procedures. He eventually focused on the theory that it could be what was in their normal daily food intake that was coming into play.

Unfortunately, he was forced to leave the USA due to an expired work visa. Restarting his research in Canada, he aimed to discover which foodstuff could affect healing and recovery. It became clear that the most likely candidate would be a protein. In Dr. Bounous's course of investigation, it became apparent that certain proteins and amino acids were having an effect on immune responses in the animals he was studying. Having no formal background in immunology, he sought out a partner to expand on this thesis. He found the perfect match.

Dr. Patricia Kongshavn at the time was an up-and-coming PhD at McGill University who played a critical pioneering role in the new field of clinical immunology. Together, the two published their first joint article in 1978 'The effect of dietary amino acids on immune reactivity'. The quest to find an effective protein that would enhance immune function continued for Drs. Bounous and Kongshavn. By great fortune, a protein extract was mailed to Dr. Bounous to examine for its potential benefits. The protein was at the time a near-worthless byproduct of the dairy industry. As it turns out, this protein extract demonstrated nothing short of spectacular effects when tested in animals. Its immune system effects were noteworthy enough to allow moving on to human studies.

Their human studies proved just as successful as their studies with animals. A company was formed to focus on furthering this research. 'Immunotec' was officially launched in 1996 (Canada) and 1997 (United States). A commitment was made to reinvest a significant proportion of funds straight back into research.
John Molson took the position of Vice President of Research & Development and made tremendous strides in securing high-level research partners worldwide.

Under his direction, the studies rapidly accumulated and established this natural protein isolate as one of the most promising supplements with research validation. Immunocal was eventually listed in the American PDR (Physician's Desk Reference) and the Canadian CPS (Compendium of Pharmaceuticals and Specialties).

This book examines the progress of Immunotec's rich research history by presenting the 'abstract' (executive summary) of each published study relating to Immunocal.



DISCLAIMER
This book is intended for educational and scientific interest only. It is not intended as a source of medical advice. The contents feature published research articles. Research articles do not translate into clinical practice or treatment guidelines. The reader is urged to consult with a health professional before using any supplements. Immunocal is a natural dietary supplement. It is not intended to diagnose, treat, cure, or prevent any disease. The views expressed by Dr. Gutman do not necessarily reflect the views of Immunotec.



Dr. Gustavo Bounous
Discoverer of Immunocal



Dr. Patricia Kongshavn
Co-Discoverer of Immunocal



Dr. Wulf Dröge
Discoverer of Immunocal Platinum



John Molson
Former Vice President Research & Development



Annie Karabadjian
MBA, BSc Clinical Trials Director

It took years of effort by talented, dedicated people to bring Immunocal to the world

Acknowledgements

To Dr. Gustavo Bounous, whose genius brought this breakthrough science to the world.

To Dr. Patricia Kongshavn, who as a real pioneer in immunology, took these ideas and ensured they be turned into reality.

To Dr. Wulf Dröge, eminent immunologist and expert on anti-aging medicine who joined the Immunotec project and helped bring us renown.

To John Molson, who guided the R&D efforts for over 20 years and opened up otherwise unattainable doors for us.

To Annie Karabadjian, whose incredibly adept skills managed so many of Immunocal's most challenging studies as Clinical Trials Director.

From Dr. Jimmy Gutman



This book was produced in an effort to make the majority of Immunotec's published studies easily available to any reader wanting to see the tremendous body of work done to support the scientific validation behind Immunocal.

For over 20 years I've received requests to compile these studies into one place. The reader will be able to see all levels of development involved in taking steps through conception, theory, lab studies, animal studies, and ultimately what counts the most: human studies.

Traditionally, every study published in modern peer-reviewed scientific and medical journals open with an 'abstract'. This abstract is essentially an executive summary of the paper or study. Rather that print entire journal articles (which would take up many hundreds of pages) the abstracts are presented. Each abstract is followed by my comments which try to put the findings into plain language and put the article in context.

This was truly a work of passion—going through these articles gave me a fresh perspective on the wealth of information and a renewed admiration for all the authors and scientists who spent countless time bringing this most valuable contribution to science and medicine.

Jimmy Gutman MD
Chief Science Officer, Immunotec

Index of Immunocal published studies

Human Studies

Blinded Studies

The Effect of Supplementation with a Cysteine Donor on Muscular Performance 15

Improved Glutathione Status in Young Adult Patients with Cystic Fibrosis Supplemented with Whey Protein 16

Effects of Cysteine Donor Supplementation on Exercise-Induced Bronchoconstriction 17

Cysteine-Rich Protein Reverses Weight Loss in Lung Cancer Patients Receiving Chemotherapy or Radiotherapy 18

Effect of Cysteine-Rich Whey Protein (Immunocal®) Supplementation in Combination with Resistance Training on Muscle Strength and Lean Body Mass in Non-Frail Elderly Subjects: A Randomized, Double-Blind Controlled Study . 19

Biochemical and Clinical Effects of Whey Protein Supplementation in Parkinson's Disease 20

ABD Bioactives Alleviate Chemotherapy-Induced Myelosuppression 21

Improving Antioxidant Capacity in Children with Autism: A randomized, double-blind controlled study with cysteine-rich whey protein 22

Immunocal blinded human prehabilitation studies 23

Blinded Prehabilitation Studies

Prehabilitation Versus Rehabilitation a Randomized Control Trial in Patients Undergoing Colorectal Resection for Cancer 24

Prehabilitation with Whey Protein Supplementation on Perioperative Functional Exercise Capacity in Patients Undergoing Colorectal Resection For Cancer: A Pilot Double-Blinded Randomized Placebo-Controlled Trial 25

Multimodal Prehabilitation Improves Functional Capacity Before and After Colorectal Surgery for Cancer: A Five-Year Research Experience 26

Four-Week Prehabilitation Program is Sufficient to Modify Exercise Behaviors and Improve Preoperative Functional Walking Capacity in Patients with Colorectal Cancer 27

Effect Of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial 28

Evaluation of Supervised Multimodal Prehabilitation Programme in Cancer Patients Undergoing Colorectal Resection: A Randomized Control Trial 29

Maximizing Patient Adherence To Prehabilitation: What Do The Patients Say? 30
Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial 31
Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial 32
Trimodal Prehabilitation for Colorectal Surgery Attenuates Post-surgical Losses in Lean Body Mass: A Pooled Analysis of Randomized Controlled Trials 33
Depression and Functional Status in Colorectal Cancer Patients Awaiting Surgery: Impact of a Multimodal Prehabilitation Program 34
Medical Supervision for Cancer Patient's Healthy Lifestyle (MCL) Improves Postoperative Rehabilitation 35
Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial 36
Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial 37
Multimodal Prehabilitation for Lung Cancer Surgery: A Randomized Controlled Trial 38
Functional capacity of prediabetic patients: effect of multimodal prehabilitation in patients undergoing colorectal cancer resection 39
Older frail prehabilitated patients who cannot attain a 400m 6-min walking distance before colorectal surgery suffer more postoperative complications 40
Malnourished lung cancer patients have poor baseline functional capacity but show greatest improvements with multimodal prehabilitation 41
Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery - The PREHAB Randomized Clinical Trial 42

Non-Blinded Studies

Treatment of Chronic Hepatitis Using Whey Protein (Non-Heated) 45
Effect of Whey Protein to Modulate Immune Response in Children with Atopic Asthma 46
Open-Labeled Pilot Study of Cysteine-Rich Whey Protein Isolate Supplementation for Nonalcoholic Steatohepatitis Patients 47
The effects of glutathione enhancement on sensorineural hearing loss 48
Cysteine/Cystine-Rich Undenatured Whey Protein Supplement in Patients' Pressure Ulcers Outcomes: An Open Label Study 49

Pilot Studies

Whey Proteins as a Food Supplement in HIV-Seropositive Individuals 51
The Use of a Whey Protein Concentrate in the Treatment of Patients with Metastatic Carcinoma: A Phase I-II

Clinical Study 52
Oral Tolerability of Cysteine-Rich Whey Protein Isolate in Autism: A Pilot Study 53
Psoriasis Improvement in Patients Using Glutathione-Enhancing, Nondenatured Whey Protein Isolate: A Pilot Study 54

Case Reports

Treatment of Obstructive Airway Disease with a Cysteine Donor Protein Supplement: A Case Report 56
Whey Protein Concentrate (WPC) and Glutathione Modulation in Cancer Treatment 57
Does the use of cysteine-rich whey protein supplements (Immunocal) improve the health well-being of COVID-19 patients? A qualitative study 58
Use of a Cysteine-Rich whey Protein Isolate as Adjuvant Therapy in Patients with COVID-19 Pneumonia: A Case Series .. 59

Theoretical Papers, Opinion Papers, Reviews

Evolutionary Traits in Human Milk Proteins 61
Whey Proteins in Cancer Prevention 62
Place for an Antioxidant Therapy in Human Immunodeficiency Virus (HIV) Infection 63
Nutriceutical Modulation of Glutathione With a Humanized Native Milk Serum Protein Isolate, Immunocal™: Application in AIDS and Cancer 64
Competition for Glutathione Precursors Between the Immune System and the Skeletal Muscle: Pathogenesis of Chronic Fatigue Syndrome 65
Therapeutic Functions of Whey Proteins 66
The Antioxidant System 67
Molecular Pathogenesis and Prevention of Prostate Cancer 68
Oxidative Stress and Ageing: Is Ageing a Cysteine Deficiency Syndrome? 69
Children's Oncology Group (COG) Nutrition Committee 70
Aberrant Insulin Receptor Signaling and Amino Acid Homeostasis as a Major Cause Of Oxidative Stress in Aging? 71
Bringing Evidence to Complementary and Alternative Medicine in Children With Cancer: Focus on Nutrition-Related Therapies 72
Immunocal® and Preservation of Glutathione as a Novel Neuroprotective Strategy for Degenerative Disorders of the Nervous System 73
Editorial: Therapeutic Antioxidants for Neurodegenerative Disease 74
Progress in Application of Whey Protein Concentrate in the Treatment For Malignancies 75
Therapeutic Potential of Glutathione Augmentation in Cancer Patients Receiving Chemotherapy or Radiotherapy 76
Trimodal Prehabilitation for Colorectal Surgery Attenuates Post-Surgical Losses in Lean Body Mass: A Pooled Analysis of Randomized Controlled Trials 77
Glutathione Precursors Shield the Brain from Trauma 78

Effect of Whey Protein Supplementation on Perioperative Outcomes in Patients with Cancer— A Systematic Review and Meta-Analysis 79

In Vivo Animal Studies

Influence of Dietary Lactalbumin Hydrolysate on The Immune System of Mice and Resistance to Salmonellosis 81
Influence of Dietary Proteins on the Immune System of Mice 82
Influence of Dietary Protein Type on the Immune System of Mice 83
Differential Effect of Dietary Protein Type on the B-Cell and T-Cell Immune Responses in Mice 84
Mechanism of Altered B-Cell Response Induced By Changes in Dietary Protein Type in Mice 85
Glutathione Augments the Activation of Cytotoxic T Lymphocytes 'In Vivo' 86
The Immunoenhancing Property of Dietary Whey Protein Concentrate 87
Immunoenhancing Property of Dietary Whey Protein in Mice: Role of Glutathione 88
The Influence of Dietary Whey Protein on Tissue Glutathione and the Diseases of Aging 89
Changes in Biliary Secretory Immunoglobulins a in Mice Fed Whey Proteins 90
Dietary Milk Proteins Inhibit the Development of Dimethylhydrazine-Induced Malignancy 91
The Biological Activity of Undenatured Dietary Whey Proteins: Role of Glutathione 92
Milk Whey Protein Decreases Oxygen Free Radical Production in a Murine Model of Chronic Iron-Overload Cardiomyopathy 93
Dietary protein, immune function and colon carcinogenesis in the mouse 94
Effects of Whey Protein Concentrate (WPC) on the Distributions of Lymphocyte Subpopulations in Rats with Excessive Alcohol Intake 95
A whey-based glutathione-enhancing diet decreases allergen-induced airway contraction in a guinea-pig model of asthma 96
A Cysteine-Rich Whey Supplement (Immunocal®) Delays Disease Onset and Prevents Spinal Cord Glutathione Depletion in the Hsod1 (G93a) Mouse Model of Amyotrophic Lateral Sclerosis 97
Cysteine-Rich Whey Protein Isolate (Immunocal®) Ameliorates Deficits in The GFAP.HMOX1 Mouse Model of Schizophrenia 98
Whey Protein Concentrate and Dexamethasone Protected Rat Cerebellum from Gamma-radiation Injury 99
Selective effects of whey protein concentrate on glutathione levels and apoptosis in rats with mammary tumors 100
The Nutritional Activity of Active Whey Protein in Pancreatic Tumor-Bearing Nude Mice 101
The Cysteine-Rich Whey Protein Supplement, Immunocal® , Preserves Brain Glutathione and Improves Cognitive, Motor, and Histopathological Indices of Traumatic Brain Injuury in a Mouse Model of Controlled Cortical Impact 102
Effect study of active whey protein on the nutritional therapy of pancreatic cancer xenografts in nude mice 103
Effects of Active Whey Protein on Nutritional and Immune Status of Mice Bearing Triple-Negative Breast Cancer with Chemotherapy 104

Glutathione Augments the Activation of Cytotoxic T Lymphocytes 'in Vivo' 105
Dietary Whey Protein Inhibits the Development of Dimethylhydrazine-Induced Malignancy 106
Cysteine-Rich Whey Protein Isolate (CR-WPI) Ameliorates Erectile Dysfunction by Diminishing Oxidative Stress via DDAH/ADMA/NOS Pathway 107
Immunocal limits gliosis in mouse models of repetitive mild-moderate traumatic brain injury 108

In Vitro Laboratory Studies

Anti-HIV and Anti-Apoptotic Activity of the Whey Protein Concentrate: Immunocal 110
In Vitro Selective Modulation of Cellular GSH by a Humanized Native Milk Protein Isolate in Normal Cells and Rat Mammary Carcinoma Model 111
Enhancing Effect of Patented Whey Protein Isolate (Immunocal®) on the Cytotoxicity of Anti-Cancer Drug 112
Whey Protein Concentrate Promotes the Production of Glutathione (GSH) By Gsh Reductase in The PC12 Cell Line after Acute Ethanol Exposure 113
Effects of Alcohol-Induced Human Peripheral Blood Mononuclear Cell (PBMC) Pretreated Whey Protein Concentrate (WPC) on Oxidative Damage 114
Whey Protein Concentrate Renders MDA-MB-231 Cells Sensitive to Rapamycin by Altering Cellular Redox State and Activating GSK3ß/ mTOR Signaling 115
A Cysteine-Rich Whey Supplement (Immunocal®) Provides Neuroprotection from Diverse Oxidative Stress-Inducing Agents In Vitro by Preserving Cellular Glutathione 116

Human Studies

Many types of human studies exist, all with different nuances and more importantly different levels of significance. Here are a few various types of published papers, with increasing levels of importance and relevance:



Case reports

Occasionally a patient is treated that shows a very unusual disease process or outcome. Because these situations are rare, they are often 'written up' and the description of the case is submitted for publication. If the authors of the journal fell that the case 'report' adds significant value in advancing our knowledge, it is approved for entry into the journal. Case reports can be on a single individual or often on a group of patients that share similar features or outcomes. Although these reports have no statistical significance, they are a window into what may be 'going on' and may help in giving direction for future studies.



Pilot studies

Before committing vast amounts of time, effort and resources into large human studies, it is often judicious to do a small trial that will give a better feel as to the potential success of a larger trial. In the process of accessing funding or ethical permission to do large studies, often these pilot studies are necessary to show 'proof of concept'. Because the numbers of subjects are often too small to achieve 'statistical relevance' they lack the power to be as convincing as a large trial, where meaningful statistics are obtainable. For example, if a treatment is successful 30% of the time (this is actually quite common for many drugs), it takes a large amount of individuals to be sure that the results found are not just by 'chance'. Pilot studies are a major step towards gaining the confidence (and often the authority) to do a large human trial.

Non-blinded studies

The 'Placebo Effect' is real. Patients who 'take' something often believe that because they are receiving an intervention, that they will improve. It has long been shown that if belief is strong enough, positive changes may in fact occur. There are many factors involved far beyond the scope of this discussion to explain this phenomenon, the reader is welcome to explore this by other means. Similarly, researchers who are using a drug or a methodology who are convinced that this intervention is valid, may make unconsciously biased observations or subtle manipulations to 'prove' that their theories are right. This may not be intentionally done, but then again, there are many who just 'cheat'. The concept of 'blinding' implies that either the patients or the researchers, or both, are unaware whether the subject is receiving the real intervention or the placebo. This offers some protection from placebo effect or researcher bias.

A non-blinded study does however carry weight if it is properly and ethically conducted. They are far simpler to do than a 'double-blind' study (see below).

There are many other variations on study design; single-blind studies; case-control studies; retrospective analysis, and more. The description of all of these too weighty to consider in a full discussion in this document.

Immunotec has carried out a good number of these different study methodologies. They are the penultimate step before completing a double-blind study.

Blinded studies

Here we move into what is considered the 'gold standard' of human trials. In a double-blind study, neither the researcher nor the subject knows whether the treatment each receives is real or placebo. Of course, this is a simplified explanation, there are different nuances that may occur like a '3-arm' or '4-arm study', where several different groups are combined into a study, and other variations. The other term that you will see in great use is 'randomized'. This means that the subjects, all from a similar pool of individuals, are randomly selected to receive either placebo or treatment. This is important in ensuring non-biased homogeneity in the two groups. Finally, the term 'statistically relevant' is critical in describing whether in fact a treatment group has shown any difference from placebo. The two most common measurements of statistical relevance you will see are the 'p' or 'probability' indices. When you read 'p<0.05' this means that the likelihood of a fluke occurrence in the numbers is less than 5%. A p-value of p<0.01 means that you can be 99% sure that the results obtained are right.

You now should be getting the idea that 100% 'proof' rarely if ever exists. A study that is described as 'proven' really means that shows that in 'great likelihood' that the results are meaningful. And what to do when two similar studies show completely opposite outcomes? One says 'yes' and the other a clear 'no'? This is a reflection of the fragility of the scientific method. It is extremely difficult to come up with the 'perfect' experiment. Study design, patient selection, statistical methodology, proper hypothesis, measuring techniques and even financial pressures can affect outcome.

I urge you to keep an open and critical mind when reading any study. And an even more critical mind when reading someone else's opinions on a study! This is a wonderful exercise and will only result in broadening your knowledge and awareness.



Immunocal blinded human studies



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

The Effect of Supplementation with a Cysteine Donor on Muscular Performance

LC Lands, MD, PhD*†, VL Grey, PhD†‡, AA Smountas, BSc* *Division of Respiratory Medicine, † Department of Pediatrics, ‡Department of Biochemistry, McGill University Health Centre-Montreal Children's Hospital, Montreal, Quebec, Canada



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). Followup 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.

Dr. Gutman's Comments:

Dr. Larry Lands of McGill University conceived this study after hearing repeated reports of improved performance by athletes taking Immunocal. As a scientist, he sought evidence to validate these claims. Young athletic adults were given either a placebo or Immunocal. All underwent the same physical training program. Three months later, when measured for muscle strength and endurance, their performance indicators (strength and endurance) had improved by 10-15%—a substantial advantage in competitive sports. At the same time, glutathione levels in this healthy population climbed a significant 35%. Subsequent studies on muscular performance and Immunocal have since reinforced these results.

Improved Glutathione Status in Young Adult Patients with Cystic Fibrosis Supplemented with Whey Protein

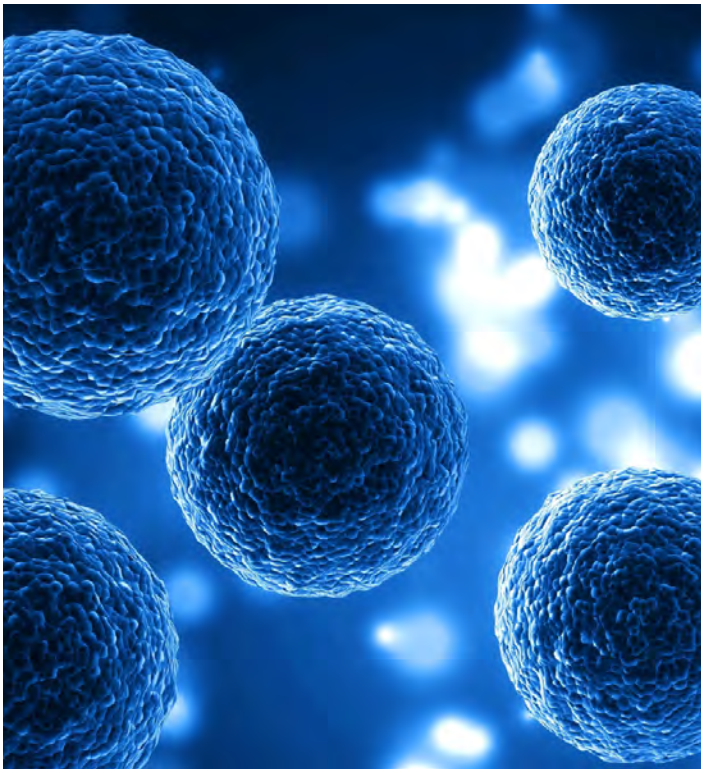
V Greya , SR Mohammedb , AA Smountasb , R Bahloolb , LC Landsb
a The Department of Pathology and Molecular Medicine, McMaster Division, Hamilton Health Sciences, Hamilton, Ontario, Canada b The Department of Respiratory Medicine, McGill University Medical Center, Montreal Children's Hospital, Montreal, Quebec, Canada

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.

Dr. Gutman's Comments:

Cystic fibrosis is a severe, chronic disease that appears at an early age. Lungs are often the worst affected. They are chronically inflamed, and a thick mucus develops within the airways obstructing their function and leading to further inflammation and infection. It has long been known that decreased glutathione levels are to be expected in cystic fibrosis. This Canadian study used Immunocal to successfully raise glutathione levels in 32 young adults with cystic fibrosis. The researchers observed a 45-50% increase in white blood cell glutathione levels.



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

Effects of Cysteine Donor Supplementation on Exercise-Induced Bronchoconstriction

JM Baumann, KW Rundell, TM Evans, AM Levine
American College of Sports Medicine. Marywood University, Human Performance Laboratory, Scranton, Pennsylvania

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 postEVH 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 preand 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.

Dr. Gutman's Comments:

This very interesting study done on otherwise healthy college hockey players, addressed the issue of young athletes who are suffering from exercise- induced asthma secondary to exposure to engine exhaust from Zambonis (ice-rink cleaning vehicles). A higher than expected rate of asthma is seen in indoor hockey players than in age-matched athletes performing other sports. Asthmatic players were randomly assigned to either an Immunocal group or a placebo group. After 4 weeks pulmonary function tests were significantly better in the Immunocal group than in the control (placebo) group. This difference was even greater after 8 weeks. The takeaway message from this study was not only that asthma was improved on Immunocal, but that Immunocal may offer protection from air pollution resulting from combustion engine exhaust.

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

Cysteine-Rich Protein Reverses Weight Loss in Lung Cancer Patients Receiving Chemotherapy or Radiotherapy

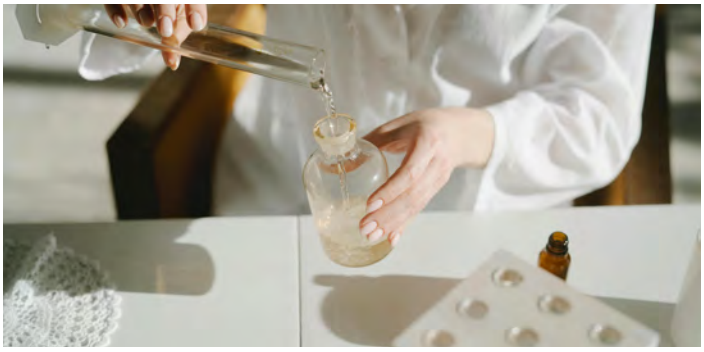
R. Tozera , P. Taib , W. Falconerc , T. Ducruetd , A. Karabadjiane , G. Bounousf , J. Molsonf , and W. Drögef a Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada b Radiation Oncology, Allan Blair Cancer Center, Regina, Saskatchewan, Canada c Cancer Nutrition & Rehabilitation Program, Department of Oncology, McGill University, Montreal, Quebec. Canada d Boreal Primum Inc., Montreal, Quebec, Canada e Medscope Communications Inc., St. Laurent, Quebec, Canada f Immunotec Research Ltd. Vaudreuil, Quebec, Canada

Abstract

Oxidative stress plays a role in the tumorcytotoxic 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 nonsmall 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 caseintreated 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.

Dr. Gutman's Comments:

This landmark study was the first to directly tackle the question, "Does raising glutathione protect cancer cells from chemotherapy?" Laboratory studies had shown that cancer cells may use glutathione to resist chemotherapy. However, this had been demonstrated in test-tube studies only—not in living bodies. Only a definitive study in humans would reveal whether this translated into a real-life situation. Led by eminent immunologist Wulf Droge, a team of Canadian researchers initiated a double-blind, placebo-controlled, gold-standard study in major cancer-treatment centers across the country. Lung cancer patients on chemotherapy or radiotherapy were fed Immunocal or placebo. The patients selected already showed significant muscle wasting (cachexia), signifying advanced disease. All were estimated to survive no more than 3 months. In contrast to the test-tube experiments, the Immunocal did not "protect" the cancer. On the contrary, Immunocal-fed patients actually increased their muscle mass (reversal of cachexia)—a very rare result of nutritional intervention. In addition, their qualityof-life measurements improved significantly. Finally, survival statistics were equally impressive. After one year, 80% of the Immunocal-fed patients survived, whereas fewer than half the placebo group was still alive.



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

Effect of Cysteine-Rich Whey Protein (Immunocal®) Supplementation in Combination with Resistance Training on Muscle Strength and Lean Body Mass in Non-Frail Elderly Subjects: A Randomized, Double-Blind Controlled Study

Karelis AD1,2, Messier V3, Suppère P3, Briand R3, Rabasa-Lhoret R3,4,5
1Department of Kinanthropology, Université du Québec à Montréal, Canada; 2Centre de recherche de l'Institut universitaire de gériatrie de Montréal; 3Institut de recherches cliniques de Montréal (IRCM), Canada; 4Department of Nutrition, Université de Montréal, Canada; 5Montreal Diabetes Research Center (MDRC), Montréal, Canada. Corresponding author: Antony Karelis PhD, Department of Kinanthropology, Université du Québec à Montréal, Montréal, Quebec, Canada

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.

Dr. Gutman's Comments:

Dr. Karelis, Dr. Rabasa-Lhoret and their research teams in Montreal, Canada, conducted a controlled clinical trial on Immunocal in a non-frail elderly population. This was the first Immunocal trial with the participation of a large number of older subjects; One group consumed Immunocal, the other another a milk protein called casein. Both groups followed the same resistance training program three times per week. The Immunocal group compared to the casein group demonstrated a statistically significant increase in muscle strength of about 10%. This strong favorable data led Immunotec to secure a new health claim for Immunocal for "increasing muscle strength" from Health Canada's NHPD (Natural Health Products Directorate).

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

Biochemical and Clinical Effects of Whey Protein Supplementation in Parkinson's Disease

Piyaratana Tosukhowong a, Chanchai Boonla a, Thasinas Dissayabutra a, Lalita Kaewwilai b, Sasipa Muensri a, Chanisa Chotipanich c, Juho Joutsa d, Juha Rinne d, Roongroj Bhidayasiri b,e a Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand b Chulalongkorn Center of Excellence for Parkinson's Disease and Related Disorders, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok 10330, Thailand c National Cyclotron and PET Center, Chulabhorn Hospital, Bangkok, Thailand. d Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland. e Department of Rehabilitation Medicine, Juntendo University, Tokyo, Japan



Abstract

Background: Parkinson's Disease (PD) is an oxidative stress-mediated degenerative disorder. Elevated plasma homocysteine (Hcy) is frequently found in the levodopatreated 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, doubleblind 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 Wheysupplemented 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.

Dr. Gutman's Comments:

An international team of researchers contributed to this double-blind, placebocontrolled trial on patients with Parkinson's Disease. Each participant was given either Immunocal or soy protein isolate. Glutathione measurements improved in the Immunocal group. The researchers felt a larger study would provide evidence of clinical improvement.

ABD Bioactives Alleviate Chemotherapy-Induced Myelosuppression

1Luo M 2Wu XJ 2Jhang X 3Dong G 4Xiong LL 4Wang PC 1Gao K 1Yu P 1He M 5Du C 5Jiang O 6Shi HP 1Cancer Nutritional Treatment Center, Neijiang Second People's Hospital, Neijiang, Sichuan, China 2Marryhealth Enterprises (Chongqing) Ltd., Chongqing, China, 3The Second Retired Cadre Sanatorium in Harbin, Heilongjiang Provincial Military District, Harbin, Heilongjiang, China 4Medical Department/ Department of Clinical Nutrition/Department of Psychiatry, Neijiang Second People's Hospital, Neijiang, Sichuan, China 5Cancer Center, Neijiang Second People's Hospital, Neijiang, Sichuan, China 6Department of Gastrointestinal Surgery/Clinical Nutrition, Beijing Shijitan Hospital/Capital Medical University Beijing International Science and Technology Cooperation Base for Cancer Metabolism and Nutrition Department of Oncology, Capital Medical University, Beijing, China

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 signifi cantly 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.

Dr. Gutman's Comments:

This human study was performed in lung cancer patients. 44 patients were randomly divided into control (standard treatment) or intervention (Immunocal added) groups. (Immunocal is called "ABD Bioactives" in China). One of the major potential adverse effects of chemotherapy is a depression of immune function. The measurement that most often is used to measure immune system health is the white blood cell numbers, a group of cells referred to as "myelocytes", with sub-groups such as leukocytes, granulocytes and so on. "Myelosuppression" is the condition where these white blood cells (which are the front line soldiers of the immune system) are knocked back in numbers, leading to a weakened immune state. Immunocal was successful in improving this condition, a major issue in chemotherapy success or failure.



Improving Antioxidant Capacity in Children with Autism: A randomized, double-blind controlled study with cysteine-rich whey protein

Castejon AM, Spaw JA, Rozenfeld I, Sheinberg N, Kabot S, Shaw A, Hardigan P, Faillace R, Packer EE. Dept. Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, USA Center for Collaborative Research, Institute for Neuro Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA Mailman Segal Center, Nova Southeastern University, Fort Lauderdale, FL, USA Statistical Consulting Center, College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA Dept. of Pediatrics, College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA

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 nonsignificant. 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.

Dr. Gutman's Comments:

This study was a major step forward after my original pilot study on Immunocal and autism was published. The auspicious autism research team in Florida led by Dr. Ana Castejon set out to assess whether the use of Immunocal can accomplish two things; 1) raise glutathione, and 2) improve behavioral outcomes in children with autism. They showed both to be true. Determining accurate glutathione blood test results was one thing, but measuring multifaceted parameters of behavior required enormous time and resources - this study took ten years to reach publication. Significant studies often call for even more significant work. In this case, there appeared to be two distinct types of responses, with greater improvements in kids who were; a) older, and; b) starting off with less depressed glutathione measurements. Having studied 3-5 year old patients, this suggested that an older group should be studied and that higher doses of Immunocal may be required. Follow-up studies are pending

Immunocal blinded human prehabilitation studies



ANESTHESIOLOGY, 2014, 121:937-47

Prehabilitation Versus Rehabilitation a Randomized Control Trial in Patients Undergoing Colorectal Resection for Cancer

Gillis C1 , Li C2 , Lee L2 , Awasthi R1 , Agustin B1 , Gamsa A3 , Liberman AS2 , Stein B2 , Charlebois P2 , Feldman LS2 , Carli F3 , Phil M
1 Department of Anesthesia, McGill University Health Centre, Montreal, Quebec, Canada
2 Department of Surgery, McGill University, Montreal, Quebec, Canada.
3 Department of Anesthesia, McGill University, Montreal, Quebec, Canada



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 homebased 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.

Dr. Gutman's Comments:

As researchers seek to improve the recovery of colon cancer patients from surgery, this randomized control trial compared the advantages of prehabilitation to those of rehabilitation. Using an Immunocal diet, the prehabilitation program was significantly better at restoring muscular performance than any post-surgical method.

Prehabilitation with Whey Protein Supplementation on Perioperative Functional Exercise Capacity in Patients Undergoing Colorectal Resection For Cancer: A Pilot Double-Blinded Randomized Placebo-Controlled Trial

Chelsia Gillis, MSc, RD*, Sarah-Eve Loiselle, PDt**, Julio F. Fiore, Jr, PhD, PT; Rashami Awasthi, Linda Wykes, PhD, A. Sender Liberman, MD, Barry Stein, MD; Patrick Charlebois, MD; Francesco Carli, MD, MPhil *Certified in Canada; **Professional dietitian certified in Quebec (equivalent to RD); Department of Anesthesia, McGill University Health Centre, Montreal, QC, Canada; Department of Surgery, McGill University, Montreal, Quebec, Canada; Department of Anesthesia, McGill University, Montreal, Quebec, Canada

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.

Dr. Gutman's Comments:

One of the first double-blind, randomized control trials to examine the benefits of prehabilitation with dietary Immunocal was led by Dr. Carli at McGill University in Montreal. Even in this small trial, patients undergoing surgery for bowel cancer benefited with meaningful results, fueling interest in larger studies.



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

Multimodal Prehabilitation Improves Functional Capacity Before and After Colorectal Surgery for Cancer: A Five-Year Research Experience

Minnella EM, Bousquet-Dion G, Awasthi R, Scheede-Bergdahl C, Carli F
Department of Anesthesia, McGill University Health Center, Montreal, Quebec, Canada



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. 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.

Dr. Gutman's Comments:

Dr. Carli's team reviewed five years of prehabilitation trials in cancer surgery patients in order to re-examine the resulting statistics. Combining evidence from several smaller trials into this larger analysis resulted in greater statistical significance and greater confidence in the findings.

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

Four-Week Prehabilitation Program is Sufficient to Modify Exercise Behaviors and Improve Preoperative Functional Walking Capacity in Patients with Colorectal Cancer

1,2Chen BP, 1,3Awasthi R, 1,2Sweet SN, 4Minnella EM, 3 Bergdahl A, 5,6Santa Mina D, 4Carli F, 7,8,9Scheede-Bergdahl C 1 Department of Kinesiology and Physical Education, McGill University, Montreal, Quebec, Canada. 2 McGill Research Centre for Physical Activity & Health, McGill University, Montreal, Quebec, Canada. 3 Department of Exercise Science, Concordia University, Montreal, Quebec, Canada. 4 Department of Anesthesia, McGill University, Montreal, Quebec, Canada. 5 Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada. 6 Cancer Rehabilitation and Survivorship Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada. 7 Department of Kinesiology and Physical Education, McGill University, Montreal, Quebec, Canada 8 McGill Research Centre for Physical Activity & Health, McGill University, Montreal, Quebec, Canada 9 Department of Anesthesia, McGill University, Montreal, Quebec, Canada

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 vigorousintensity 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.

Dr. Gutman's Comments:

Dr. Carli's team fed Immunocal to patients preparing for bowel cancer surgery, and showed that this prehabilitation improved their physical performance and physical activity levels afterwards. These important recovery indicators help determine when patients can be safely discharged and recover their independence.



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

Effect Of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial

1 Minella EM, 1 Awasthi R, 1 Loiselle SE, 2 Agnihotram RV, 3 Ferri LE, 1 Carli F
1 Department of Anesthesia, McGill University Health Centre, Montreal General Hospital, Montreal, Quebec, Canada.
2 Research Institute, McGill University Health Centre, Glen Site, Montreal, Quebec, Canada.
3 Division of Thoracic Surgery, McGill University Health Centre, Montreal General Hospital, Montreal, Quebec, Canada



Abstract

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.

Dr. Gutman's Comments:

This randomized clinical trial by Dr. Carli's team tested a two-pronged prehabilitation program (exercise and nutrition) on patients prior to stomach and esophagus surgery. Those on the program recovered better from surgery than those on standard treatment.

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

Evaluation of Supervised Multimodal Prehabilitation Programme in Cancer Patients Undergoing Colorectal Resection: A Randomized Control Trial

R. Tozera , P. Taib , W. Falconerc , T. Ducruetd , A. Karabadjiane , G. Bounousf , J. Molsonf , and W. Drögef
a Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada b Radiation Oncology, Allan Blair Cancer Center, Regina, Saskatchewan, Canada c Cancer Nutrition & Rehabilitation Program, Department of Oncology, McGill University, Montreal, Quebec. Canada d Boreal Primum Inc., Montreal, Quebec, Canada e Medscope Communications Inc., St. Laurent, Quebec, Canada f Immunotec Research Ltd. Vaudreuil, Quebec, Canada

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.

Dr. Gutman's Comments:

In patients undergoing surgery for bowel cancer, this randomized control trial examines the benefits of prehabilitation using Immunocal as a dietary intervention.



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

Maximizing Patient Adherence To Prehabilitation: What Do The Patients Say?

Ferreira V1 2 Agnihotram RV3 Bergdahl A4 Van Rooijen SJ5 Awasthi R2 Carli F2 Scheede-Bergdahl C1 2 6
1 Department of Kinesiology and Physical Education, McGill University, Montreal, Quebec, Canada
2 Department of Anesthesia, McGill University, Montreal General Hospital, Montreal, Quebec, Canada
3 Research Institute - McGill University Health Center, Montreal, QC, Canada
4 Department of Exercise Science, Concordia University, Montreal, Canada
5 Department of Surgery, School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, The Netherlands
6 Faculty of Education, McGill Research Centre for Physical Activity and Health, McGill University, Montreal, Quebec, Canada



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 homebased 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.

Dr. Gutman's Comments:

This paper was the result of surveying patients who had undergone a multimodal prehabilitation program for cancer treatment. This included strategies such as exercise, dietary intervention and psychological counseling. The dietary intervention was Immunocal. Elements of the program were examined in an effort to make the patients adhere more closed and comply with the directives.

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

Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial

1Minnella EM, 2Awasthi R, 3Loiselle SE, 4Agnihotram RA, 5Ferri LE, 6Carli F 1 2 3 6Department of Anesthesia, McGill University Health Centre, Montreal General Hospital, Montreal, Quebec, Canada 4Research Institute,McGill University Health Centre, Glen Site, Montreal, Quebec, Canada 5Division of Thoracic Surgery, McGill University Health Centre, Montreal General Hospital, Montreal, Quebec, Canada 6Department of Anesthesia, McGill University Health Centre, Montreal General Hospital, Montreal, Quebec, Canada

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.

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.

Dr. Gutman's Comments:

In a bimodal prehabilitation strategy, where cancer patients were pre-treated with nutritional optimization and exercise. These patients with either stomach or esophageal cancer were randomly selected to undergo prehabilitation or standard treatment. The nutritional optimization used Immunocal as an active intervention. The prehabilitation group fared much better recovering from their surgery.



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

Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial

Minnella EM[a] Awasthi R[a] Bousquet-Dion Ga Ferreira Va Austin Ba Audi Ca Tanguay Sb Aprikian Ab Carli F[a] Kassouf Wb
[a]Department of Anesthesia, McGill University Health Centre, Montreal, Quebec, Canada
bDivision of Urology, Department of Surgery, McGill University Health Centre, Montreal, Quebec, Canada

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.

Dr. Gutman's Comments:

Dr. Franco Carli's team did a randomized control study on bladder cancer patients receiving a total cystectomy (bladder removal). One group received prehabilitation before surgery consisting of exercise, nutritional optimization using Immunocal, and relaxation techniques to alleviate anxiety. When compared t a group receiving standard therapy, the prehabilitation group resulted in faster recovery, and were able to regain their strength and energy to get back to normal life.

CLINICAL NUTRITION 2019 Jun;38(3):1053-1060

Trimodal Prehabilitation for Colorectal Surgery Attenuates Post-surgical Losses in Lean Body Mass: A Pooled Analysis of Randomized Controlled Trials

aGillis C, bFenton TR, cSajobi TT, dMinnella EM, dAwasthi R, eLoiselle SÈ, fLiberman AS, fStein B, fCharlebois P, dCarli F
aCumming School of Medicine, Department of Community Health Sciences, University of Calgary, Alberta, Canada bCommunity Health Sciences, Institute of Public Health, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, and Nutrition Services, Alberta Health Services, Alberta, Canada cCumming School of Medicine, Department of Community Health Sciences & O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada dDepartment of Anesthesia, McGill University, Montreal, Quebec, Canada eDepartment of Nutrition and Food Services, McGill University, Montreal, Quebec, Canada fDepartment of Surgery, McGill University, Montreal, Quebec, Canada

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, presurgery, 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.

Dr. Gutman's Comments:

Loss of muscle mass is always a serious consequence of cancer and cancer treatment. In a joint study between the University of Calgary and McGill University (both in Canada), a pooled analysis of two separate prehabilitation trials on colon cancer patients was performed. The prehabilitation patients had undergone presurgical intervention with three separate strategies, 1) an exercise program, 2) nutritional optimization using Immunocal, and 3) psychological counseling. Compared to a similar group receiving only standard care, the prehabilitation patients suffered significantly less lean muscle mass loss.

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

Depression and Functional Status in Colorectal Cancer Patients Awaiting Surgery: Impact of a Multimodal Prehabilitation Program

Meagan Barrett-Bernstein, Department of Psychiatry, McGill University Francesco Carli, Department of Anesthesia, McGill University Health Centre Ann Gamsa, Clinical Psychology, McGill University Celena Scheede-Bergdahl, Department of Kinesiology and Physical Education, McGill University Enrico Minnella, McGill University Agnihotram V. Ramanakumar, Department of Oncology, Research Institute, McGill University Health Centre, Montreal, Canada Leon Tourian, Department of Psychiatry, McGill University

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 preand 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.

Dr. Gutman's Comments:

This paper looked at the potential psychological benefits of a prehabilitation program on colon cancer patients receiving surgery. Pooling the results of three previous randomized studies on these patients, their levels of depression and how this may have affected their outcome was focused upon. Patients who had prehabilitation (presurgical exercise, dietary optimization with Immunocal, and psychological counseling) showed greater improvement in depressive scores than comparable groups not receiving prehabiltative care.

Medical Supervision for Cancer Patient's Healthy Lifestyle (MCL) Improves Postoperative Rehabilitation

Zhang X, 2Wu XJ, 3Luo M, 4Xiong LL, 5Du C, 6Shi HP
1Marryhealth Enterprises (Chongqing) Ltd., Chongqing, China 2Cancer Nutritional Treatment Center, Neijiang Second People's Hospital, Neijiang, Sichuan, China 3Medical Department/Department of Clinical Nutrition / Department of Psychiatry, Neijiang Second People's Hospital, Neijiang, Sichuan, China 4Cancer Center, Neijiang Second People's Hospital, Neijiang, Sichuan, China 5department of Gastrointestinal/Clinical Nutrition Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing, China

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 ($P<0.05$). PGSGA 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.

Dr. Gutman's Comments:

In an offshoot of several prehabilitation lectures presented in China by Dr. Franco Carli and myself, the Chinese went on to pursue this strategy themselves. In this variant, patients were placed on a dietary and lifestyle modification program (MCL), which included Immunocal as an interventional agent. Randomly selected to receive either standard treatment or MCL, the MCL group showed improvement in hospital stay, postoperative complications, nutritional status and physical symptoms such as nausea, vomiting, anorexia, diarrhea and emotional wellbeing



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

Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial

1Carli F, 1Bousquet-Dion G, 1Awasthi R, 2Elsherbini N, 3Liberman S, 4Boutros M, 3Stein B, 3Charlebois P, 4Ghitulescu G, 4Morin N, 5Jagoe T, 6Scheede-Bergdahl C, 1Minnella EM, 3Fiore JF Jr. 1Department of Anesthesia, Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada; 2Currently a medical student at Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada; 3Department of Surgery, Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada; 4Department of Surgery, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada; 5Department of Medicine, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada; 6Department of Anesthesia, McGill Research Centre for Physical Activity and Health, McGill University, Montreal, Quebec, Canada.



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.

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.

Continued on next page.

Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial

1Carli F, 1Bousquet-Dion G, 1Awasthi R, 2Elsherbini N, 3Liberman S, 4Boutros M, 3Stein B, 3Charlebois P, 4Ghitulescu G, 4Morin N, 5Jagoe T, 6Scheede-Bergdahl C, 1Minnella EM, 3Fiore JF Jr. 1Department of Anesthesia, Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada; 2Currently a medical student at Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada; 3Department of Surgery, Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada; 4Department of Surgery, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada; 5Department of Medicine, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada; 6Department of Anesthesia, McGill Research Centre for Physical Activity and Health, McGill University, Montreal, Quebec, Canada.

Abstract

Continued from previous page.

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.

Dr. Gutman's Comments:

Having already published a wealth of studies showing the benefits of prehabilitation strategies, this trial failed to improve outcomes in these very frail patients. Having an average age of 78 years, it appears that in this fragile group of cancer surgery patients that modifications to the prehabilitation program in place would need to be adjusted to better fit this demographic.



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

Multimodal Prehabilitation for Lung Cancer Surgery: A Randomized Controlled Trial

Ferreira V, Minnella EM, Awasthi R, Gamsa A, Ferri L, Mulder D, Sirois C, Spicer J, Schmid S, Carli F. Department of Kinesiology and Physical Education, McGill University, Montreal, Canada Department of Anesthesia, McGill University, Montreal, Canada Division of Thoracic Surgery, McGill University Health Centre, Montreal, Canada



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.

Dr. Gutman's Comments:

Continuing to expand the literature establishing the effectiveness of prehabilitation in cancer surgery, Dr. Carli's team found that in this particular trial, prehabilitation was equal to rehabilitation in improving functional capacity in these patients. More studies are to follow..

ACTA ONCOL. 2021 AUG;60(8):1025-1031

Functional capacity of prediabetic patients: effect of multimodal prehabilitation in patients undergoing colorectal cancer resection

Katherine Chabot , Chelsia Gillis , Enrico Maria Minnella , Vanessa Ferreira , Rashami Awasthi , Gabriele Baldini , Francesco Carli
Department of Anesthesia, McGill University, Montreal, Canada;
Department of Anesthesia and Intensive Care, San Raffaele Scientific Institute, Milan, Italy;
Department of Kinesiology and Physical Education, McGill University, Montreal, Canada

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:

Having well established the benefits of prehabilitation on colorectal cancer surgery patients, the team at McGill University wanted to better define in which subcategories of patients the strategy might have particular importance. In this paper, they focused on prediabetic patients. This demographic is known to be at higher risk for both surgery and its complications. The use of prehabilitation, which included Immunocal as the nutritional intervention, demonstrated clear improvement in clinical recovery.



EUROPEAN JOURNAL OF SURGICAL ONCOLOGY. 2021 Apr;47(4):874-881

Older frail prehabilitated patients who cannot attain a 400m 6-min walking distance before colorectal surgery suffer more postoperative complications

Chelsia Gillis, Tanis R Fenton, Leah Gramlich, Tolulope T Sajobi, S Nicole Culos-Reed, Guillaume Bousquet-Dion, Noha Elsherbini, Julio F Fiore Jr, Enrico M Minnella, Rashami Awasthi, A Sender Liberman, Marylise Boutros, F Carli
Cumming School of Medicine, Department of Community Health Sciences, University of Calgary
Peri Operative Program, McGill University, Montreal
Department of Community Health Sciences, Alberta Children's Hospital Research Institute
Department of Medicine, University of Alberta, Edmonton, Alberta, Canada.
O'Brien Institute for Public Health, University of Calgary, Calgary, Canada.
Faculty of Kinesiology and Department of Oncology, Cumming School of Medicine, University of Calgary.
Psychosocial Resources, Tom Baker Cancer Centre, Cancer Care, Alberta Health Services, Calgary, Alberta.
Department of Surgery, McGill University Health Center, Montreal, QC, Canada.
Faculty of Medicine, McGill University, Montreal, Quebec, Canada.
Department of Anesthesia, McGill University Health Center, Montreal, QC, Canada

Abstract

Introduction: Recent efforts to prehabilitate intermediately frail and frail (Fried frailty criteria ≥2) elective colorectal cancer patients did not influence clinical nor functional outcomes. The objective of this secondary analysis was to describe the subset of intermediately frail and frail prehabilitated patients who could not attain a minimum 400 m (a prognostic cut-point used in other patient populations) 6-min walking distance (6MWD) before elective surgery.

Materials and methods: Secondary analysis of a randomized controlled trial. Patients participated in multimodal prehabilitation at home and in-hospital for approximately four weeks before colorectal surgery. Primary outcome was incidence of postoperative complications within 30 days of hospital discharge.

Results: Sixty percent of the patients who participated in prehabilitation did not reach a minimum walking distance of 400 m in 6 min before surgery. Compared to the group that attained ≥400 m 6MWD (n = 19), the <400 m group (n = 28) were older, had higher percent body fat, lower physical function, lower self-reported physical activity, higher American Society of Anesthesiologists (ASA) classification, and twice as many were in critical need of a nutrition intervention at baseline. No group differences were observed regarding frailty status (P = 0.775). Sixty-one percent of the <400 m 6MWD group experienced at least one complication within 30 days of surgery compared to 21% in the ≥400 m group (P = 0.009).

Conclusion: Several preoperative characteristics were identified in the <400 m 6MWD group that could be useful in screening and targeting future prehabilitative treatments. Future trials should investigate use of a 400 m standard for the 6MWD as a minimal treatment target for prehabilitation

Dr. Gutman's Comments:

Continuing to expand the literature establishing the effectiveness of prehabilitation in cancer surgery, Dr. Carli's team found that in this particular trial, prehabilitation was equal to rehabilitation in improving functional capacity in these patients. More studies are to follow.

NUTRITION IN CLINICAL PRACTICE. 2021 Oct;36(5):1011-1019

Malnourished lung cancer patients have poor baseline functional capacity but show greatest improvements with multimodal prehabilitation

Vanessa Ferreira MSc1* Claire Lawson BSc2*
Chelsia Gillis PhD, RD3
Celena Scheede-Bergdahl PhD1 Stéphanie Chevalier PhD, RD2 Francesco Carli MD, MPhil4
1 Department of Kinesiology and Physical Education, McGill University, Montreal, Quebec, Canada
2 School of Human Nutrition, McGill University, Montreal, Quebec, Canada
3 Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
4 Department of Anesthesia, McGill University Health Centre, Montreal, Quebec, Canada

Abstract

Objective: The objective is to characterize the presence of malnutrition, examine the association between malnutrition and baseline functional capacity (FC), and the extent to which patients benefit from preoperative multimodal prehabilitation in patients undergoing lung resection for cancer.

Methods: Data from 162 participants enrolled in multimodal prehabilitation or control before lung cancer surgery were analyzed. Malnutrition was measured using the Patient-Generated Subjective Global Assessment (PG-SGA) according to triage levels: low-nutrition-risk (PG-SGA 0-3), moderate-nutrition- risk (4–8) and high-nutrition-risk (≥9). Baseline differences in FC, measured by the 6-minute walk test (6MWT), were compared. Factorial analysis of covariance (ANCOVA) was conducted to examine the effect of nutrition status and intervention on mean change in 6MWT preoperatively.

Results: 51.2% patients were considered low-nutrition-risk, 37.7% moderate- nutrition-risk, and 11.1% high-nutrition-risk. Low-nutrition-risk patients had significantly higher 6MWT at baseline (mean of 484 m [standard deviation (SD) = 88]) compared with moderate-nutrition-risk (432 m [SD = 107], P = .005) and high-nutrition-risk groups (416 m [SD = 90], P = .022). The adjusted mean change in 6MWT between prehabilitation vs control was 18.1 (95% confidence interval, 3.8 to 32.3) vs 5.6 m (–14.1 to 25.4) in low-nutrition-risk (P = .309), 28.5 (11 to 46) vs –4 m (–31.3 to 23.4) in moderate-nutrition-risk (P = .053), and 58.9 (16.7 to 101.2) vs –39.7 m (–80.2 to 0.826) in high-nutrition-risk group (P = .001).

Conclusions: Lung cancer patients at high-nutrition-risk awaiting surgery had significantly lower baseline FC compared with low-nutrition-risk patients but experienced significant improvements in preoperative FC upon receiving multi- modal prehabilitation.

Dr. Gutman's Comments:

Focusing on lung cancer surgery patients, the team questioned whether patients who were malnourished responded differently from those with normal nutritional status from intervention with prehabilitation intervention. This intervention consisted of a presurgical exercise program, nutritional intervention with Immunocal and psychological support. Although both populations benefitted from the prehabilitation, the nutritionally-compromised group showed even greater benefit.

JAMA SURGERY. March 2023 doi:10.1001/jamasurg.2023.0198

Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery – The PREHAB Randomized Clinical Trial

Charlotte Johanna Laura Molenaar, MD; Enrico Maria Minnella, MD, PhD; Miquel Coca-Martinez, MD, MSc; David Wouter Gerard Cate, MD; Marta Regis, PhD; Rashami Awasthi, MSc; Graciela Martínez-Palli, MD, PhD; Manuel López-Baamonde, MD; Raquel Sebio-Garcia, MSc, PhD; Carlo Vittorio Feo, MD; Stefanus Johannes van Rooijen, MD, PhD; Jennifer Marijke Janneke Schreinemakers, MD, PhD; Rasmus Dahlin Bojesen, MD, PhD; Ismail Gögenur, MD, PhD; Edwin R. van den Heuvel, MSc, PhD; Francesco Carli, MD, MPhil; Gerrit Dirk Slooter, MD, PhD
The PREHAB Study Group
• 1Department of Surgery, Máxima Medical Center, Veldhoven, the Netherlands
• 2Department of Anesthesia, Montreal General Hospital, McGill University Health Center, Montreal, Quebec, Canada
• 3Department of Anesthesia, Hospital Clínic de Barcelona, Barcelona, Spain
• 4Department of Mathematics and Computer Science, Eindhoven University of Technology, Eindhoven, the Netherlands
• 5IDIBAPS, University of Barcelona, Barcelona, Spain
• 6Physical Medicine and Rehabilitation Department, Hospital Clínic de Barcelona, Barcelona, Spain
• 7Department of Medical Sciences, University of Ferrara, Ferrara, Italy
• 8Unit of Provincial General Surgery, Azienda Unità Sanitaria Locale Ferrara, Ferrara, Italy
• 9Department of Surgery, Amphia, Breda, the Netherlands
• 10Center for Surgical Science, Zealand University Hospital, Roskilde, Denmark
• 11Department of Surgery, Slagelse Hospital, Slagelse, Denmark
• 12Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
• 13Department of Surgery, Zealand University Hospital, Køge, Denmark

Abstract

IImportance: Colorectal surgery is associated with substantial morbidity rates and a lowered functional capacity. Optimization of the patient's condition in the weeks prior to surgery may attenuate these unfavorable sequelae.

Objective: To determine whether multimodal prehabilitation before colorectal cancer surgery can reduce postoperative complications and enhance functional recovery.

Design, Setting, and Participants: The PREHAB randomized clinical trial was an international, multicenter trial conducted in teaching hospitals with implemented enhanced recovery after surgery programs. Adult patients with nonmetastasized colorectal cancer were assessed for eligibility and randomized to either prehabilitation or standard care. Both arms received standard perioperative care. Patients were enrolled from June 2017 to December 2020, and follow-up was completed in December 2021. However, this trial was prematurely stopped due to the COVID-19 pandemic.

Interventions: The 4-week in-hospital supervised multimodal prehabilitation program consisted of a high-intensity exercise program 3 times per week, a nutritional intervention, psychological support, and a smoking cessation program when needed.

Main Outcomes and Measures: Comprehensive Complication Index (CCI) score, number of patients with CCI score more than 20, and improved walking capacity expressed as the 6-minute walking distance 4 weeks postoperatively. Results: In the intention-to-treat

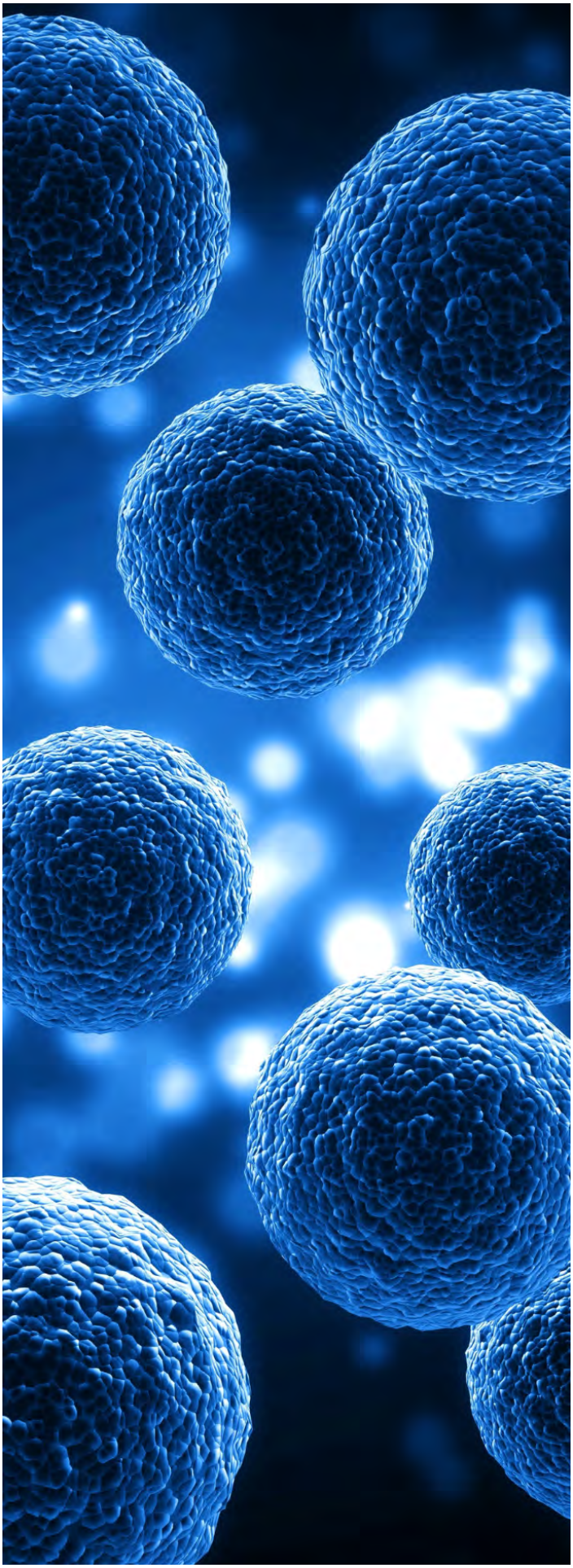
population of 251 participants (median [IQR] age, 69 [60-76] years; 138 [55%] male), 206 (82%) had tumors located in the colon and 234 (93%) underwent laparoscopic- or robotic-assisted surgery. The number of severe complications (CCI score >20) was significantly lower favoring prehabilitation compared with standard care (21 of 123 [17.1%] vs 38 of 128 [29.7%]; odds ratio, 0.47 [95% CI, 0.26-0.87]; P = .02). Participants in prehabilitation encountered fewer medical complications (eg, respiratory) compared with participants receiving standard care (19 of 123 [15.4%] vs 35 of 128 [27.3%]; odds ratio, 0.48 [95% CI, 0.26-0.89]; P = .02).

Four weeks after surgery, 6-minute walking distance did not differ significantly between groups when compared with baseline (mean difference prehabilitation vs standard care 15.6 m [95% CI, −1.4 to 32.6]; P = .07). Secondary parameters of functional capacity in the postoperative period generally favored prehabilitation compared with standard care.

Conclusions and Relevance: This PREHAB trial demonstrates the benefit of a multimodal prehabilitation program before colorectal cancer surgery as reflected by fewer severe and medical complications postoperatively and an optimized postoperative recovery compared with standard care.

Dr. Gutman's Comments:

As evidenced by this huge international, multicenter trial conducted in many teaching hospitals, prehabilitation is becoming an established tool for improving outcomes in cancer surgery. Focusing on cancer of the colon and rectum, patients were randomized to receive either standard care or prehabilitative intervention (preoperative exercise program, nutritional intervention using Immunocal, psychological support and, smoking cessation when needed). The prehab-treated group clearly showed fewer complications and an optimized recovery compared to standard care.



Immunocal non-blinded human studies



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

Treatment of Chronic Hepatitis Using Whey Protein (Non-Heated)

A. Watanabe, K. Higuchi, K. Okada, Y. Shimizu, Y. Kondo* and H. Kohri*
Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan, and *Otsuka Pharmaceutical Factory, Inc., Nutrition Research Institute, Tokushima, Japan



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 (followup 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.

Dr. Gutman's Comments:

Very early in its development, a number of different drug companies considered acquiring Immunocal. One of these was the Japanese giant Otsuka Pharmaceuticals. What interested Dr. Watanabe, Dr. Kondo and the other authors was hepatitis. In this study they report improved liver function and elevated glutathione levels in patients with hepatitis B compared to placebo.

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

Effect of Whey Protein to Modulate Immune Response in Children with Atopic Asthma

James B. Lothian1 , Vijaylaxmi Grey2 , Larry C. Lands1
1 The Department of Respiratory Medicine, McGill University Medical Centre, Montreal Children's Hospital, Montreal, Quebec 2 The Department of Pathology and Molecular Medicine, McMaster University, Hamilton Health Sciences, Hamilton, Ontario

Abstract

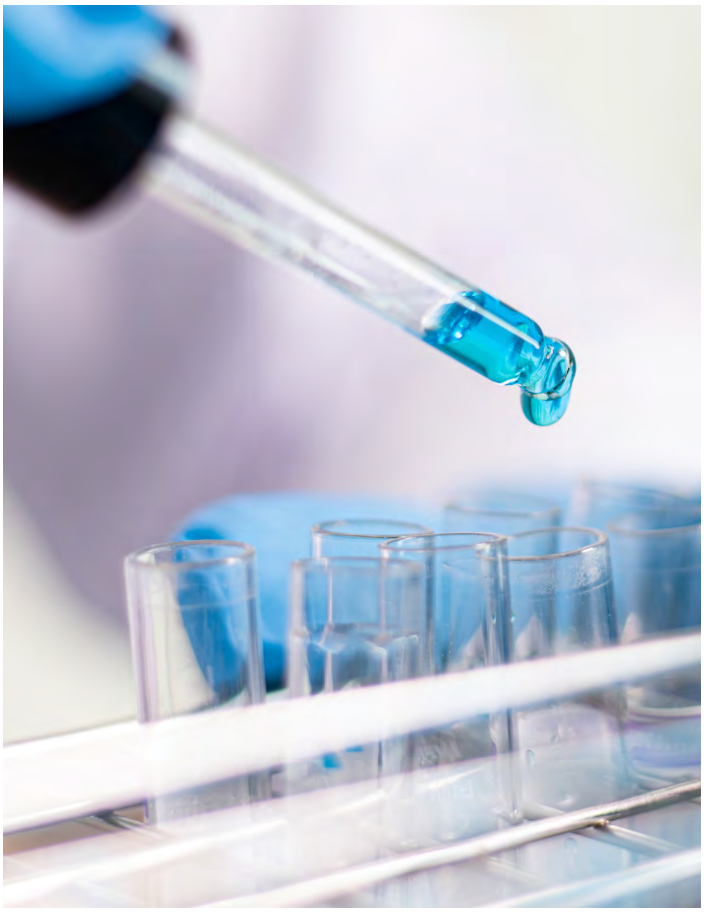
Background: Levels of glutathione (GSH) in antigen-presenting cells promote a T-helper type 2 (Th2) cytokine response in mice. We have previously demonstrated that we can increase intracellular GSH levels in healthy young adults using a wheybased oral supplement (HMS90TM). We hypothesized that such supplementation 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).Dr. Gutman's Comments: 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 wheybased supplements, currently under development, may prove more beneficial.

Dr. Gutman's Comments:

This McGill University research team had previously shown success in raising glutathione in healthy adults using "HMS90" an earlier form of Immunocal. They believed that raising GSH in children with atopic (allergic) asthma would prove to be helpful since inflammation was a large part of this type of pathology. The children who's glutathione level went up demonstrated improvement in their lung function tests.



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

Open-Labeled Pilot Study of Cysteine-Rich Whey Protein Isolate Supplementation for Nonalcoholic Steatohepatitis Patients

Taned Chitapanarux* Prasong Tienboon† , Suwalee Pojchamarnwiputh‡ and Donrawee Leelarungrayub§ *Division of Gastrohepatology, Department of Medicine, † Division of Nutrition, Department of Pediatrics, ‡ Division of Diagnostic Radiology, Department of Radiology, Faculty of Medicine, Chiang Mai University, and § Department of Physical Therapy, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand



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.

Dr. Gutman's Comments:

NASH (Non-Alcoholic Steatohepatitis, commonly called 'Fatty Liver') is a liver disorder found in patients who are not alcohol abusers. NASH patients are often diagnosed when routine liver function blood tests (LFTs) reveal impaired liver function. People are more prone to NASH when overweight, diabetic or suffering from metabolic or similar syndromes. In this study, a non-blinded (no placebo control) group of patients was fed Immunocal for three months. Blood tests compared their initial (baseline) glutathione status, antioxidant status, CT-scans and (most importantly) liver function tests to the same parameters after treatment. All patients showed improvements.

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

The effects of glutathione enhancement on sensorineural hearing loss

Robert T Sataloff, Therese Bittermann, Linda Marks, Deborah Lurie, Mary Hawkshaw
Department of Otolaryngology-Head and Neck Surgery, Drexel University College of Medicine, Philadelphia, PA, USA.

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:

This team of ear-nose-and-throat researchers were aware that antioxidant treatment could be useful in the prevention of hearing loss in animals. They set out to see if this was also the case in humans. Although the results did not reach statistical significance, the trend was such that they suggested larger studies be done as follow up.



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

Cysteine/Cystine-Rich Undenatured Whey Protein Supplement in Patients' Pressure Ulcers Outcomes: An Open Label Study

Gutman JBL1 , Kongshavn PAL2



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.

Dr. Gutman's Comments:

After hearing anecdotes from the field that Immunocal was having beneficial effects on certain skin lesions including pressure ulcers (bedsores), it was decided to take this to an official study. Bedsores are called "pressure ulcers" because they occur in patients that are lying in bed for prolonged periods of time and the skin that is under pressure from the weight of the patient begins to break down. This is extremely distressing and requires tremendous resources to take care of. This paper shows that a simple dietary intervention using Immunocal can relieve much suffering

Immunocal human pilot studies



CLINICAL INVESTIGATIVE MEDICINE, 16:204-209, 1993

Whey Proteins as a Food Supplement in HIV-Seropositive Individuals

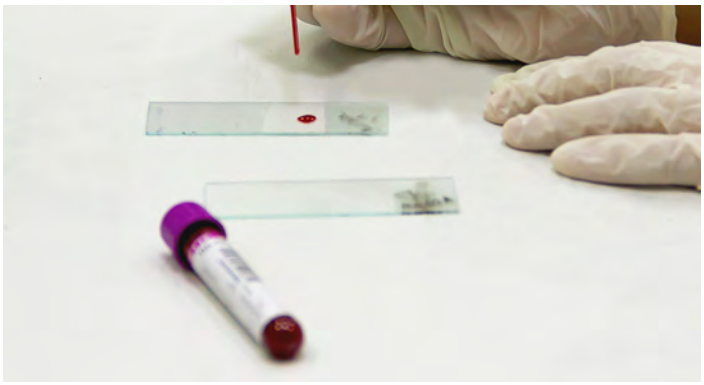
G. Bounous, S. Baruchel, J. Falutz, P. Gold
Departments of Surgery and Medicine, The Montreal General Hospital and McGill University, Montreal, Quebec

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.

Dr. Gutman's Comments:

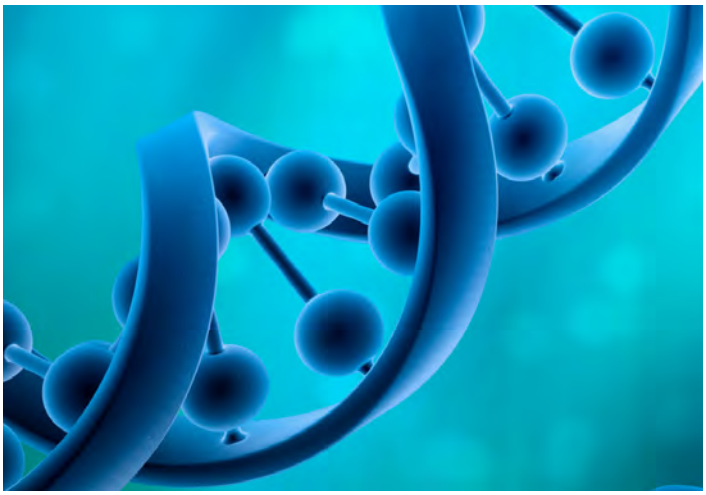
This small study was the first trial of Immunocal in humans. Following successful experiments on animals with AIDS/HIV, the Montreal General Hospital team felt confident enough to move up to clinical trials by collaborating with McGill researchers. Permission to experiment on humans is strictly regulated by review boards, ethics boards and governmental agencies, and access to these patients with advanced AIDS was granted only because their prognosis was so poor. Dr. Bounous's team documented significant weight gain in all of these otherwise muscle-wasted individuals, leaving the door wide open for further studies. These severely compromised patients also benefited from increased glutathione levels—in one case by over 70%. Although this was a small trial, it garnered much attention and secured funding for further research.



ANTICANCER RESEARCH 15, 2643-2650, 1995

The Use of a Whey Protein Concentrate in the Treatment of Patients with Metastatic Carcinoma: A Phase I-II Clinical Study

Renee S. Kennedy1 , George P. Konok1 , Gustavo Bounous2 , Sylvain Baruchel3 and Timothy D.G. Lee4
1 Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada 2 Department of Surgery, McGill University, Montreal, Quebec, Canada 3 Department of Pediatrics and Oncology, McGill University, Montreal, Quebec, Canada 4 Department of Immunology and Microbiology, Dalhousie University, Halifax, Nova Scotia, Canada



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.

Dr. Gutman's Comments:

This was one of the first clinical studies of Immunocal in humans, conducted before the product was widely known and even before the official launch of Immunotec. A large human trial at this stage would have been premature, so the team began with smaller studies to first satisfy safety concerns and confirm the method of inquiry. All patients were in advanced stages of cancer of the breast, liver or pancreas and the researchers obtained ethical approval to treat them. For three months, each patient was given 30 grams daily of HMS90 (an early name for Immunocal). Tumors in two patients shrank, the tumors of two others stabilized and the red blood cell count of two others improved. This study was too small to establish reliable statistical evidence, but it opened the door to the larger studies that followed.

Oral Tolerability of Cysteine-Rich Whey Protein Isolate in Autism: A Pilot Study

Janet K. Kern1 , Bruce D. Grannemann1 , Jimmy Gutman2 , Muadhukar H. Trived1
1 University of Texas Southwestern Medical Center, Dallas, Texas
2 McGill University, Canada and Immunotec Inc. Montreal, Quebec, Canada

Abstract

Purpose: To examine the tolerability of nondenatured 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.

Dr. Gutman's Comments:

I am one of the authors of this paper. By the time I wrote it, I had been approached by the parents of many autistic children who claimed their symptoms had improved with Immunocal. However, without clinical evidence to support these claims I was reluctant to share them. In 2004 Jill James's team in Arkansas demonstrated that more than more than 80% of autistic children suffered abnormally low glutathione levels. This was my starting point. I contacted Janet Kern in Texas—a researcher into Autistic Spectrum Disorder (ASD)— to collaborate on a clinical trial with Immunocal. There was some initial hesitation, as autistic children are often warned to "avoid milk products" on the grounds that they could exacerbate symptoms. In fact, the culprit was the one milk protein that is absent from Immunocal—'casein.' A small pilot study soon demonstrated that it was safe, and we noted improvements in behavior as well. The number of people recruited for the study was insufficient to establish statistical significance, but it opened the door to larger subsequent studies.



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

Psoriasis Improvement in Patients Using Glutathione-Enhancing, Nondenatured Whey Protein Isolate: A Pilot Study

a,bRonald Prussick, MD, a Lisa Prussick, BSc, c,dJimmy Gutman, MD
a Washington Dermatology Center, North Bethesda, Maryland, b Assistant Clinical Professor, George Washington University, Washington, DC, c McGill University, Montreal, Canada, d Immunotec Research, Vaudreuil-Dorion, Quebec, Canada



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, nonblinded 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.

Dr. Gutman's Comments:

A small group of psoriatic patients in the Washington area was fed Immunocal to see what clinical benefits could be measured on a standard psoriasis severity score. They also compared photographs of affected skin. Patients improved in all cases, opening the door to larger studies in the future.

Immunocal human case reports



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

Treatment of Obstructive Airway Disease with a Cysteine Donor Protein Supplement: A Case Report

Bryce Lothian, MD*, Vijaylaxmi Grey, PhD*†, R. John Kimoff, MD‡, Larry Lands, MD, PhD*§
*Department of Pediatrics, †Department of Biochemistry,
§Division of Respiratory Medicine, McGill University Health Centre-Montreal Children's Hospital, Montreal, Canada ‡Division of Respiratory Medicine, McGill University Health Centre-Royal Victoria Hospital, Montreal, Canada



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 wheybased 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.

Dr. Gutman's Comments:

This case study was of particular interest to me because the subject of the study was one of my own patients—a single mother who practiced law. Following radiation exposure for treatment of Hodgkin's lymphoma when she was younger, she developed "Pulmonary Fibrosis," which scarred the lung so much that she became housebound and dependent on an oxygen mask. When she started taking Immunocal she was able to resume much of her previous lifestyle. I referred her to Dr. Lands, a lung specialist. One-by-one, he removed drugs from her daily regimen to determine what was actually helping her feel better. Two weeks after he removed Immunocal, she was admitted to the emergency department. The Immunocal was reinstated and her pulmonary function tests improved so dramatically that her case was presented to Grand Rounds at the Royal Victoria Hospital at McGill University in Montreal, which provoked the writing of the article.

ANTICANCER RESEARCH 20, 4785-4792, 2000

Whey Protein Concentrate (WPC) and Glutathione Modulation in Cancer Treatment

Gustavo Bounous, M.D., F.R.C.S. (C)
Research and Development Department
Immunotec Research Ltd., Vaudreuil-Dorion,
Quebec, Canada

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 antitumor 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.

Dr. Gutman's Comments:

Dr. Gustavo Bounous discovered Immunocal. Here he reviews the glutathione antioxidant system and revisits some earlier work with Immunocal in immune deficiency and cancer. He also reports the benefits of Immunocal for cancer patients. He calls for further and larger studies, which were later completed.



Does the use of cysteine-rich whey protein supplements (Immunocal) improve the health well-being of COVID-19 patients? A qualitative study

Canari B, Moya-Salazar J, Bussalleu D, Conteras-Pulache, H.
South American Center for Research in Education and Public Health, Universidad Norbert-Weiner, Lima, Peru
Hospital Nacional Docente Madre Nino San Bartolome, Lima, Peru.

Abstract

Introduction: In the context of SARS-CoV-2 infection, it has been proposed that oxidative stress may contribute to the management of COVID-19 severity. The impact on the well-being of patients with COVID-19 using cysteine- providing supplements has not yet been evaluated and there is a need to understand the benefits and limitations they may offer.

Aim: The aim of this study is to understand the experiences of improved well-being with cysteine-rich whey protein supplementation (Immunocal®) in patients with COVID-19.

Methods: A qualitative study was conducted by conducting semi-structured interviews with four participants taking Immunocal® while they had COVID-19. Participants were randomly recruited through internet networking. Ethical approval was obtained from the University ethics committee. Participants were informed of the study objectives two days in advance and consent was obtained before interviews began. We used the 16-item "Use of Immunocal supplement for COVID-19" (USIC-19) questionnaire to inquire about COVID-19 behavior (time of illness, symptoms, and severity of illness) and the experience of using the supplement during illness. Confidentiality was maintained throughout this study.

Results: All participants presented mild discomfort such as headache, weakness, and tiredness when they had COVID-19 impacting most of them emotionally. The use of Immunocal® produced a partial improvement in all patients as only two continued to experience fatigue. Immunocal® improved the mood (50%) and physical health of the participants. In addition, participants reported that the supplement was recommended and dosed primarily by a consultant and that they did not feel hesitant to use it because of previous experiences of friends and family. The daily dosage of half of the participants was two sachets and all felt the need to consume the supplement which resulted in daily use.

Conclusion: Following the daily dosage indications of the consultants, the participants who have consumed Inmunocal® have presented a partial improvement of the symptoms related to COVID-19, however, they feel the need to consume the supplement daily to improve their quality of life.

Dr. Gutman's Comments:

A small group of patients with COVID-19 were treated with cysteine-rich whey protein isolate (Immunocal) 20 grams/day. They reported improvements in fatigue, mood, and general physical health. This study calls for larger studies looking at this intervention.

Use of a Cysteine-Rich whey Protein Isolate as Adjuvant Therapy in Patients with COVID-19 Pneumonia: A Case Series

Arturo Arias[1], Catalina Camacho[2], Maria Padron[2], Gilberto Bustamante[3], Fernando Villamizar[3], Eduardo Scholcoff[2] and Ruben D Restrepo[4]*

[1]de Ciencias de la Salud, Bogotá, Colombia

[2]Immunotec Incorporated, Victoria, BC, Canada

[3]Clínica Norte, Cúcuta, Colombia

[4]The University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 has infected more than 283 million people world- wide and is responsible for nearly 5.5 million deaths. While a significant number of people have recovered from this infection, nearly 40% of the patients who leave the ICU have important complications that compromise their activity of daily living. It is estimated that without a specific effective antiviral treatment, new waves due to emerging variants may further compromise healthcare systems and potentially delay herd immunity. Several previous studies have demonstrated that glutathione (GSH) deficiency may play an important pathophysiological role in severe COVID-19 morbidity and mortality. Historically, administration of N-acetylcysteine (NAC), a GSH precursor, has been found to significantly reduce the incidence of clinically apparent influenza and influenza-like episodes. Such benefits have created enormous interest in the use of NAC to target severe lung cell injury in patients with acute respiratory distress syndrome (ARDS). Despite the advent of vaccines against the virus, it has not yet been possible to identify a single agent or cocktail of drugs that effectively modulates the cytokine storm associated with SARS-CoV-2 infection. The addition of cysteine-rich whey protein isolate (CRWPI) supplementation as adjuvant therapy in treating patients with severe respiratory symptoms associated with COVID-19 pneumonia has not been reported in the literature. This article describes the results of adding a CRWPI to the treatment of four patients diagnosed with severe COVID pneumonia admitted to a medical ICU in Cucuta, Colombia.

Dr. Gutman's Comments:

In this case study, four middle-aged to elderly females with COVID-19 who were admitted to the hospital were studied. These four were transferred to the ICU (Intensive Care Unit) from the medical unit that they were originally admitted to because they had displayed progressive deterioration. In addition to the standard treatment, they all received 30 grams (three pouches) of Immunocal for 2 weeks. All four patient showed rapid improvement over 4 days on the Immunocal. They continued to improve. The authors suggest that the use of Immunocal needs to be considered as a novel coadjuvant to standard treatment and should be further studied.



Theoretical papers, opinion papers, reviews

Science. A rigid field of analysis seeking proof. Sounds like there is little room for creativity and imagination, but quite the opposite is true. Science is based on validating a 'theory' or 'hypothesis'. These ideas often require much inspiration and ingenuity. Stories abound about great scientists who find these ideas during dreams, resting or even drug-induced states of mind. Einstein's 'Theory of Relativity' was a result of 'thought experiments' while daydreaming at his desk working at the patent office.

Theories are the fuel for setting up a hypothesis which can subsequently be tested by the 'scientific method'. You will find in the next pages published papers by incredibly visionary Immunotec-related scientists that were critical in the pursuit in establishing clinical trials for this product.

Opinion papers do not follow the scientific method per se. They are written to address concerns, ideas or controversies that exist in our current knowledge base. Although difficult to totally avoid bias in these papers, they are an effort to shed light on or resolve many areas in question.

Finally, review papers have tremendous value in interpreting the collective opinions of many research papers that have already been published. Although many people have the idea that there is something called 'proof' that comes from research, this absolute certainty is usually very elusive. One can find multiple 'results' that seem to point to answers that are in complete disagreement with each other. A review paper tries to garner a 'consensus' on these topics. A good review paper will highlight that these differences exist and generally will make suggestions about what research strategies may be required going forward to get closer to the 'truth'.

Enjoy this collection of articles!

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

Evolutionary Traits in Human Milk Proteins

Bounous G, 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.

Dr. Gutman's Comments:

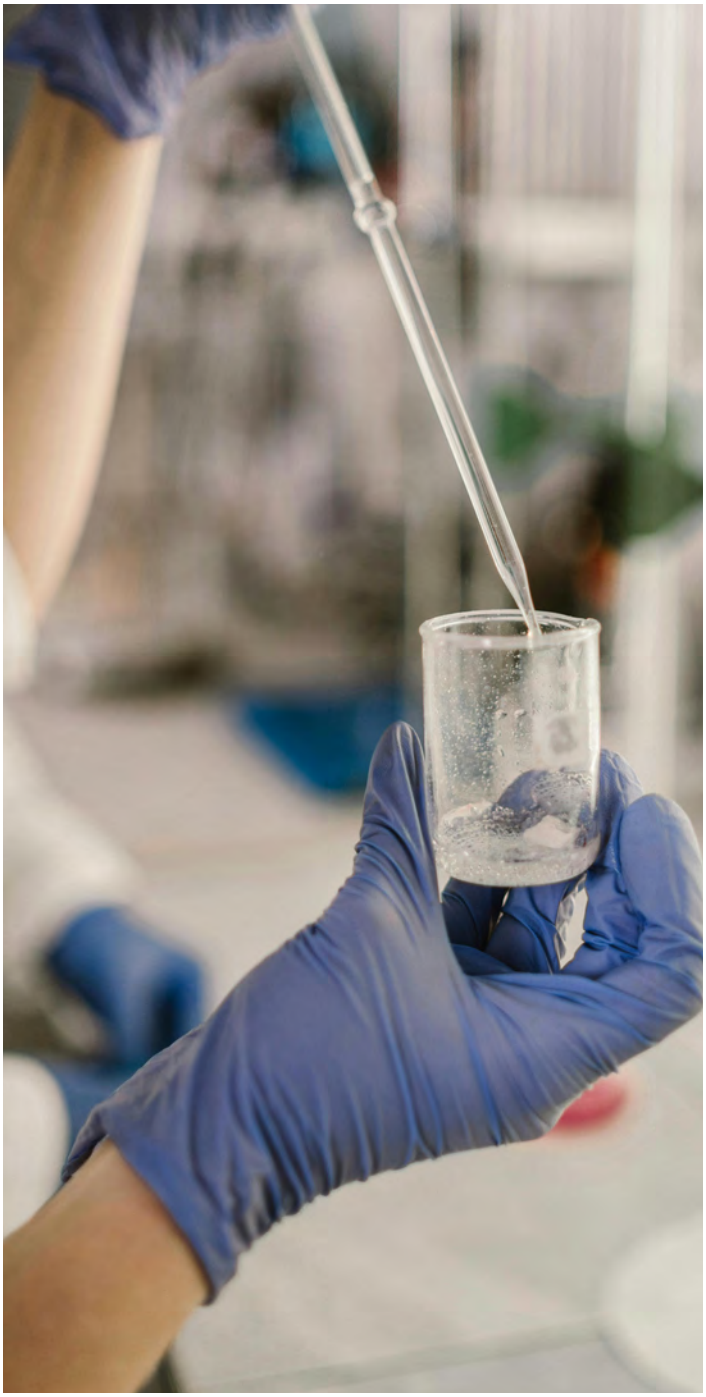
This is a fascinating theoretical paper in which Dr. Bounous examines the variety of milk proteins in mammals. He points out that a) Human milk has the lowest concentration of protein (possibly explaining why humans take so long to reach adulthood), and 2) Human milk has the highest concentration of whey as compared to casein. Dr. Bounous' point is that preponderance of whey in human milk may help explain the slow development of human infants and the longevity of the human species.stress and free radical damage and may lead to the death (apoptosis) of these cells. Exposure of these cells to Immunocal both increased their glutathione parameters and protected them from damage.



CANCER LETTERS, 57: 91-94, 1991

Whey Proteins in Cancer Prevention

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.

Dr. Gutman's Comments:

Gerry Batist was a prominent Canadian oncologist and researcher, while Dr. Phil Gold was chief of Medicine at Montreal General Hospital. In this paper, they join Dr. Bounous and his colleagues to review research that was conducted early in the development of Immunocal. They identify the components of whey protein responsible for raising glutathione and open a discussion of how it might be used to combat cancer. The team later applied for and received international patents for the use of Immunocal in cancer treatment.

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

Place for an Antioxidant Therapy in Human Immunodeficiency Virus (HIV) Infection

S. Baruchel1,2 G. Bounous2 , P. Gold2
1 McGill University, Department of Pediatrics; McGill AIDS Centre, Montreal, Quebec, Canada
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 suc 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.

Dr. Gutman's Comments:

The AIDS virus is known to thrive even in an environment of oxidative stress and free radicals. This review examines Immunocal's potential to suppress its growth, and constitutes preliminary findings at McGill University with what was then a novel glutathione precursor.



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

Nutriceutical Modulation of Glutathione With a Humanized Native Milk Serum Protein Isolate, Immunocal™: Application in AIDS and Cancer

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 pharmacoepidemiological 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.

Dr. Gutman's Comments:

This article first appeared in a book compiled by Dr. Luc Montagnier, the discoverer of the AIDS virus and winner of the 2008 Nobel Prize for medicine. Dr. Montagnier had previously studied earlier work on HIV/AIDS patients with Immunocal, and highlighted them in his opening address to an international AIDS conference in Japan. A close colleague working with him at the Pasteur Institute in Paris, Dr. Richard Olivier, continued these investigations in collaboration with the original McGill team studying Immunocal. Of these authors, Sylvain Baruchel was an eminent pediatric Oncologist who studied Immunocal in children's cancer, and Dr. Wainberg served several terms as president of an international AIDS research foundation. This article reviews some of the clinical trials that tested Immunocal in AIDS and cancer.

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

Competition for Glutathione Precursors Between the Immune System and the Skeletal Muscle: Pathogenesis of Chronic Fatigue Syndrome

G. Bounous1 , J. Molson2
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.



Dr. Gutman's Comments:

Dr. Gustavo Bounous and John Molson had been communicating with Dr. Paul Cheney in the late 1990s. Dr. Cheney, a member of the team that coined the term "Chronic Fatigue Syndrome" had just recently completed several successful courses of treatments on his CFS patients using Immunocal. They could see that the strategy worked, but not why. This theoretical article was one of the first to ponder the question.

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

Therapeutic Functions of Whey Proteins (Turkish)

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.

Dr. Gutman's Comments:

Working out of a major food science faculty, this Turkish researcher wanted to review the potential clinical applications of whey proteins for potential opportunities for the dairy industry. As one would expect, the majority of articles cited in the review were those from Immunocal scientists, which at the time were clearly ahead of any other researchers in that realm. The author Dr. Elmin Yilmaz was quite correct in stating "more research was needed" as the problem remained as to how to scale up this technology for commercial use. Truly inexpensive technologies on how to produce undenatured whey protein isolates are still elusive.

ANTICANCER RESEARCH 23, 1411-1416 (2003)

The Antioxidant System

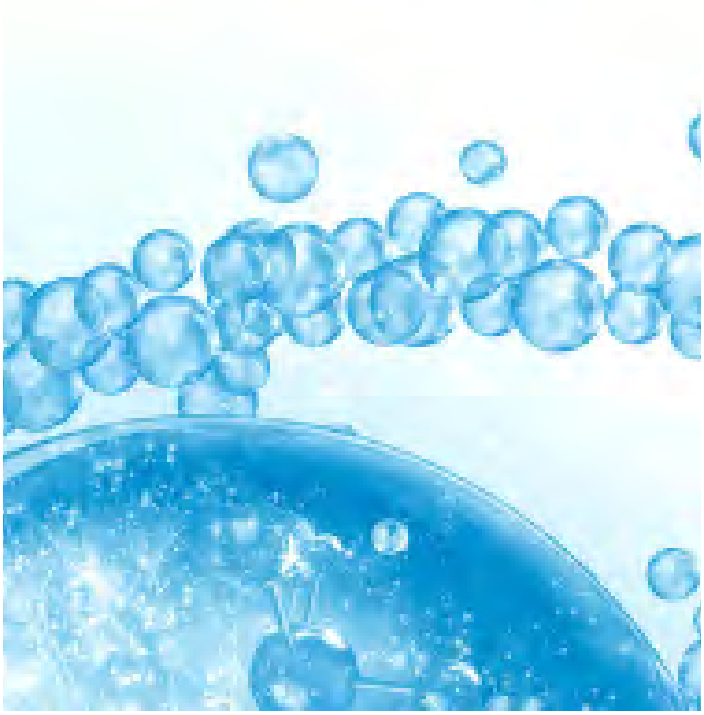
G. Bounous and J. H. Molson
Research and Development Department
Immunotec Research Ltd., Vaudreuil-Dorion,
Quebec, Canada

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.

Dr. Gutman's Comments:

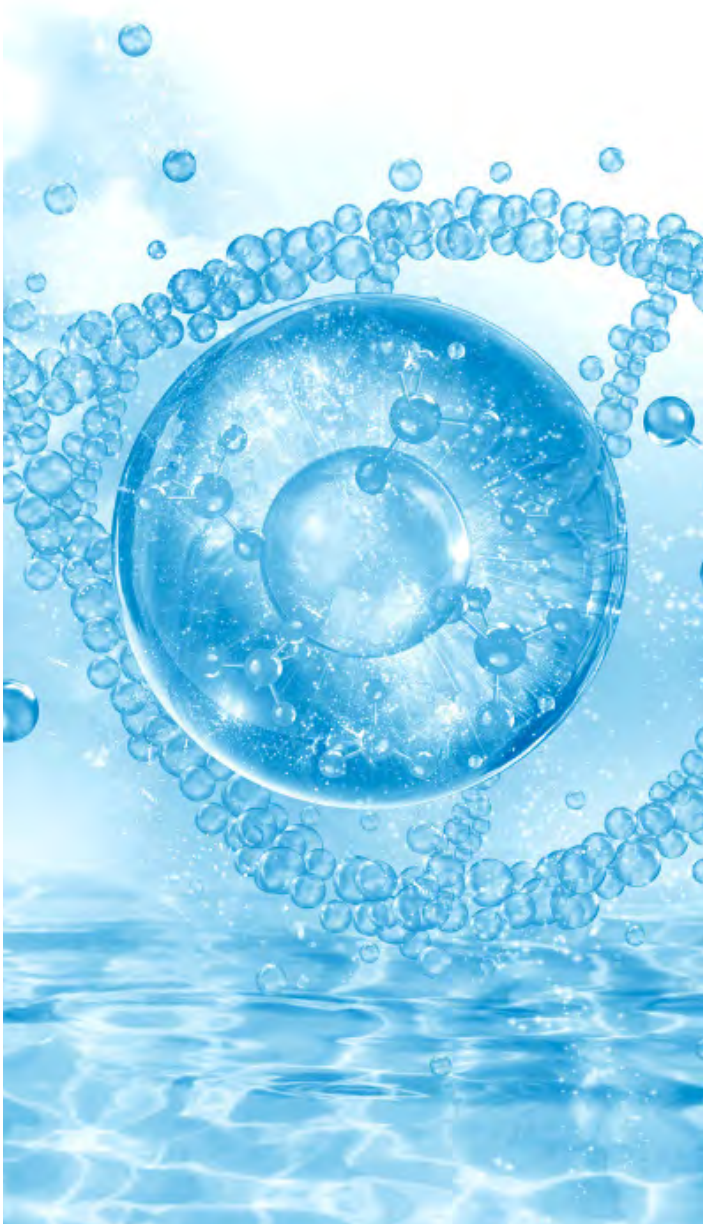
In this short theoretical paper, Dr. Gustavo Bounous and John Molson highlight the role of glutathione as the key antioxidant in sustained immune response. They review some earlier work, in which Immunocal was used to trigger anticancer activity.



ANTICANCER RESEARCH 24, 553-554 (2004)

Molecular Pathogenesis and Prevention of Prostate Cancer

G. Bounous, D. Beer
Research and Development Department,
Immunotec Research Ltd., Vaudreuil-Dorion,
Quebec, Canada



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.

Dr. Gutman's Comments:

In this theoretical discussion, Dr. Bounous suggests that just as higher cysteine levels lower the risk of developing breast cancer, protection may also extend to cancer of the prostate. In later research, his team reported improved PSA values (a blood test for prostate cancer) using Immunocal.

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

Oxidative Stress and Ageing: Is Ageing a Cysteine Deficiency Syndrome?

W. Dröge
Division of Redox Physiology and Aging Research, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

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

Dr. Gutman's Comments:

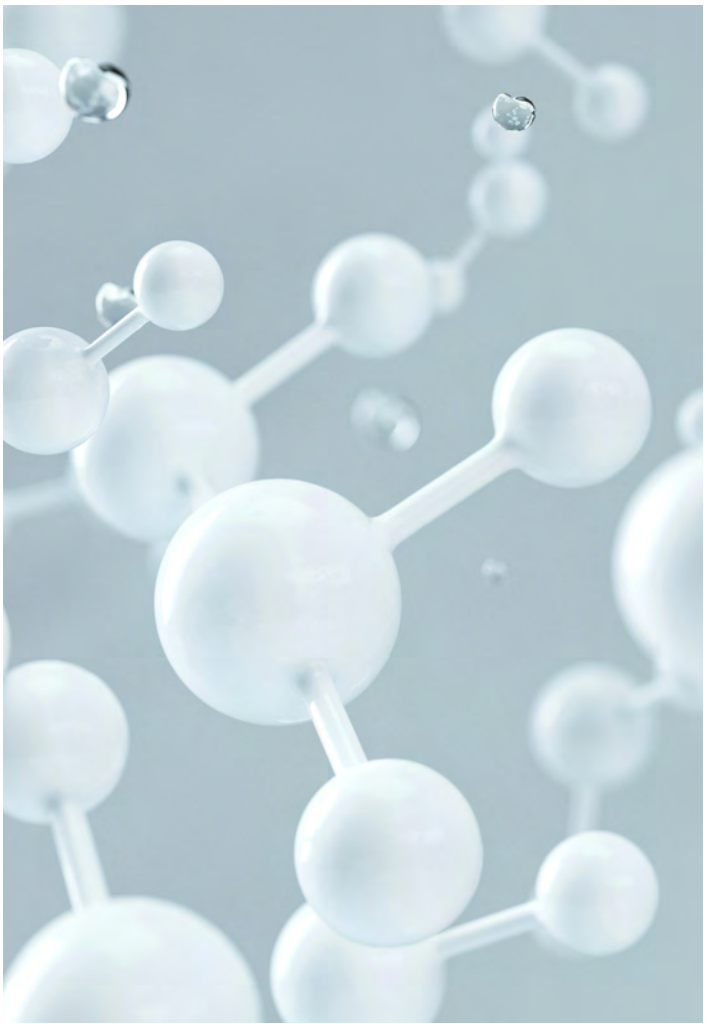
In this theoretical article, anti-aging specialist Wulf Droge draws attention to the accepted theory that oxidative stress and free radical damage are major culprits in the aging process. He points out that earlier studies have demonstrated how the glutathione precursor cysteine successfully reversed such symptoms of aging as muscle mass, increased inflammation, immune compromise and other parameters. He suggests that youthfulness and quality of life are lost in part due to declining rates of cysteine and glutathione levels that are well documented in aging.



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

Children's Oncology Group (COG) Nutrition Committee

Paul C. Rogers, MB ChB, MBA1 Steven J. Melnick, MD, PhD2 , Elena J. Ladas, MS3 Jacqueline Hamilton, MD4 Jacques Baillargeon, PhD5 and Nancy Sacks, MS6 1 British Columbia Children's Hospital, Vancouver, British Columbia, Canada, 2 Miami Children's Hospital, Miami, Florida, 3 Columbia University, Children's Hospital of New York, NY, 4Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada, 5 University of Texas Health Science Center, San Antonio, Texas, 6 The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania



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.

Dr. Gutman's Comments:

The 'Children's Oncology Group' is a North American organization that examines the effectiveness of nutrition in treating pediatric cancer and in clinical trials. This article reports their first pilot experiment. Children fed with Immunocal experienced increased glutathione levels. More importantly, they gained weight—a crucial survival factor. This report served as a good launch pad for further studies.

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

Aberrant Insulin Receptor Signaling and Amino Acid Homeostasis as a Major Cause Of Oxidative Stress in Aging?

W. Dröge1 R. Kinscherf2
1 Department of Research & Development, Immunotec Inc., Vaudreuil, Quebec, Canada
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" diseaserelated mechanisms of oxidative stress. Studies on cysteine supplementation show therapeutic promise.

Dr. Gutman's Comments:

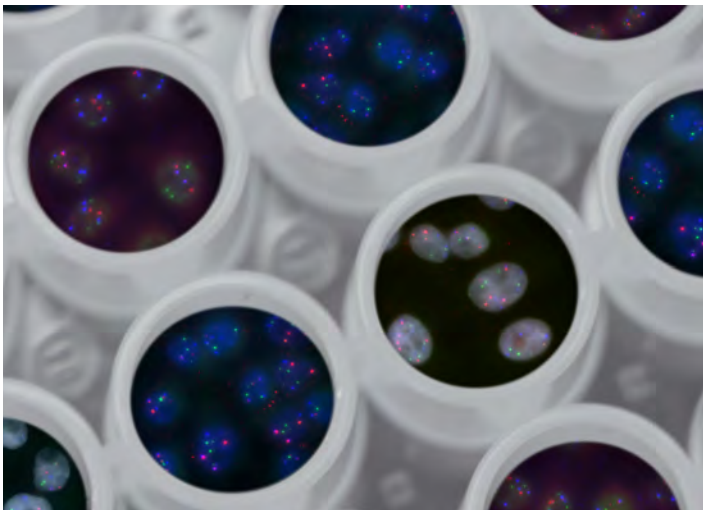
Drs. Droge and Kinsherf are recognized authorities in the field of aging, oxidative stress and anti-aging. In this article they review evidence that free radical damage affects insulin signaling, which in turn leads to muscle and protein loss. They advance the idea that one of the underlying mechanisms of aging is the decline of glutathione and cysteine levels.



PEDIATRIC BLOOD CANCER, 2008, 50:490-493

Bringing Evidence to Complementary and Alternative Medicine in Children With Cancer: Focus on Nutrition-Related Therapies

Kelly Kara M., MD
Division of Pediatric Oncology, Columbia University Medical Center, New York, New York



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 TRAUMEELS®, 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.

Dr. Gutman's Comments:

This review article appeared in a major childhood leukemia/lymphoma journal that discusses the usefulness of natural products (Complementary & Alternative Medicine, or CAM treatments) in patients with this group of blood cancers. A handful of these products appear to mitigate the side-effects of chemotherapy, among them Immunocal. The authors point out that this field requires further study before it is fully accepted by the medical community. Immunotec has since published more work in this area, boosting acceptance of Immunocal as a complementary therapy.

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

Immunocal® and Preservation of Glutathione as a Novel Neuroprotective Strategy for Degenerative Disorders of the Nervous System

Ross EK1 , Gray JJ, Winter AN, Linseman DA
1 Department of Biological Sciences, University of Denver, Denver, Colorado, USA

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.

Dr. Gutman's Comments:

This paper reviewed earlier Immunocal studies, as well as the patents granted for Immunocal's use in raising glutathione. Glutathione depletion is a key feature of many neurodegenerative diseases, including Alzheimer's Disease, Parkinson's Disease, ALS and others. The authors suggest this strategy could be a potential intervention, and should be investigated.



Editorial: Therapeutic Antioxidants for Neurodegenerative Disease

Linseman DA
Department of Biological Sciences and Eleanor Roosevelt Institute, University of Denver, Denver, Colorado, USA.
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.

Dr. Gutman's Comments:

The journal in which this editorial appears publishes novel strategies for neurological treatments. The paper was written by researcher Dr. Dan Linseman who has extensively explored Immunocal and the links between glutathione and neurodegenerative disorders. In this editorial he suggests that strategies like this should receive heightened attention for further research investigations.

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

Progress in Application of Whey Protein Concentrate in the Treatment For Malignancies

Cai YY1 Ai Z2 Sun HL3
1Jisheng Jiai Hospital, Yongchuan District, Chongqing, Chongqing, China
2Marry Health Enterprises (Chongqing) Inc., Chongqing, China
3Daping Hospital, The Third Military Medical University, Chongqing, China

Abstract

As a safe and effective cysteine carrier, whey protein concentrate (WPC) effectively promote the body's glutathione synthesis thereby 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.



Dr. Gutman's Comments:

This Chinese paper reviews the application of whey protein in cancer treatment. An unfortunate error in translation refers to the whey as a "concentrate" when in fact most of the studies reviewed were using whey isolates. They conclude that the literature is suggestive of potential improvements in nutritional status, immune function, quality of life measurements, weight maintenance, and side-effects of chemo- and radiation therapy.

Therapeutic Potential of Glutathione Augmentation in Cancer Patients Receiving Chemotherapy or Radiotherapy

Jimmy Gutman MD
Immunotec Research Inc., 300 Joseph Carrier, Vaudreuil-Dorion, Montreal, Canada



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.

Dr. Gutman's Comments:

One of the most common questions I receive from both medical professionals and patients alike, is the question "does glutathione 'feed' cancer cells" and could it "protect" cancer cells from chemotherapy and radiotherapy. These questions come as a result of many studies that show this may happen in cell cultures and in the "test tube". It must be emphasized that laboratory studies are not a reflection of what goes on in a living human being. I have not been able to find a single study done in humans where raising glutathione promoted cancer growth or enhance cancer against treatment. On the contrary, many studies have shown just the opposite – that raising glutathione is a worthwhile strategy in cancer treatment. In this review article, I explain why based on all the available literature.

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

Trimodal Prehabilitation for Colorectal Surgery Attenuates Post-Surgical Losses in Lean Body Mass: A Pooled Analysis of Randomized Controlled Trials

1 Gillis C, 2 Fenton TR, 3 Sajobi TT, 4Minnella EM, 4Awasthi R, 5 Loiselle SE, 6 Liberman AS, 6 Stein B, 6 Charlebois P, 4Carli F 1 Cumming School of Medicine, Department of Community Health Sciences, University of Calgary, Alberta, Canada 2 Community Health Sciences, Institute of Public Health, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, and Nutrition Services, Alberta Health Services, Alberta, Canada 3 Cumming School of Medicine, Department of Community Health Sciences & O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada 4 Department of Anesthesia, McGill University, Montreal, Quebec, Canada 5 Department of Nutrition and Food Services, McGill University, Montreal, Quebec, Canada 6 Department of Surgery, McGill University, Montreal, Quebec, Canada

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, presurgery, 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.

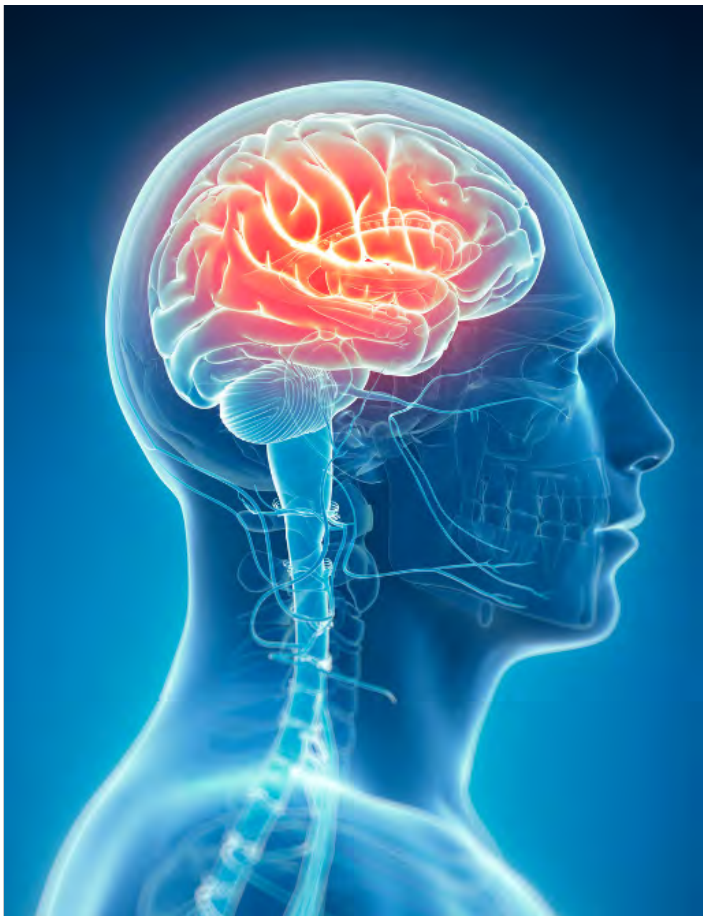
Dr. Gutman's Comments:

This paper reviews a series of prehabilitation studies. Immunocal was used as the nutritional component of a trimodal intervention (nutrition, exercise & psychological support). The paper concludes that patients receiving prehabilitation recover better than those on standard care.



Glutathione Precursors Shield the Brain from Trauma

Koza Lilia, Daniel A. Linseman
Department of Biological Sciences, University of Denver, Denver, Colorado, USA.
Knoebel Institute for Healthy Aging, University of Denver, Denver, Colorado, USA



Abstract

In the United States, approximately onethird 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).

Dr. Gutman's Comments:

This review written by University of Denver neuroscientist Dan Linseman and his team examines the way that free radicals and oxidative stress increase brain damage following physical trauma. Dr. Linseman focuses on glutathione's protective role in traumatic brain injury. He has written numerous articles about glutathione, including in-vivo animal studies, exploring Immunocal as a potential intervention.

NUTR CANCER. 2021 DEC 28;1-14.

Effect of Whey Protein Supplementation on Perioperative Outcomes in Patients with Cancer—A Systematic Review and Meta-Analysis (PROSPERO 2020: CRD42020188666)

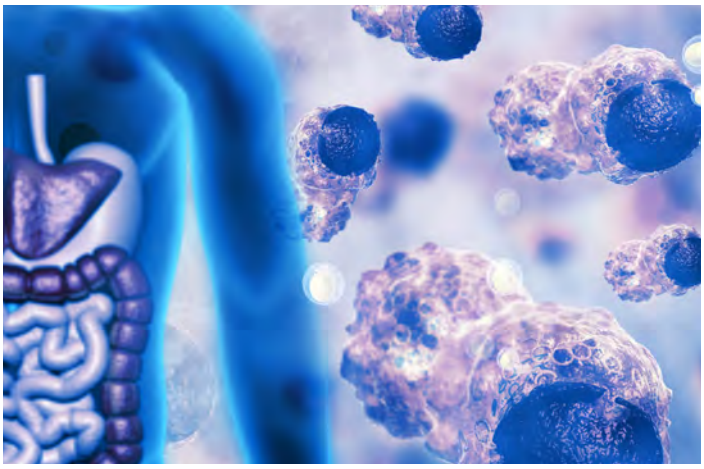
Nivedhyaa Srinivasaraghavan, Nairita Das, Kalpana Balakrishnan, Swaminathan Rajaram
Department of Anesthesiology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
Department of Biostatistics and Cancer Registry, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Abstract

Whey protein has several biochemical characteristics which make it an ideal nutritional supplement in cancer. This metaanalysis 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). Thirtyday 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.

Dr. Gutman's Comments:

The terms "systematic review" and "metanalysis" require some definition here. A "systematic review" requires an in-depth search of all available research articles on a particular topic. This can be quite an ordeal depending on how much is available. Before the internet was the tool that it represents today, such a review could take up an enormous amount of time. A "metanalysis" is the process of "pooling" results from different trials and analyzing the results as a whole. When done properly, this can be an effective way to solidify a thesis or overall perspective. In this study, both were done, validating again the strategy of using whey protein in improving perioperative (postsurgical) outcomes of cancer patients. Given the preponderance of articles written up on Immunocal in this situation, it is not surprising that much of review and metanalysis used Immunocal data.





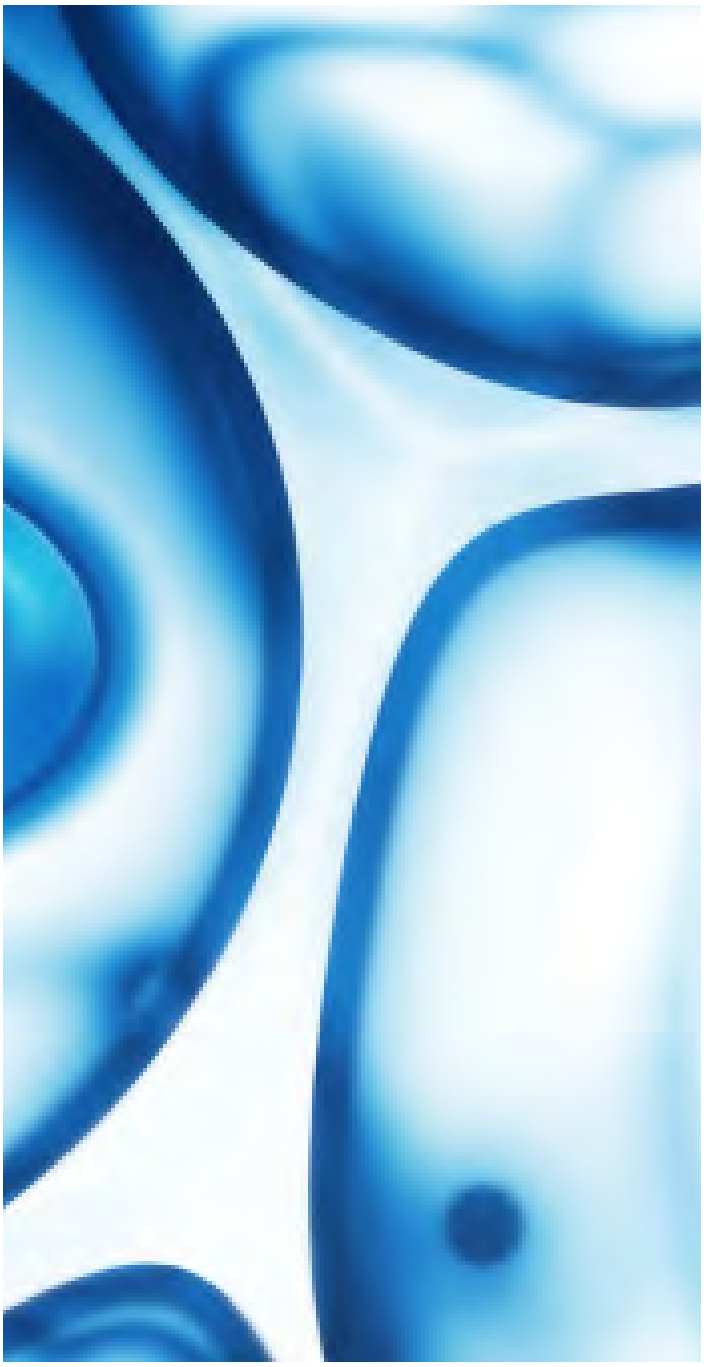
In vivo animal studies

These papers are presented first because they contain the earliest articles written by Dr. Bounous and Dr. Kongshavn on the origins of the Immunocal product. It was these foundational articles that set the basis for all further work to follow. Successful animal studies give researchers much more impetus to go on to human studies. Far from offering a guarantee that a strategy will work in humans, they are nevertheless a giant leap forward from test-tube or tissue culture research. The surprising reality however, is that very few interventions that prove to work in animals actually ever show the same successes in human beings. Undertaking an animal study is far more arduous than it may seem. In order to gain access to this type of research, scientists must show adequate theoretical and laboratory evidence to review boards and boards of ethics that potentially putting animals in harm's way has enough 'justification'. Many animal activists feel that there rarely is any reason to experiment on animals, but the practice is still an essential step required before going on to do studies on humans. Fortunately, current guidelines are far stricter than previous years in exposing these creatures to undue suffering. In looking at some of the animal studies in this section used in Immunocal research studies, you will note the improvements in the Immunocal-treated animals that served as essential for these teams to go onto more relevant human trials.

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

Influence of Dietary Lactalbumin Hydrolysate on The Immune System of Mice and Resistance to Salmonellosis

G. Bounous* and PAL Kongshavn†
* Centre Hospitalier Universitaire, Sherbrooke, Quebec, Canada, J1H 5N4
†Montreal General Hospital Research Institute and Department of Physiology, McGill University, Montreal, Quebec, Canada, H3G 1Y6



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.

Dr. Gutman's Comments:

This is the earliest of all papers in this compilation of Immunocal research. Work by Drs. Bounous and Kongshavn had laid the groundwork of Immunocal-related research, but the product at that time was not as refined as today's Immunocal. Dr. Bounous was at the University of Sherbrooke in Quebec and had already established a working relationship with Dr. Kongshavn—a promising pioneer in clinical immunology at Montreal's McGill University. Dr. Bounous' team identified the clinical potential of certain protein components of whey and commissioned the Swiss dairy Nestlé to produce small batches of whey derivative according to their specifications. This unique mixture was the 'great-grandfather' of Immunocal. This study shows that mice fed on this type of whey benefited from improved immune system parameters and became more resistant to the common bacterial infection 'salmonella.'

JOURNAL OF NUTRITION, 112:1747-1755, 1982

Influence of Dietary Proteins on the Immune System of Mice

G. Bounous* and PAL Kongshavn†
* Centre Hospitalier Universitaire, Sherbrooke, Quebec, Canada, J1H 5N4
†Montreal General Hospital Research Institute and Department of Physiology, McGill University, Montreal, Quebec, Canada, H3G 1Y6

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.

Dr. Gutman's Comments:

Continuing their studies on mice, Drs. Bounous and Kongshavn sought more data to better understand the effects of the specially-prepared whey protein derivative that would later become Immunocal. By evaluating a variety of immune response measurements, they gathered data that would enable them to refine the product, increasing its effectiveness in the immune response.



JOURNAL OF NUTRITION, 113: 1415-1421, 1983

Influence of Dietary Protein Type on the Immune System of Mice

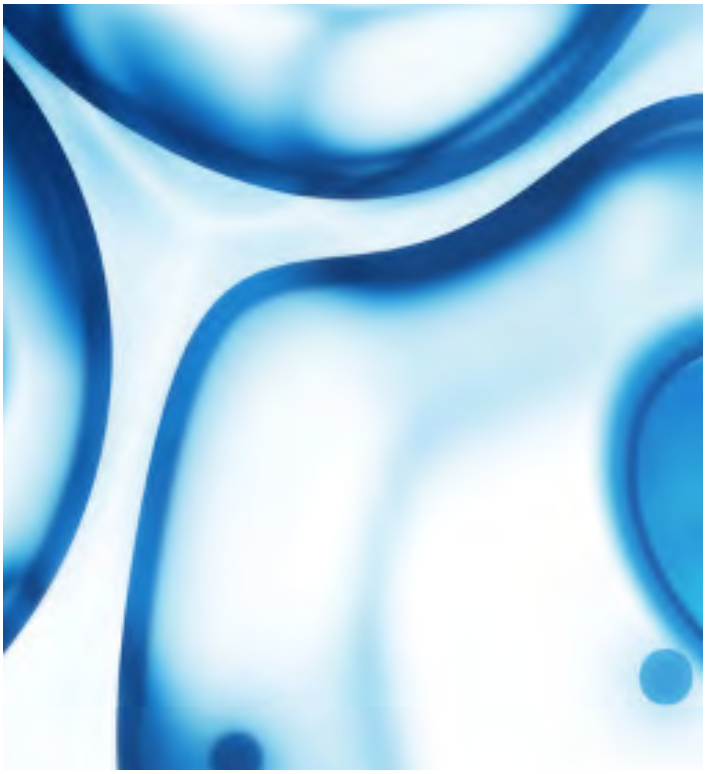
G. Bounous, L. Létourneau and P.A.L. Kongshavn†
Centre hospitalier universitaire, Sherbrooke, Quebec, Canada; J1H 5N4
†Montreal General Hospital Research Institute and Department of Physiology, McGill University, Montreal, Quebec, Canada, H3G 1Y6

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 Mycobacterium 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.

Dr. Gutman's Comments:

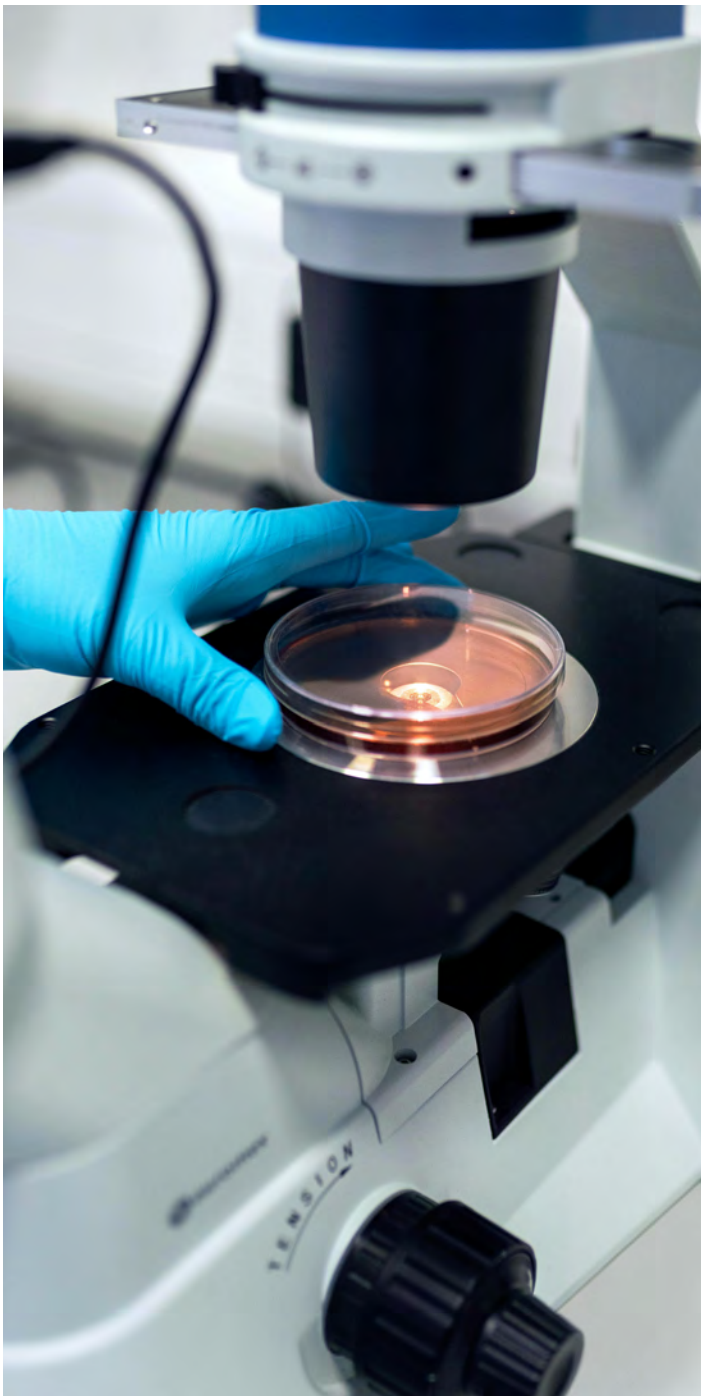
Drs. Bounous and Kongshavn had established beyond doubt that their whey protein derivative enhanced the immune response, but they still couldn't explain why. Their scientific peers questioned whether it was just a result of improved nutrition. If not, it would be necessary to identify some sort of "specific biological activity" in the whey. Using proteins similar in their amino acid makeup, this study and others that followed proved that the protein's ability to raise immune parameters had nothing to do with its nutritional effects. An unknown substance was stimulating the immune response. It would be years before they discovered that it was glutathione.



JOURNAL OF NUTRITION, 115: 1403-1408, 1985

Differential Effect of Dietary Protein Type on the B-Cell and T-Cell Immune Responses in Mice

Gustavo Bounous and Patricia A.L. Kongshavn*
Centre Hospitalier Universitaire, Sherbrooke, Québec, Canada, J1H 5N4 and *Montreal General Hospital Research Institute and Department of Physiology, McGill University, Montreal, Quebec, Canada, H3G 1Y6



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 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.

Dr. Gutman's Comments:

As they continued to evaluate the whey protein derivative they had developed, Drs. Bounous and Kongshavn compared them to other sources of dietary protein. In this study, an early version of Immunocal was evaluated alongside proteins of casein, soy and wheat. Only the whey-derived protein provoked a heightened immune response, reconfirming earlier animal and laboratory experiments.

JOURNAL OF NUTRITION, 115: 1409-1417, 1985

Mechanism of Altered B-Cell Response Induced By Changes in Dietary Protein Type in Mice

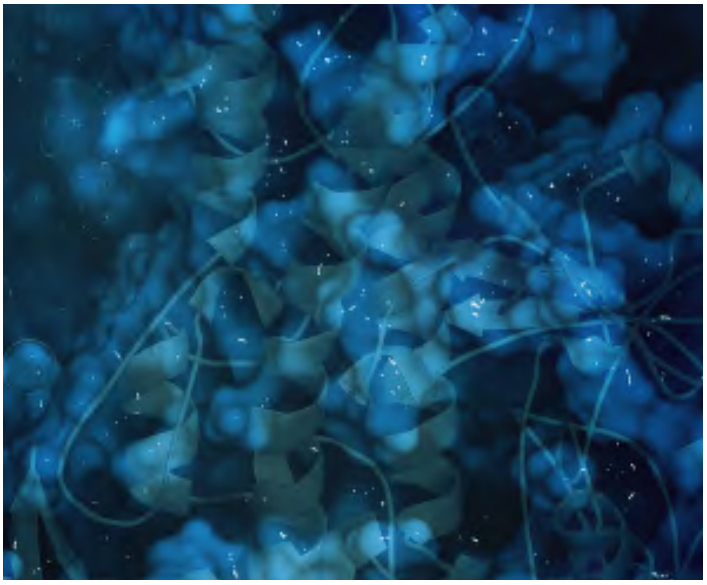
G. Bounous, L. Létourneau and P.A.L. Kongshavn†
Centre hospitalier universitaire, Sherbrooke, Quebec, Canada; J1H 5N4
†Montreal General Hospital Research Institute and Department of Physiology, McGill University, Montreal, Quebec, Canada, H3G 1Y6

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

Dr. Gutman's Comments:

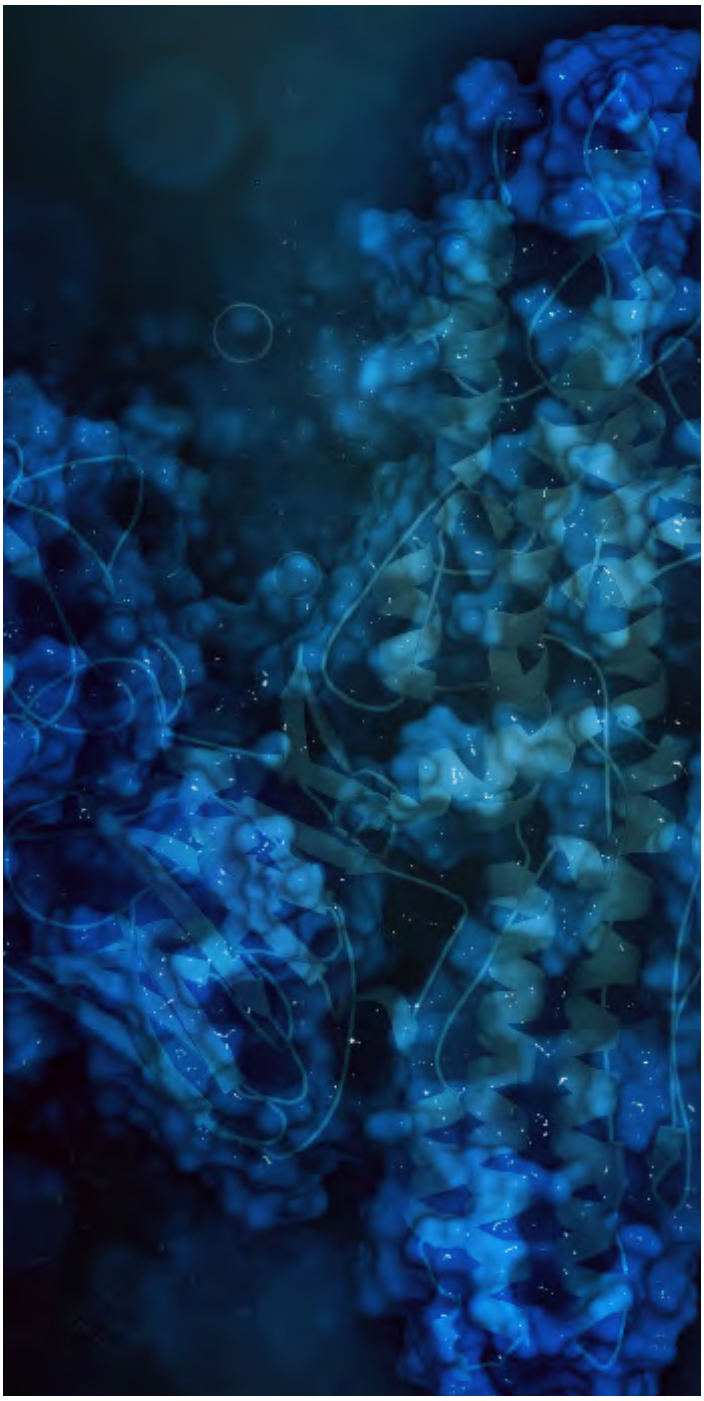
Having confirmed its unique action on the immune system, Drs. Bounous and. Kongshavn recruited other scientists for further research on "dietary lactalbumin" (their early version of Immunocal). It had already been shown to improve the activity of T-cells (white blood cells that attack microbes directly), and this study additionally confirmed a similar effect on B-cells (white blood cells that attack microbes with antibodies). What is significant is that the activation of both B-cells and T-cells implicates almost all the immune system's front-line soldiers.



IMMUNOLOGY, 172:151-156, (1986)

Glutathione Augments the Activation of Cytotoxic T Lymphocytes 'In Vivo'

Wulf Dröge, Christiane Pottmeyer-Gerber, Heike Schmidt, and Sabine Nick
Institut für Immunologie und Genetik, Deutsches Krebsforschungszentrum, Heidelberg



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.

Dr. Gutman's Comments:

Although not specifically an Immunocal study, I included this paper because it was the first to explore the direct impact of glutathione on the immune system of a living creature (in vivo). Dr. Wulf Droge, the principal author, was an eminent European immunologist with a special interest in glutathione. At the time of writing, Dr. Droge had not yet joined Immunotec. This landmark paper later gave clues as to how the Immunotec team back in Canada was successfully using their specific whey protein derivative. Dr. Droge years later would be instrumental in formulating Immunocal "Platinum," and most importantly leading research at Immunotec after the passing of Dr. Bounous

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

The Immunoenhancing Property of Dietary Whey Protein Concentrate

Gustavo Bounous[1,2], Patricia A.L. Kongshavn[1,3] and Phil Gold[1,4]

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

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.

Dr. Gutman's Comments:

Drs Bounous, Kongshavn and Gold (Chief of Medicine at McGill University) felt it necessary to further test the whey protein derivative developed by the team, in particular to confirm that it was clinically better at enhancing the immune system than other proteins. Here, the progenitor of Immunocal was compared to protein extracted from casein, soy, wheat, corn, egg, albumin, beef, fish and algae. The Immunocal-fed group was the only one to benefit.



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

Immunoenhancing Property of Dietary Whey Protein in Mice: Role of Glutathione

G. Bounous, G. Batist, P. Gold
Montreal General Hospital, Quebec

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.

Dr. Gutman's Comments:

Dr. Bounous's earlier work attracted the attention of other prominent McGill University researchers, who subsequently contributed to the scientific understanding of his wheyderived glutathione precursor. These scientists included Gerry Batist, a prominent Canadian oncologist and researcher, and Dr. Phil Gold, who was Chief of Medicine at Montreal General Hospital. In this mouse study, they showed that the animals fed on an early version of Immunocal benefited from raised glutathione levels and—even more importantly—increased production of white blood cells (the immune system's frontline defense).



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

The Influence of Dietary Whey Protein on Tissue Glutathione and the Diseases of Aging

Gustavo Bounous1,2, Francine Gervais1,3, Victor Amer1,3, Gerald Batist3 , and Phil Gold1,3
The Montreal General Hospital Research Institute1 and McGill University, Departments of Surgery2, and Medicine3



Abstract

This study compared the effects of a wheyrich 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.

Dr. Gutman's Comments:

This mouse experiment was a 'breakthrough' study. The outcome was surprising, attracted great attention and had profound implications. Three groups were set up: 1) received standard mouse feed, 2) received a casein-rich diet (casein is a major milk protein), and 3) received an early version of Immunocal. As expected, the Immunocal-fed group showed higher tissue levels of glutathione. Additionally, their lifespan increased by over 6 months! In human terms this is like extending an average lifespan of 55 years to 80 years. Humans are not mice and we can't expect any direct correlation, but the results significantly raised the optimism of the research team and greatly impacted other scientists and researchers to pursue this strategy

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

Changes in Biliary Secretory Immunoglobulins a in Mice Fed Whey Proteins

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.



Dr. Gutman's Comments:

Building on earlier evidence that Immunocal enhances the immune response in animals, this study focused on a particular measure of immune responsiveness. The team showed that animals fed on an early formulation of Immunocal had better antibody levels and immune response than animals on a standard diet or a diet of casein (the principal protein in milk). By combining these findings with existing evidence, the researchers filed and secured a patent for the immune-enhancing benefits of Immunocal.

TUMOR BIOLOGY 11: 129-136, 1990

Dietary Milk Proteins Inhibit the Development of Dimethylhydrazine-Induced Malignancy

R. Papenburga , G. Bounousa, D. Fleiszera, P. Goldb
Departments of a Surgery and b Medicine, The Montreal General Hospital and McGill University, Montreal, Quebec, Canadas



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.

Dr. Gutman's Comments:

Mice with malignant tumors were fed on three different nutritional formulas: 1) standard mouse chow, 2) casein (the principal protein in milk), and 3) an early formulation of Immunocal. After four weeks, the total mass of tumor in the Immunocal-fed animals was substantially lower than in the other two groups. This established once again that the proteins extracted offered clear advantages over other protein sources in combating cancer. These were very encouraging results for these early days, and inspired further research.

CLINICAL AND INVESTIGATIVE MEDICINE, 14: 296-309, 199

The Biological Activity of Undenatured Dietary Whey Proteins: Role of Glutathione

G. Bounous, P. Gold
Department of Surgery, Montreal General Hospital, Research Institute, Quebec Abstrac

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.



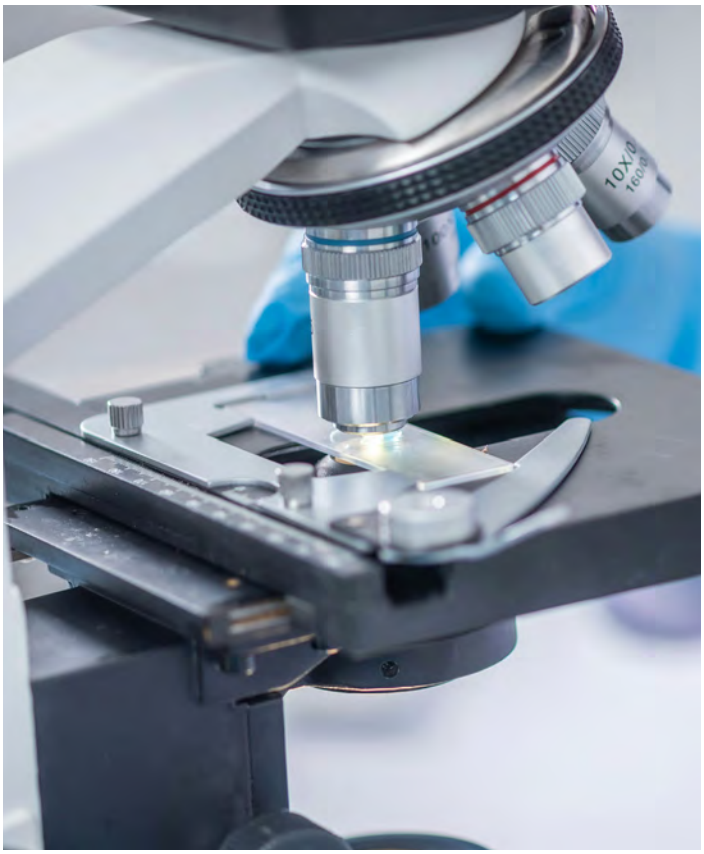
Dr. Gutman's Comments:

At this time Dr. Bounous and his team knew that certain protein groups in whey could raise glutathione levels, but not yet which ones. This study determined which were active, how to extract them without losing their biological availability and which formulation improved immune response the best. The study confirmed that the most effective protein groups are: a) rich in cystine and cysteine and, b) not denatured (broken down) by exposure to heat. With these two critical facts established, scientists finetuned production techniques to yield the most suitable form of whey protein isolate for raising glutathione.

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

Milk Whey Protein Decreases Oxygen Free Radical Production in a Murine Model of Chronic Iron-Overload Cardiomyopathy

WJ Bartfay, MT Davis, JM Medves, S Lugowski
Faculty of Nursing, University of Windsor, Windsor, Ontario, Canada



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-hydroxynonenal (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.

Dr. Gutman's Comments:

Iron is a two-edged sword (pun intended). It is a critical necessity in humans, but only at low levels. Otherwise, it is toxic. Excess iron prompts the failure of various organs, including the heart. The medical term is "iron-overload cardiomyopathy." This group of researchers wanted to know whether dietary Immunocal could improve the condition of animals suffering from similar disease. The mice benefited from elevated glutathione levels and there was less evidence of heart tissue damage.

Lait 86 (2006) 213–226

Dietary protein, immune function and colon carcinogenesis in the mouse

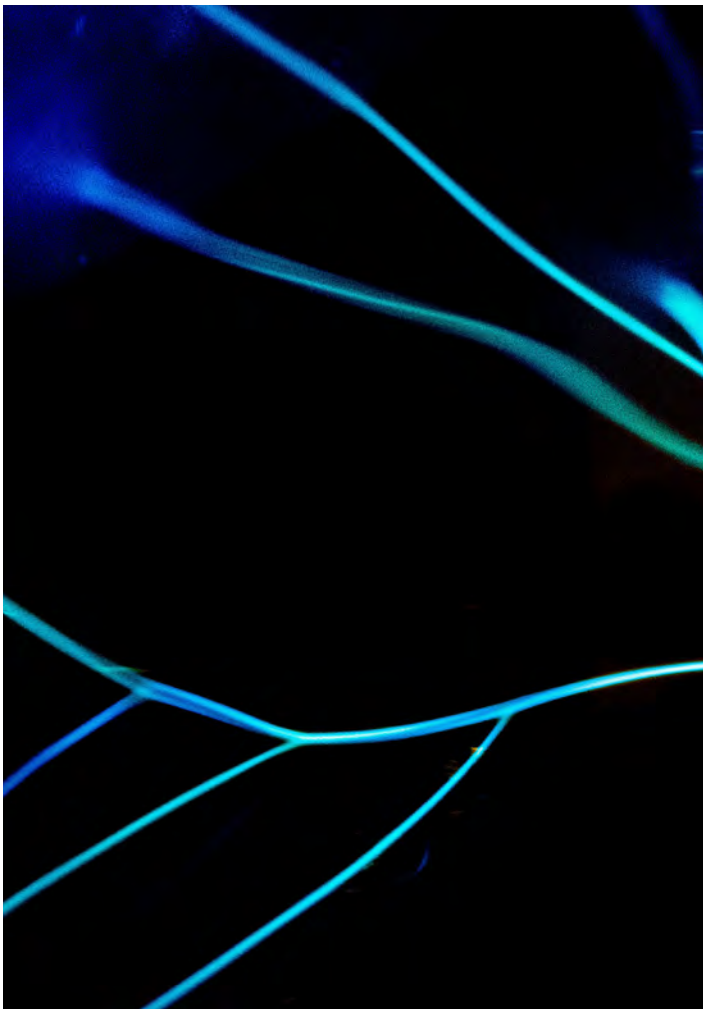
Nádia Fátima G. PEREIRA DIAS, Valdemiro Carlos SGARBIERI, Helaine Beatriz JACOBUCCI, Humberto Araújo RANGEL, Cristina TANIKAWA
Department of Food and Nutrition, Faculty of Food Engineering, State University of Campinas, Campinas, São Paulo, Brazil

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 (PlaqueForming Cells) in the spleen. Response was equal and significantly higher for WPCand 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.

Dr. Gutman's Comments:

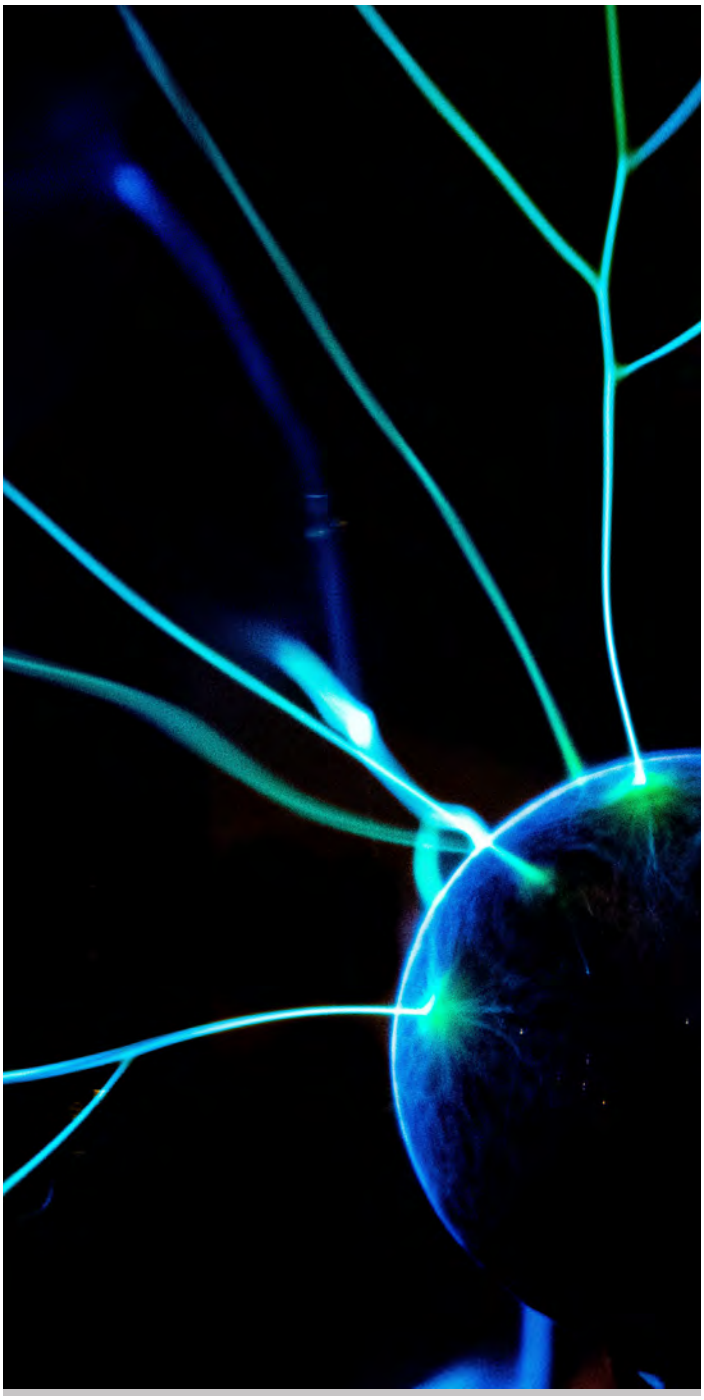
This Brazilian team had a focus on food biochemistry and potential clinical applications of milk derivatives. Gaining familiarity of Dr. Bounous and Kongshavn's work on Immunocal and colonic cancer, they wanted to repeat and validate the beneficial results. Using a mouse model exposed to a powerful carcinogen (cancer-causing chemical) they confirmed the protective nature of Immunocal in this disease.



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

Effects of Whey Protein Concentrate (WPC) on the Distributions of Lymphocyte Subpopulations in Rats with Excessive Alcohol Intake

Tseng YM, Tsai SM, Lin WS, Huang ZR, Lin CC, Yeh WH, Wu YR, Tsai LY
Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Number 386, Tachung 1st road, Kaohsiung 81346 Taiwa



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.

Dr. Gutman's Comments:

Giving Immunocal to animals subjected to alcohol toxicity, this Taiwanese team found measurable benefits to the immune system. Although this study was conducted only on animals, there are reasons to believe it could benefit humans too. More studies are warranted.

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

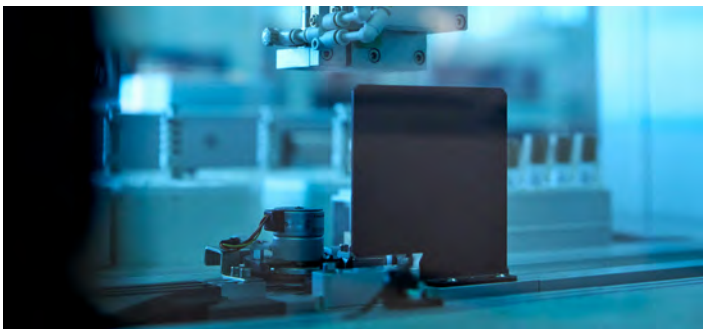
J. Kloek, E. Mortaz, I. Van Ark, N. Bloksma, J. Garssen, F. P. Nijkamp and G. Folkerts
Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Sciences, Utrecht University, Utrecht, The Netherlands
Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran Danone Research Centre for Specialised Nutrition, Wageningen, The Netherlands

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 allergenspecific 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.

Dr. Gutman's Comments:

This multinational research team was interested in seeing whether asthma, and more critically, anaphylaxis (life-threatening allergic reaction) can be made less severe by pre-treating animals with a glutathione enhancing protein. The protein UWPC (undenatured whey protein concentrate) used in this trial was "HMS 90", an earlier version of Immunocal developed by Drs. Bounous and Kongshavn. HMS 90 was the name used in Canada for the first few years that Immunocal was available commercially in Canada at that time. The results were clear. Animals exposed to an allergen (allergy-provoking substance) did significantly better. Glutathione levels were improved but more importantly, clinical improvement in both asthma and anaphylaxis were "profoundly" better.



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

A Cysteine-Rich Whey Supplement (Immunocal®) Delays Disease Onset and Prevents Spinal Cord Glutathione Depletion in the Hsod1 (G93a) Mouse Model of Amyotrophic Lateral Sclerosis

Ross EK1 , Winter AN1 , Wilkins HM1 , Sumner WA1 , Duval N1 , Patterson D, Linseman DA1,2,3 1 Dept. of Biological Sciences & Eleanor Roosevelt Institute, University of Denver, 2 Research Service, Veterans Affairs Medical Center, Denver, CO, 3 Div. of Clinical Pharmacology & Toxicology, University of Colorado Denver, USA



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.

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.

Dr. Gutman's Comments:

ALS (Amyotrophic Lateral Sclerosis) is also known as 'Lou Gehrig's Disease', a devastating neurodegenerative process that degrades muscle function and leads to eventual paralysis. Mice suffering from a similar disease are used in the laboratory to explore possible treatments for humans. Feeding Immunocal to these mice, Linseman's team in Denver found significant increases in glutathione levels and—more importantly— clinical improvement in muscle strength. Immunocal also delayed onset of the disease. The mice survived even better when their diet combined Immunocal with the drug Riluzole.

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

Cysteine-Rich Whey Protein Isolate (Immunocal®) Ameliorates Deficits in The GFAP.HMOX1 Mouse Model of Schizophrenia

1 Song W, 2 Tavitian A, 3 Cressatti M, 4Galindez C, 5 Liberman A, 6 Schipper HM 1 Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada 2 Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada; Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada 3 Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada; Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada 4 Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada 5 Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada 6 Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada; Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada

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.

Dr. Gutman's Comments:

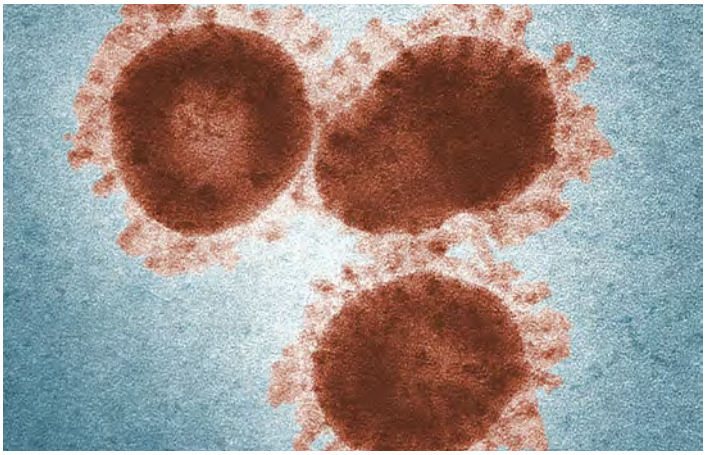
ALS (Amyotrophic Lateral Sclerosis) is also known as 'Lou Gehrig's Disease', a devastating neurodegenerative process that degrades muscle function and leads to eventual paralysis. Mice suffering from a similar disease are used in the laboratory to explore possible treatments for humans. Feeding Immunocal to these mice, Linseman's team in Denver found significant increases in glutathione levels and—more importantly— clinical improvement in muscle strength. Immunocal also delayed onset of the disease. The mice survived even better when their diet combined Immunocal with the drug Riluzole.



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

Whey Protein Concentrate and Dexamethasone Protected Rat Cerebellum from Gamma-radiation Injury

Onatola O.A, Owoeye O, Elumelu T.N, Shokunbi M.T and Malomo O.A
Department of Anatomy, College of Medicine, University of Ibadan, Ibadan, Nigeria
Department of Radiotherapy, College of Medicine/ University College Hospital, Ibadan, Nigeria
Department of Surgery, University of Ibadan/ University College Hospital, Ibadan, Nigeria



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.

Dr. Gutman's Comments:

Nigerian researchers investigated strategies to lower brain swelling and damage from radiation exposure. This has relevance in cancer treatment since many brain tumors are treated with radiotherapy. Although all efforts are made to focus the radiation on the tumor only, inevitably normal tissues will suffer collateral damage. One of the standard treatments for these adverse effects is the use of strong steroid medication like dexamethasone. In this study, Immunocal was compared to dexamethasone in their ability to limit radiation damage. Immunocal proved equally effective as steroid medication in alleviating the damage.

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

Selective effects of whey protein concentrate on glutathione levels and apoptosis in rats with mammary tumors

Shih-Hsuan Cheng , Yang-Ming Tseng , Szu-Hsien Wu , Shih-Meng Tsai , Li-Yu Tsai Department of Medical Laboratory Science and Biotechnology, College of Health Sciences, Kaohsiung Medical University, Kaohsiung Taiwan. Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung Taiwan. Division of Plastic Surgery, Department of Surgery, Taipei Veterans General, Taipei, Taiwan. Department of Environmental and Public Health, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan. Department of Medical Laboratory Science and Biotechnology, College of Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan

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.

Dr. Gutman's Comments:

I always stress the importance of human studies over animal or laboratory studies, but I was very impressed with what this Taiwanese team demonstrated in an animal model of breast cancer. One of the prevalent misconceptions in oncology is that glutathione may "feed" the tumor. Although this has been demonstrated in tissue culture it has never been shown in living organisms. Here, the opposite has been demonstrated – using glutathione precursors in a live model will increase glutathione levels in normal cells at the same time down-regulate glutathione in cancer cells. This is in keeping with other Immunocal studies in cancer.



The Nutritional Activity of Active Whey Protein in Pancreatic Tumor-Bearing Nude Mice

Zhang J, Liu X, Yu W, Miao M, Shi H
Department of Endocrinology, Affiliated Huai'an Hospital of Xuzhou Medical College/Huai'an Second People's Hospital, Emergency Department of Changhai, Affiliated Second Military Medical University, Department of biochemistry and Molecular biology College of Basic Medical Sciences Second Military Medical University, Department of Clinical Nutrition/ Gastrointestinal Surgery, Beijing Shijitan Hospital, Capital Medical University



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.

Dr. Gutman's Comments:

This Chinese team grafted pancreatic cancer tissue in mice to examine Immunocal's effect as an intervention. Three groups were used: the first had a standard diet; the second consumed a standard diet supplemented with soy protein; the third group was given Immunocal (in China called "ABD"). The Immunocal-fed mice had better glutathione levels, suffered less weight loss (cancer cachexia), and survived considerably longer.

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

The Cysteine-Rich Whey Protein Supplement, Immunocal® , Preserves Brain Glutathione and Improves Cognitive, Motor, and Histopathological Indices of Traumatic Brain Injuury in a Mouse Model of Controlled Cortical Impact

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, 10Linseman DA 1 2 5 6 7University of Denver, Department of Biological Sciences, Denver, Colorado, USA 3 4University of Denver, Knoebel Institute for Healthy Aging, Denver, Colorado, USA 8 9University of Colorado Cancer Center, Aurora, Colorado, USA 10University of Denver, Department of Biological Sciences and Knoebel Institute for Healthy Aging, Denver, Colorado, USA

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.

Dr. Gutman's Comments:

Using an animal model of mild brain trauma, Dan Linseman's team at the University of Denver examined mice fed either Immunocal or placebo. When tested for markers of oxidative stress and other signs of brain injury, those on Immunocal showed improved glutathione levels. They also revealed less evidence of microscopic brain injury and—most importantly—improved motor function (ability to move) and cognitive function (ability to think). The team suggests that further studies be done in hope of extending these benefits to athletes, military personnel and others at risk of head trauma.



Effect study of active whey protein on the nutritional therapy of pancreatic cancer xenografts in nude mice

1Zhang J, 2Liu X, 1Yu WN, 3Miao MY, 4Shi HP
1Department of Endocrinology, Affiliated Huai'an Hospital of Xuzhou Medical College, Jiangsu, China 2Emergency department of Changhai, Affiliated Second Military Medical University Shanghai, China 3Department of biochemistry and Molecular biology College of Basic Medical Sciences Second Military Medical University, Shanghai, China 4Department of General Surgery / Nutrition, Beijing Shijitan Hospital, CMU, Beijing, China



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.

Dr. Gutman's Comments:

These Beijing scientists grafted pancreatic cancer tissue into mice. Three treatment groups were randomly selected: 1) normal diet, 2) standard diet with soy protein, and 3) standard diet with Immunocal (here called "ABD"). There were statistically relevant improvements in survival and prevention of weight loss from cancer in the Immunocaltreated group. Further evidence against "glutathione feeding the cancer".

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

Effects of Active Whey Protein on Nutritional and Immune Status of Mice Bearing Triple-Negative Breast Cancer with Chemotherapy

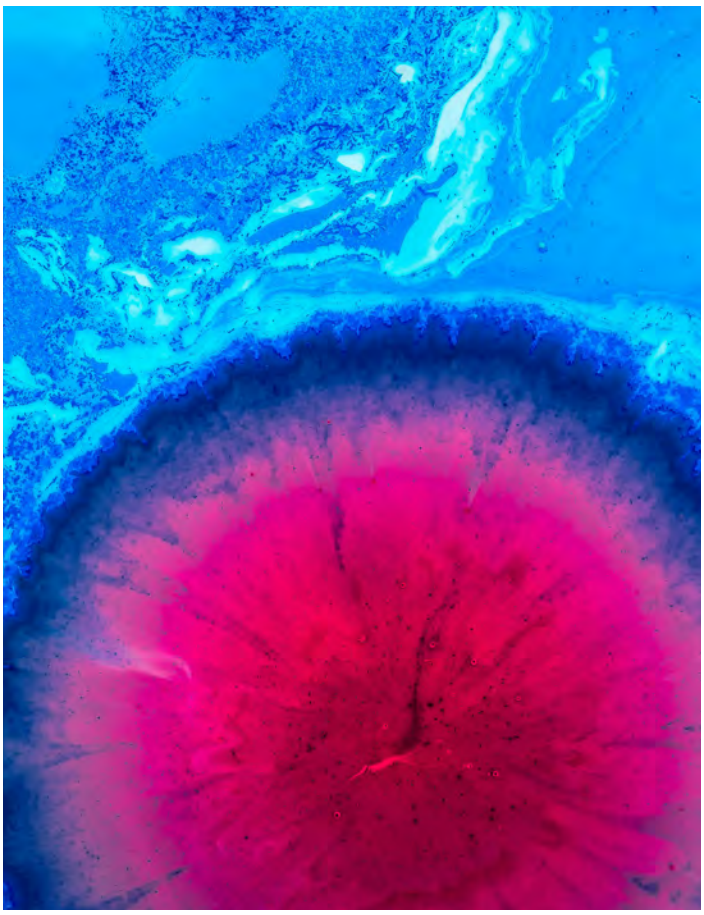
Zeng Z1 Du C2 Tu L1 Wang L1 Wang Y1 Luo F1
1State Key Laboratory of Biotherapy, West China Hospital, Sichuan University Chengdu, China
2Neijiang Second People's Hospital, Neijiang, China

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/L respectively. 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.

Dr. Gutman's Comments:

Breast cancer was induced in mice. Four treatment groups were randomly selected: 1) control (no treatment), 2) Paclitaxel (chemotherapy), 3) Paclitaxel (chemotherapy) with casein, and 4) Paclitaxel (chemotherapy) with Immunocal (here called "ABD"). The Immunocal group did best in terms of weight loss and survival. Further evidence of the compatibility of Immunocal and this chemotherapy.



IMMUNOLOGY, 172:151-156, (1986)

Glutathione Augments the Activation of Cytotoxic T Lymphocytes 'in Vivo'

Wulf Dröge, Christiane Pottmeyer-Gerber, Heike Schmidt, and Sabine Nick
Institut für Immunologie und Genetik, Deutsches Krebsforschungszentrum, Heidelberg



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.

Dr. Gutman's Comments:

Although not specifically an Immunocal study, I included this paper because it was the first to explore the direct impact of glutathione on the immune system of a living creature (in vivo). Dr. Wulf Droge, the principal author, was an eminent European immunologist with a special interest in glutathione. At the time of writing, Dr. Droge had not yet joined Immunotec. This landmark paper later gave clues as to how the Immunotec team back in Canada was successfully using their specific whey protein derivative. Dr. Droge years later would be instrumental in formulating Immunocal "Platinum," and most importantly leading research at Immunotec after the passing of Dr. Bounous.

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

Dietary Whey Protein Inhibits the Development of Dimethylhydrazine-Induced Malignancy

G. Bounous*, R. Papenburg*, P.A.L Kongshavn**, P. Gold†, and D. Fleiszer*
Departments of Surgery*, Physiology**, and Medicine†, Montreal General Hospital and McGill University

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

Dr. Gutman's Comments:

This is a fascinating theoretical paper in which Dr. Bounous examines the variety of milk proteins in mammals. He points out that a) Human milk has the lowest concentration of protein (possibly explaining why humans take so long to reach adulthood), and 2) Human milk has the highest concentration of whey as compared to casein. Dr. Bounous' point is that preponderance of whey in human milk may help explain the slow development of human infants and the longevity of the human species.



Cysteine-Rich Whey Protein Isolate (CR-WPI) Ameliorates Erectile Dysfunction by Diminishing Oxidative Stress via DDAH/ADMA/NOS Pathway

Kefan Li1 Aiyun Zhu1,2 Jimmy Gutman3 Qiang Fu1,2 and Shuai Liu1,2

1Department of Urology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250021, China

2Department of Urology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong 250021, China

3McGill University, Canada



Abstract

Objective Nitric oxide synthase- (NOS-) dependent endothelial dysfunction induced by oxidative stress (OS) is assumed to play a pivotal role in the pathogenesis and progression of diabetes mellitus-related erectile dysfunction (DMED). Cysteine-rich whey protein isolate (CR-WPI) is a widely used protein supplement and has been confirmed to reduce reactive oxygen species (ROS) by increasing cellular antioxidant glutathione (GSH). However, it is currently unknown whether CR-WPI elicits therapeutic effects in DMED. Here, we provide diabetic rats with CR-WPI to determine its effect on DMED and the underlying mechanisms.

The results suggest that CR-WPI supplementation increased GSH biosynthesis and reduced ROS content and simultaneously upregulated the dimethylargininedimethylaminohydrolase (DDAH)/asymmetrical dimethylarginine (ADMA)/nitric oxide synthase (NOS) metabolic pathway. Evaluation of intracavernous pressure (ICP) also showed an improvement of penile erectile function in CR-WPI-treated rats. The results of the vitro cell culture showed that glutathione pretreatment protected corpus cavernosum smooth muscle cells (CCSMC) from H2O2-induced apoptosis by decreasing Caspase 9 and Caspase 3 expressions. These results augur well for the potential therapeutic application of dietary CR-WPI supplementation for treating diabetic erectile dysfunction.

Dr. Gutman's Comments:

Erectile dysfunction (the inability to obtain or sustain an erection) is an all to common problem, many cases a result of diabetes. Oxidative stress/free radical formation has been identified as a causative factor. In this study, researchers used cysteine-rich whey protein isolate (Immunocal) as a potential intervention in erectile dysfunction.The success demonstrated led the team to suggest that this treatment be considered a treatment for this disorder.

BRAIN RESEARCH, 2023 Jun 1;1808:148338

Immunocal limits gliosis in mouse models of repetitive mild-moderate traumatic brain injury

Lilia A Koza [1] Claudia Pena [1] Madison Russell [1] Alec C Smith [1] Jacob Molnar [1] Maeve Devine [1] Natalie J Serkova [2] Daniel A Linseman [3]

[1]University of Denver, Department of Biological Sciences, Denver, CO , United States; University of Denver, Knoebel Institute for Healthy Aging, Denver, CO 80208, United States

[2]University of Colorado Cancer Center, Department of Radiology, Aurora, CO 80045, United States

[3]University of Denver, Department of Biological Sciences, Denver, CO 80208, United States; University of Denver, Knoebel Institute for Healthy Aging, Denver, CO 80208, United States

Abstract

Successive traumatic brain injuries (TBIs) exacerbate neuroinflammation and oxidative stress. No therapeutics exist for populations at high risk of repetitive mild TBIs (rmTBIs). We explored the preventative therapeutic effects of Immunocal®, a cysteine-rich whey protein supplement and glutathione (GSH) precursor, following rmTBI and repetitive mild-moderate TBI (rmmTBI). Populations that suffer rmTBIs largely go undiagnosed and untreated; therefore, we first examined the potential therapeutic effect of Immunocal® long-term following rmTBI. Mice were treated with Immunocal® prior to, during, and following rmTBI induced by controlled cortical impact until analysis at 2 weeks, 2 months, and 6 months following the last rmTBI. Astrogliosis and microgliosis were measured in cortex at each time point and edema and macrophage infiltration by MRI were analyzedat2 months post-rmTBI. Immunocal® significantly reduced astrogliosis at2 weeks and2 months post-rm TBI. Macrophage activation was observed at 2 months post-rmTBI but Immunocal® had no significant effect on this endpoint.

We did not observe significant microgliosis or edema after rmTBI. The dosing regimen was repeated in mice subjected to rmmTBI; however, using this experimental paradigm, we examined the preventative therapeutic effects of Immunocal® at a much earlier timepoint because populations that suffer more severe rmmTBIs are more likely to receive acute diagnosis and treatment. Increases in astrogliosis, microgliosis, and serum neurofilament light (NfL), as well as reductions in the GSH:GSSG ratio, were observed 72 hours post-rmmTBI. Immunocal® only significantly reduced microgliosis after rmmTBI. In summary, we report that astrogliosis persists for 2 months post-rmTBI and that inflammation, neuronal damage, and altered redox homeostasis present acutely following rmmTBI. Immunocal® significantly limited gliosis in these models; however, its neuroprotection was partially overwhelmed by repetitive injury. Treatments that modulate distinct aspects of TBI pathophysiology, used in combination with GSH precursors like Immunocal®, may show more protection in these repetitive TBI models.

Dr. Gutman's Comments:

Expanding on the findings that traumatic brain injuries lead to inflammation and oxidative stress/free radical formation, this team led by Dr. Dan Linsesman focused on repetitive traumatic brain injury. Repetitive brain injury is commonly seen in sports such as boxing and American Football. The diagnosis often goes undiagnosed and leads to serious long-term consequences such as depression and dementia. Using a mouse model, the team intervened with Immunocal, both prior to and after repeated mild and mild-moderate head trauma. Demonstrating neuroprotective effects on repeated mild brain injury, the effect was less when looking at repeated moderate brain injury. These positive results call for more studies and possible human traumatic brain injury studies.



In Vitro laboratory studies: test tube, cell cultures, etc.

Committing to an animal or human study requires much ground work to demonstrate whether the huge expenditures in time, resources and efforts will be worthwhile. This also is important in making ethical decisions whether living animals (including humans) can be put at risk during an experiment. These lab studies ('in vitro') often are a requirement to go onto studies in live creatures ('in vivo').

These in vitro laboratory studies are of great interest and will ultimately decide or direct where further trials are feasible. However, it must be emphasized that the results of these studies do not necessarily translate into application in the 'real world'. Even clinical trials in animals cannot extend their conclusions into what goes on in a living human being. The vast majority of the conclusions made in in vitro studies never pan out to be applicable in human experiments.

Nevertheless, in vivo animal or human studies absolutely are built upon the results of these lab experiments. On the following pages you will find the papers published which represent the foundation of Immunotec's clinical trials.

Anti-HIV and Anti-Apoptotic Activity of the Whey Protein Concentrate: Immunocal

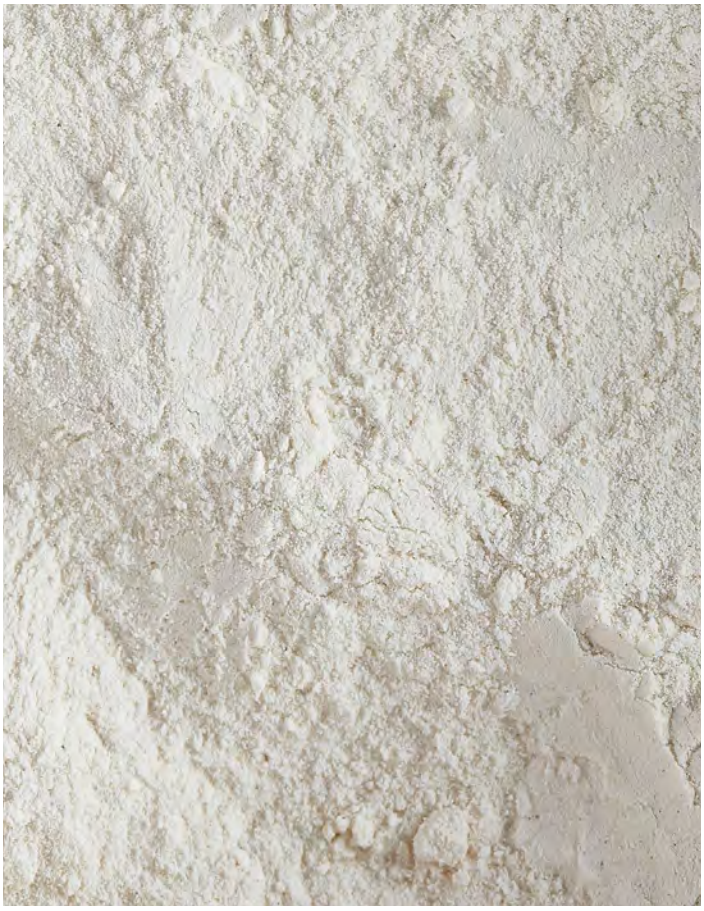
Baruchel S, Olivier R, Wainberg M Montreal Children's Hospital, Montreal, Quebec, Canada

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.

Dr. Gutman's Comments:

Building on the promising results of earlier studies with Immunocal, these prominent researchers at McGill University designed this in-vitro cell study to determine whether Immunocal could trigger anti-viral activity by raising glutathione levels. The hypothesis was confirmed, encouraging the continuation of human studies already underway in pediatric AIDS.



ANTICANCER RESEARCH, 16:1095-1100 (1996)

In Vitro Selective Modulation of Cellular GSH by a Humanized Native Milk Protein Isolate in Normal Cells and Rat Mammary Carcinoma Model

Sylvain Baruchel & Ginette Viau Department of Pediatrics and Oncology and Montreal Children's Research Institute, McGill University, Montreal, Canada

Abstract

We report the in vitro selective inhibitory activity of a humanized whey protein concentrate ImmunocalTM 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.

Dr. Gutman's Comments:

Drs. Baruchel and Viau were among the first to observe what was later called "Selective modulation," using glutathione precursors to show how glutathione levels rise and fall in normal and in cancerous cells. Tumor cells are normally seen to contain high amounts of glutathione, offering protection against chemotherapy. The question arose, "Could glutathione or its precursors make these cancer cells resistant to treatment?" This study demonstrates that when cancer cells are already high in glutathione, "pushing" them to make more triggers "negative feedback inhibition," which lowers glutathione production. Normal cells—often low in glutathione because of the cancer—now absorb these precursors, up-regulating their own glutathione production and increasing the resistance of healthy tissue to chemotherapy. This explains the term "selective modulation," in which glutathione levels fall in cancer cells and rise in normal cells, as elegantly demonstrated by this study.

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

Enhancing Effect of Patented Whey Protein Isolate (Immunocal®) on the Cytotoxicity of Anti-Cancer Drug

Wayne Y. Tsai, Wen-Huei Chang, Ching-Hsein Chen, and Fung-Jou Lu Department of Biochemistry, College of Medicine National Taiwan University, Taipei, Taiwan, R.O.C.

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.

Dr. Gutman's Comments:

Tsai and his team questioned whether cancer cells could feed on glutathione precursors and so protect themselves from immune response. This first Immunocal study in Taiwan establishes a clear, "No, it can't." On the contrary. When Immunocal was introduced to cancerous liver cells in the laboratory, glutathione levels in the cells actually fell. This is explained by earlier work on the "negative feedback inhibition" of glutathione in tumor cells. Additionally, the cancer cells exposed to Immunocal suffered greater than usual damage when subjected to chemotherapy. These are persuasive arguments for the use of glutathione in cancer therapy



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

Whey Protein Concentrate Promotes the Production of Glutathione (GSH) By Gsh Reductase in The PC12 Cell Line after Acute Ethanol Exposure

Tseng YM, Lin SK, Hsiao JK, Chen IJ, Lee JH, Wu SH, Tsai LY Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 81346, Taiwan; Institute of Medicine, Kaohsiung Medical University, Kaohsiung 80702, Taiwan



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 ethanolinduced 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.

Dr. Gutman's Comments:

Alcohol increases oxidative stress and free radical damage and may lead to the death (apoptosis) of these cells. This cell culture ('test-tube') study carried out in Taiwan, investigated the potential deleterious effects of alcohol on human cells. Exposure of a specific cell line (PC12) to Immunocal increased both their glutathione parameters and their antioxidant function.

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

Effects of Alcohol-Induced Human Peripheral Blood Mononuclear Cell (PBMC) Pretreated Whey Protein Concentrate (WPC) on Oxidative Damage

Tseng YM, Chen SY, Chen CH, Jin YR, Tsai SM, Chen IJ, Lee JH, Chiu CC, Tsai LY Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

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.

Dr. Gutman's Comments:

This cell culture ('test-tube') study was designed in Taiwan to investigate the potential deleterious effects of alcohol on human white blood cells. Alcohol increases oxidative stress and free radical damage and may lead to the death (apoptosis) of these cells. Exposure of these cells to Immunocal both increased their glutathione parameters and protected them from damage.



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

Whey Protein Concentrate Renders MDA-MB-231 Cells Sensitive to Rapamycin by Altering Cellular Redox State and Activating GSK3ß/mTOR Signaling

Shih-Hsuan Cheng, Yang-Ming Tseng, Szu-Hsien Wu, Shih-Meng Tsai & Li-Yu Tsai Department of Medical Laboratory Science and Biotechnology, College of Health Sciences, Kaohsiung Medical University, Kaohsiung, Taiwan. Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan. Division of Plastic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan. Department of Surgery, School of Medicine, National Yang Ming University, Taipei, Taiwan. Department of Environmental and Public Health, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.



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.

Dr. Gutman's Comments:

Already having produced earlier studies on Immunocal, this team continued its excellent work elaborating on the biochemical metabolic pathways involved in cancer progression. Using a human breast-cancer cell line they investigated the combination of Immunocal with Rapamycin (a novel chemotherapy agent). The combination proved more effective than rapamycin alone, offering a potential improved treatment strategy for breast cancer.

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

A Cysteine-Rich Whey Supplement (Immunocal®) Provides Neuroprotection from Diverse Oxidative Stress-Inducing Agents In Vitro by Preserving Cellular Glutathione

1 Winter AN, 1 Ross EK, 1Daliparthi V, 1 Sumner WA, 1 Kirchhof DM, 1 Manning E, 1 Wilkins HM, 1,2Linseman DA 1 Department of Biological Sciences, University of Denver, Denver, Colorado
2 Knoebel Institute for Healthy Aging, University of Denver, Denver, Colorado

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 ß-amyloid 1-42. The neuroprotective effects of Immunocal were blocked by inhibition of -glutamylcysteine 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.

Dr. Gutman's Comments:

These highly active neuroscientists from the University of Denver point out that many neurodegenerative diseases share two features: high oxidative stress and low glutathione levels. When exposed to oxidizing agents and free radical damage, brain cell tissue cultivated in the laboratory and incubated in an Immunocal solution fared much better than untreated cell culture. These promising results will be further explored in in-vivo (live) studies.



Authors Cited

- Agnihotram, RV.
- Ai, Z.
- Amer, V.
- Aprikian A.
- Audi, C.
- Augustin, B.
- Austin B.
- Awasthsi, R.
- Bahlool, R.
- Baillargeon, J.
- Balakrishnan, K.
- Baldini, G.
- Balzola, F.
- Bartfay, WJ.
- Barrett-Bernstein, M.
- Baruchel, S.
- Batist, G.
- Baumann, JM.
- Beer, D.
- Bergdahl, A.
- Bhidayasiri, R.
- Bitterman, T.
- Bloksma, N.
- Boonla, C.
- Bounous, G.
- Bousquet-Dion, G.
- Boutros, M.
- Briand, R.
- Cai, Y.Y.
- Carli, F.
- Castejon, AM.
- Chabot, K.
- Chang, WH.
- Charlebois, P.
- Chen, CH.
- Chen, IJ.
- Chen, SY.
- Cheng, SH.
- Chitapanarux, T.
- Chiu, CC.
- Chotipanich, C.
- Costantino, AM.
- Cressatti, M.
- Daliparthi, V.
- Das, N.
- Davis, MT.
- Dissayabutra, T.
- Dong, G.
- Droge, W.
- Du, C.
- Ducret, T.
- Duval, N.
- Elsherbini, N.
- Elumelu, TN.
- Evans, TM.
- Faillace, R.
- Falconer, W.
- Falutz, P.
- Feldman, LS.
- Fenton, TR.
- Ferri, LE.
- Ferreira V.
- Fiore, JF.
- Fleiszer,D.
- Fleming,H.
- Folkerts,G.
- Galindez,C.
- Gamsa, A.
- Garssen, J.
- Gao, K.
- Gervais,F.
- Ghitulescu, G.
- Gillis, C.
- Gold,P.
- Grannemann,BD.
- Grey, VL.
- Gutman,J.
- Hamilton,J.
- Hardigan,P.
- Hawkshaw, M.
- He, M.
- Higuchi, K.
- Hsiao, JK.
- Huang, ZR.
- Huber, K.
- Ignowski,E.
- Jacobucci.HB.
- Jagoe T.
- Jiang, O.
- Jin, YR.
- Joutsa, J.
- Kabot,S.
- Kaewwilai, L.
- Kara,KM.
- Karabadjian,A.
- Karelis, AD.
- KassoufW.
- Kennedy, RS.
- Kern, JK.
- Kimoff,RJ.
- Kinscherf,R.
- Kirchhof,DM.
- Kloek, J.
- Kohri, H.
- Kondo, Y.
- Kongshavn,PAL.
- Konok, GP.
- Koza, L.
- Ladas, EJ.
- Lands, L.
- Lee, JH.
- Lee, L.
- Lee,TDG.
- Leelarungrayub,D.
- Letourneau, L.
- Levine, AM.
- Li, C.
- Liberman,AS.
- Liberman, S.
- Lin, CC.
- Lin,SK.
- Lin, WS.
- Linseman, DA.
- Liu, X.
- Loiselle,SE.
- Lothian, B.
- Lu, FJ.
- Luo, F.
- Luo,M.
- Lugowski,S.
- Lurie,D.
- Malomo,OA.
- Manning,E.
- Marks,L.
- Medves,JM.
- Melnick,SJ.
- Messier,V.
- Miao,MY.
- Minnella,E.
- Minella,EM.
- Mohammed,SR.
- Molson,JH.
- Morin, N.
- Mortaz, E.
- Muensri, S.
- Mulder, D.
- Nijkamp,FP.
- Okada, Y.
- Olivier, R.
- Onatola,OA.
- Osmond,DG.
- Owoeye, O.
- PackerEE.
- Papenburg,R.
- Patterson,D.
- Pereira
- Dias,NFG.
- Pojchamarnwip
- uthS
- Pottmeyer-

- Gerber, C.
- Prussick,L.
- Prussick, R.
- Rabasa-
- Lhoret,R.
- AV. Rangel, HA.
- Rajaram,S.
- Ramanakumar,
- Rinne, J.
- Rogers, PC.
- Ross, EK.
- Rozenfeld, I.
- Rundell, KW.
- Sabine, N.
- Sacks, N.
- Sajobi, TT.
- Santa Mina, D.
- Sataloff, RT.
- Scheede-
- Bergdahl,C.
- Schmid, S.
- Schipper, HM.
- Schmidt, H.
- Serkova, NJ.
- Sgarbieri, VC.
- Shaw, A.
- Sheinberg,N.
  Shenouda, N.
- Shi, HP.
- Shimizu, Y.
- Shokunbi, MT.
- Sirois, C.
- Smountas, AA.
- Song, W.
- Spaw, JÁ.
- SpicerJ.
- Srinivasaraghavan,NS
- Stein, B.
- Stevenson, MM.
- Summer, WA.
- Sumner, WA.
- Sun, HL.
- Suppere, P.
- Sweet, SN.
- Tai, P.
- Tavatian, A.
- Tanguay, S.
- Tanikawa, C.
- Taveroff, A.
- Tienboon,P.
- Tosukhowong,P.
- Tourian, L.
- Tozer, R.
- Trivedi, MH.
- Tsai, LY.
- Tsai, SM.
- Tsai, WY.
- Tseng, YM.
- Tu, L.
- Van Ark, I.
- Van Rooijen, SJ.
- Viau, G.
- Wainberg, M.
- Wallace, T.
- Wang, L.
- Wang, PC.
- Wang, YY.
- Watanabe, A.
- Wilkins, HM.
- Winter, AN.
- Wu, SH.
- Wu, YR.
- Wu, XJ.
- Wykes, L.
- Xiong, LL.
- Yeh, WH.
- Yilmaz, E.
- Yu, P.
- Yu, WN.
- Zeng, Z.
- Zhang, J.
- Zhang, X.

Journals Cited

- Acta Oncolgica
- African Journal of Biomedical Research
- Anesthesiology
- Anticancer Research
- Antioxidants Antioxidants & Redox Signaling
- Canadian Journal of Cardiology
- British Journal of Nutrition
- Cancer Letters
- China Cancer
- Chest
- Clinical and Investigative Medicine
- Clinical Nutrition
- Ear Nose Throat Journal
- Electronic Journal of Metabolism & Nutrition of Cancer
- European Urology Focus
- Food & Chemical Toxicology
- Free Radical Biology And Medicine
- Frontiers in Psychiatry
- Health Psychology
- Immunology
- International Journal of Food Sciences and Nutrition
- JAMA (Journal of the American Medical Association) Surgery
- Journal of Agricultural And Food Chemistry
- Journal of Applied Physiology
- Journal of Clinical And Aesthetic Dermatology
- Journal of Cystic Fibrosis
- Journal of Gastroenterology & Hepatology
- Journal of Infectious Diseases
- Journal of Medicine
- Journal of Nutrition
- Journal of Nutrition and Diet
- Journal of Nutrition, Health & Aging
- Journal of Nutritional Oncology
- Journal of The Academy Of Nutrition And Dietetics
- Journal of The American Medical Association Surgery
- Journal of The American Nutraceutical Association
- Journal of The Neurological Sciences
- Journal of Wound Care
- Lait
- Medical Hypotheses
- Medicine & Science In Sports & Exercise
- Minerva Gastroenterologica E Dietologica
- Neural Regeneration Research
- Nutrition And Cancer
- Oxidative Medicine and Cellular Longevity
- 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

Institutions Cited

- American College of Sports Medicine, Marywood University, Human Performance Laboratory, Scranton, Pennsylvania, USA
- Boreal Primum Inc., Montreal, Quebec, Canada
- British Columbia Children's Hospital, Vancouver, British Columbia, Canada
- Canakkale Onsekiz Mart University. Faculty of Food Engineering. Canakkale. Turkey
- Cancer Center, Neijiang Second People's Hospital, Neijiang, China
- Cancer Centre, Cancer Care, Alberta Health Services, Calgary, Alberta, Canada.
- Cancer Nutrition & Rehabilitation Program, Department of Oncology, McGill University, Montreal, Quebec, Canada
- Cancer Nutritional Treatment Center, Neijiang Second People's Hospital, Neijiang, China
- Cancer Rehabilitation and Survivorship Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada
- Capital Medical University, Beijing International Science and Technology, Beijing, China
- Cooperation Base for Cancer Metabolism and Nutrition / Department of Oncology, Capital Medical University, Beijing University, Beijing, China
- Center for Collaborative Research, Institute for Neuro Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA
- Center for Surgical Science, Zealand University Hospital, Roskilde, Denmark
- Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Montréal, Canada
- Centre hospitalier universitaire, Sherbrooke, Quebec, Canada
- Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada
- Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease, Shahid
- Beheshti University of Medical Sciences, Tehran, Iran
- Chulalongkorn Center of Excellence for Parkinson's Disease and Related Disorders, Faculty of Medicine,
- Chulalongkorn University, Thailand
- Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand
- Clinica Norte, Cúcuta, Colombia
- College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
- Columbia University, Children's Hospital of New York, New York, USA
- Community Health Sciences, Institute of Public Health, Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada
- Community Health Sciences, Institute of Public Health, Alberta Children's Hospital, Calgary, Alberta, Canada
- Cumming School of Medicine, Department of Community Health Sciences, University of Calgary, Alberta, Canada
- Danone Research Centre for Specialized Nutrition, Wageningen, The Netherlands
- Daping Hospital, The Third Military Medical University, Chongqing, China
- Department of Anatomy, McGill University, Montreal, Quebec, Canada
- Department of Anatomy, College of Medicine, University of Ibadan, Ibadan, Nigeria
- Department of Anesthesia, McGill University, Montreal, QC, Canada
- Department of Anesthesia and Intensive care, San Raffaele Scientific Institute, Milan, Italy

- Department of Anesthesiology, Cancer Institute (WIA), Chennai, Tamil Nadu, India
- Department of Anesthesia, Hospital Clinic de Barcelona, Spain
- Department of Biochemistry and Molecular Biology, College of Basic medical Sciences, Second Military
- Department of Biochemistry, College of Medicine National Taiwan University, Taipei, Taiwan, R.O.C
- Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
- Department of Biochemistry, McGill University Health Centre
- Department of Biostatistics and Cancer Registry, Cancer Institute (WIA), Chennai, Tamil Nadu, India
- Department of Clinical Nutrition Beijing Shijitan Hospital, Beijing, China
- Department of Clinical Medicine, University of Copenhagen, Denmark
- Department of Clinical Nutrition, Neijiang Second People's Hospital, Neijiang, China
- Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Alberta, Canada
- Department of Endocrinology, Affiliated Huai'an Hospital of Xuzhou Medical College, Jiangsu, China
- Department of Exercise Science, Concordia University, Montreal, QC, Canada
- Department of Environmental and Public Health, College of Medicine, Kaohsiung Medical University, Taiwan
- Department of Food and Nutrition, Faculty of Food Engineering, State University of Campinas, Campinas, São Paulo, Brazil
- Department of Gastrointestinal / Clinical Nutrition Surgery, Beijing Shijitan Hospital, Capital Medical
- University, Beijing, China
- Department of Gastrointestinal Surgery Beijing Shijitan Hospital, Beijing, China
- Department of General Surgery / Nutrition, Beijing Shijitan Hospital, China
- Department of Immunology and Microbiology, Dalhousie University, Halifax, Nova Scotia, Canada
- Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan
- Department of Kinanthropology, Université du Québec à Montréal, Canada
- Department of Kinesiology and Physical Education, McGill University, Canada
- Department of Laboratory Medicine, Kaohsiung Veterans General Hospital, Taiwan
- Department of Mathematics and Computer Science, Eindhoven University of Technology, The Netherlands
- Department of Medical Laboratory Science and Biotechnology, College of Health Sciences, Kaohsiung
- Medical University, Kaohsiung, Taiwan
- Department of Medical Sciences, University of Ferrara, Italy
- Department of Medicine, Faculty of Medicine, Chiang Mai University, Thailand
- Department of Medicine, McGill University, Montreal, Quebec, Canada
- Department of Medicine, University of Alberta, Alberta, Canada
- Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada
- Department of Nutrition and Food Services, McGill University, Montreal, Quebec, Canada
- Department of Nutrition, Université de Montréal, Montréal, Canada
- Department of Oncology, McGill University, Montreal, QC, Canada
- Department of Otolaryngology-Head and Neck Surgery, Drexel University College of Medicine, Philadelphia, PA. USA
- Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
- Department of Pathology & Molecular Medicine, McMaster Division, Hamilton Health Sciences, Ontario, Canada
- Department of Pathology, Kaohsiung Veterans General Hospital, Taiwan
- Department of Pediatrics, College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale,

FL, USA
- Department of Pediatrics and Oncology, McGill University, Montreal, Quebec, Canada
- Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Thailand
- Department of Pediatrics, McGill University, Montreal, Quebec, Canada
- Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL, USA
- Department of Physical Therapy, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand
- Department of Physiology, McGill University, Montreal, Quebec, Canada
- Department of Plastic Surgery, Taipei Veterans General, Taipei, Taiwan
- Department of Psychiatry, Neijiang Second People's Hospital, Neijiang, China
- Department of Radiology, Faculty of Medicine, Chiang Mai University, Thailand
- Department of Radiotherapy, College of Medicine/University College Hospital, Ibadan, Nigeria
- Department of Rehabilitation Medicine, Juntendo University, Tokyo, Japan
- Department of Surgery, School of Medicine, National Yang Ming University, Linong Street, Taipei, 11221, Taiwan
- Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada
- Department of Surgery, Amphia, Breda, the Netherlands
- Department of Surgery, Zealand University Hospital, Koge, Denmark
- Department of Surgery, School of Nutrition and Translational Research in Metabolism, Maxima Medical
- Centre and Maastricht University Medical Centre, Maastricht, Netherlands
- Department of Surgery, Maxima Medical Center, Veldhoven, The Netherlands
- Department of Surgery, McGill University Health Center, Montreal, Canada
- Department of Surgery, Slagelse Hospital, Denmark
- Department of Surgery, University of Ibadan/University College Hospital, Ibadan, Nigeria
- Department of Surgery, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada
- Departments of Surgery, McGill University, Montreal, Quebec, Canada
- Department of Urology, Cheeloo College of Medicine, Shandong University, China
- Department of Urology, Shandong First Medical University, Jinan, China
- Department of Biological Sciences & Eleanor Roosevelt Institute, University of Denver, Colorado, USA
- Department Research & Development, Immunotec Inc., Vaudreuil, Quebec, Canada
- Department of Anatomy & Developmental Biology, University of Heidelberg, Mannheim, Germany
- Division of Clinical Pharmacology & Toxicology, University of Colorado Denver, USA
- Division of Diagnostic Radiology, Faculty of Medicine, Chiang Mai University, Thailand
- Division of Gastrohepatology, Faculty of Medicine, Chiang Mai University
- Division of Nutrition, Faculty of Medicine, Chiang Mai University, Thailand
- Division of Pediatric Oncology, Columbia University Medical Center, New York, New York, USA
- Division of Pharmacology, Utrecht Institute for Pharmacological Sciences, Utrecht University, The Netherlands
- Division of Plastic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei, 11221, Taiwan
- Division of Redox Physiology and Aging Research, Deutsches Krebsforschungszentrum, Heidelberg, Germany
- Division of Respiratory Medicine, Montreal Children's Hospital, Montreal, Quebec, Canada
- Division of Thoracic Surgery, McGill University Health Centre, Montreal General Hospital, Montreal, Quebec, Canada
- Division of Urology, Department of Surgery, McGill University Health Centre, Montreal, Quebec, Canada

- Emergency Department of Changhai, Affiliated Second Military University, Shanghai, China
- Faculty of Education, McGill Research Centre for Physical Activity and Health, McGill University, Montreal, Quebec, Canada
- Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada
- Faculty of Nursing, University of Windsor, Windsor, Ontario, Canada
- Faculty of Medicine, McGill University, Monteral, Canada
- Fundacion Universitaria de Ciencias de la Salud. Bogota, Colombia
- George Washington University, Washington, DC, USA
- Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada
- Hospital Nacional Docente Madre Nino San Bartolome, Lima, Peru
- IDIBAPS, University of Barcelona, Spain
- Institut de recherches cliniques de Montréal (IRCM), Montréal, Canada
- Institut für Immunologie und Genetik, Deutsches Krebsforschungszentrum, Heidelberg, Germany
- Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
- Jisheng Hospital, Chongqing, Yongchaun District, China
- Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada
- Mailman Segal Center, Nova Southeastern University, Fort Lauderdale, FL, USA
- McGill AIDS Centre. Montreal. Quebec, Canada
- McGill Research Centre for Physical Activity & Health, McGill University, Montreal, Quebec, Canada
- McGill University Health Center, Montreal, Quebec, Canada
- McGill University Health Centre Colorectal clinic, Montreal, Quebec, Canada
- McGill University, Montreal, Quebec, Canada
- Medical Department, Neijiang Second People's Hospital, Neijiang, China
- Medical University, Shanghai, China
- Medscope Communications Inc., St. Laurent, Quebec, Canada
- Montreal Children's Hospital, Montreal, Quebec, Canada
- Montreal Children's Research Institute, McGill University, Quebec, Canada
- Montreal Diabetes Research Center (MDRC), Montréal, Canada
- Montreal General Hospital Preoperative Clinic, Montreal, Quebec, Canada
- Montreal General Hospital Research Institute, Montreal, Quebec, Canada
- Montreal General Hospital, Montreal, Quebec, Canada
- National Cyclotron and PET Center, Chulabhorn Hospital, Bangkok, Thailand
- Neijiang Second People's Hospital, Neijiang, China
- Nutrition Services, Alberta Health Services, Alberta, Canada
- O'Brien Institute for Public Health, University of Calgary, Calgary, Canada
- Otsuka Pharmaceutical Factory, Inc., Nutrition Research Institute, Tokushima, Japan
- Pasteur Institute Paris, France
- Peri Operative Program, McGill University, Montreal, Canada
- Physical Medicine and Rehabilitation Department, Hospital Clinic de Barcelona, Spain
- Radiation Oncology, Allan Blair Cancer Center, Regina, Saskatchewan, Alberta, Canada
- Research Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
- Research Institute, McGill University Health Center, Montreal, Quebec, Canada
- Research Service, Veterans Affairs Medical Center, Denver, Colorado, USA
- Royal Victoria Hospital, Montreal, Quebec, Canada
- School of Anesthesia and Intensive Care, University of Milan, Milan, Italy

- School of Human Nutrition, McGill University, Montreal, Canada
- Servizio di Dietetica e Nutrizione Clinica, Ospedale San Giovanni Battista, Torino, Italy
- State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China
- South American Center for Research in Education and Public Health, Universidad Norbert-Weiner, Lima, Peru
- Statistical Consulting Center, College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA
- Thai Red Cross Society, Bangkok, Thailand
- The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
- The Second Retired Cadre Sanatorium in Harbin, Heilongjiang, China
- Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland
- South American Center for Research in Education and Public Health, Universidad Norbert-Weiner, Lima, Peru
- University of Calgary, Calgary, Alberta, Canada
- University of Colorado Cancer Center, Aurora, Colorado, USA
- University of Denver, Department of Biological Sciences, Denver CO, USA
- University of Denver, Knoebel Institute for Healthy Aging, Denver, Colorado , USA
- University of Texas Health Science Center, San Antonio, Texas, USA
- University of Texas Science Center, San Antonio, Texas, USA
- University of Texas Southwestern Medical Center, Dallas, Texas, USA
- Washington Dermatology Center, North Bethesda, Maryland, USA

92 Publications featured in this book

27 | ANIMAL STUDIES
07 | LABORATORY STUDIES
19 | THEORETICAL PAPERS, OPINION PAPERS, REVIEW PAPERS
39 | HUMAN STUDIES AND REPORTS

Including 26 gold-standard human trials

Representing

20 | COUNTRIES
275 | RESEARCHERS
58 | JOURNALS CITED
169 | INSTITUTIONS

Disclaimer

This book is intended for educational and scientific interest only. It is not intended as a source of medical advice. The contents feature published research articles. Research articles do not translate into clinical practice or treatment guidelines. The reader is urged to consult with a health professional before using any supplements. Immunocal is a natural dietary supplement. It is not intended to diagnose, treat, cure, or prevent any disease. The views expressed by Dr. Gutman do not necessarily reflect the views of Immunotec.

Immunotec®

www.immunotec.com

Copyright® 2024 Immunotec Inc. All Rights Reserved.