Glyconutrients: The State of the Science and the Impact of Glycomics

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The science of glycobiology has made rapid strides in the past few decades. A recent development has been the introduction of glyconutrients as nutritional supplements for health support and disease management. This article reviews the basic and clinical science of glyconutrients and presents a brief perspective on the impact of the field of glycomics.

Key words: Glyconutrients, glycomics, glycobiology, nutritional supplement

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INTRODUCTION

Glyconutrients, what are they? What are they used for? What is the science behind them? In an era of oversupply of high-glycemic foods and the consequent morbidities associated with them such as diabetes and obesity, it appears counterintuitive that glyconutrients–nutraceuticals based on simple, biologically important sugars–would be necessary to our diet.

Our food supply in contemporary society, when moving from farm to market, is often depleted of essential antioxidants, vitamins, minerals, and sugars. This occurs because of modern agricultural practices, processing, handling, shipping, storage, and other factors that make "fresh" foods rarely available to most of the population. As a result, nutritional supplements play a role in providing essential elements of our diet that have been depleted or even lost.

Direct marketing of glyconutrient products has resulted in a large industry that is strictly limited by the "structure/function" claims rules of the Food and Drug Administration. Nonetheless, potential applications are emerging for glyconutrients in the maintenance of wellness and also in the treatments of certain diseases. In addition, the good manufacturing practices of some glyconutrient companies provide a standard for quality control, packaging, bioavailability, purity, and standardization that other nutraceutical firms can emulate.

Glyconutrients have been tested in a number of chronic illnesses, from asthma, cystic fibrosis, myasthenia gravis, attention deficit disorder, autoimmune diseases, depression, for improved cognition, and even cancer and AIDS. Furthermore, parent support groups for conditions such as Tay-Sachs disease and autism have alleged the benefits of glyconutrients.

At first blush, of course, such a wide range of potential applications for any dietary supplement seems unlikely, and while manufacturers are careful not to overstate their benefits, field sales representatives, product users, and others have created a certain degree of public awareness and expectations about glyconutrients that deserve further investigation.

Basic science studies and the evolving field of glycomics offer insights into reasons why glyconutrients may have wide-ranging benefits in both promoting health and in managing disease.

BASIC SCIENCE OF GLYCONUTRIENTS

The use of the term glyconutrient is recent, being first introduced in the 1990s. It was used to refer to the sugars obtained from a nutritional supplement designed to supply a reproducible source of the principal carbohydrates found in the sugar chains of glycoproteins and glycolipids (see below). Some reasons for the development of a glyconutrient supplement are listed in Table 1. It should be noted that the sugars present in glyconutrient supplements are usually present in the form of gums and other polysaccharides derived from various plants. When ingested, the polysaccharides must be digested by enzymes in the gut to release their contained sugars. The human gut lacks enzymes capable of breaking many of the various chemical bonds present in plant polysaccharides, so we rely on bacterial enzymes to release the glyconutrients prior to absorption.

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Table 1. Some Considerations Behind the Development of Glyconutrient Supplements

Eight major sugars (see Table 2) are found in the sugar chains present in glycoconjugates.
Glycoconjugates play many important roles in wellness and disease.
The amounts of many important nutrients, including some of the eight sugars, have diminished markedly in fruits and vegetables.
Many of us are not eating sufficient amounts of fruits and vegetables, the major source of most of the eight sugars.
Until recently, it was believed that seven of the eight sugars could be derived by various enzyme reactions from glucose. However, there is now evidence indicating that glucose may not be sufficient, at least under certain circumstances. For example, mannose is incorporated into glycans without involving glucose.
Some of the sugars and the polysaccharides (plant gums) from which they are derived exert biologic effects independent of glucose (eg, the use of glucosamine in the management of osteoarthritis, and the use of mannose and fucose in the treatment of certain congenital disorders of glycosylation).

Three major classes of molecules (called glycoconjugates) contain sugar chains: glycoproteins, glycolipids, and proteoglycans (Figure 1). Glycoproteins are proteins that contain one or more sugars covalently bound. Glycolipids are lipids that contain one or more sugars covalently bound. Proteoglycans are complexes of glycosaminoglycans linked to specific proteins. Glycosaminoglycans are polymers made up of repeating disaccharide units; they were formerly known as mucopolysaccharides and include the chondroitin sulfates, dermatan sulfate, heparin, heparan sulfate, hyaluronic acid, and the keratan sulfates.

When we absorb glyconutrients, a percentage of them will be utilized by the body to synthesize the sugar chains of glycoconjugates. These molecules play many important roles in our cells and tissues, and comprise much of the subject matter of glycobiology, the study of the roles of sugars and sugar-containing molecules in health and disease.[1-3] Analyses of many sugar chains of glycoproteins and glycolipids have shown that eight sugars (Table 2) may be found. Certain other sugars may also be found in human glycoconjugates (eg, glucosamine and glucuronic and iduronic acids are present in proteoglycans).

Sugar chains (also called glycans) vary in length from one sugar, to very long chains found in glycosaminoglycans, to highly branched complex structures found in glycoproteins. The synthesis of sugar chains attached to proteins and lipids is catalyzed by a battery of enzymes named glycosyltransferases and is called glycosylation; it gives new properties to these molecules. The principal property conferred is that sugar chains can recognize and bind many other molecules. These include other proteins and glycoconjugates, hormones, drugs, toxins, bacteria, viruses, and surface molecules involved in processes such as cell-cell communication and cell adhesion.[1-3] Sugar chains thus contain biologic information. The surfaces of human cells contain many hundreds, if not thousands, of different glycans, all with unique functions, many of which wait to be discovered over the next decade.

The information in cell surface glycans is sometimes referred to as the "sugar code of life." Deciphering this code entails discovering the functions of all the sugar chains present in human cells. It is already known that glycans play important roles in cell signaling (many receptors contain glycans), and alterations in cell surface sugar chains are thought to be at least one important factor contributing to the complex process of metastasis.

Role of Glyconutrients in Metabolism

Traditionally, sugars have been viewed mainly as an energy source. While they can largely be interconverted by cellular metabolism into each other, the enzymatic processes and energy exchange necessary to provide the essential saccharides may be impaired in stress, various diseases, and certain deficiency states. By adding glyconutrients to the diet, one reduces the energy expenditures, number of conversion steps, and enzymatic reactions necessary to make them available intracellularly.

A basic consideration in understanding the importance of glyconutrients is that glycoproteins, into whose sugar chains glyconutrients are incorporated, are essential for healthy cellular

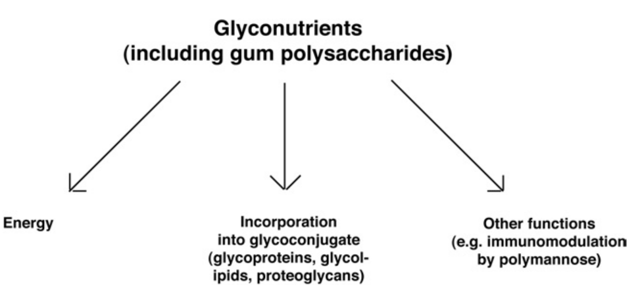

Figure 1. Fates of glyconutrients.

Table 2. The Major Simple Glyconutrients

The Eight Principal Sugars Found in Glycoconjugates
Xylose
Fucose
Galactose
Mannose
Glucose
N-acetylgalactosamine (GalNAc)
N-acetylglucosamine (GlcNAc)
N-acetylneuraminic acid

Glycosaminoglycans contain some other sugars (eg, glucosamine and glucuronic and iduronic acids). Gum polysaccharides may also be considered as glyconutrients, because they are an important dietary source of the simple glyconutrients.

Table 3. Some Functions of Glycoproteins

Glycoprotein	Function
Collagen	Structural component
Immunoglobulins and histocompatibility antigens	Involved in various functions of the immune system
Various plasma proteins except albumin	Many act as transport molecules (eg, transferrin)
Mucins	Lubricants
Human chorionic gonadotropin, TSH	Hormones
Various receptors	Involved in cell signaling and drug and hormone action
Some cell adhesion molecules (CAMs)	Cell adhesion

signaling, recognition of antigens, and many other important functions. Some of these functions are listed in Table 3. In addition, the two other major classes of glycoconjugates perform many important cellular functions[3] not described here.

Little is known as to exactly how glyconutrients may act. As discussed above, they can be incorporated into the sugar chains of glycoconjugates, which play important roles in health and disease.

Glyconutrient Deficiency?

There is no literature available as yet on how deficient our cells may be in levels of the eight major glyconutrients (or their active metabolites) in various conditions and how this may affect the synthesis of glycans. The polysaccharides from which glyconutrients are derived can affect the immune system (eg, polymannose) and may also exert prebiotic effects. As discussed below, glucosamine and *N*-acetylglucosamine have been shown to have therapeutic effects, and mannose and fucose are also of use in two well-defined genetic conditions. It is possible that various glyconutrients may affect gene activities, but this remains to be investigated. Studies in vitro have shown that various glyconutrients can inhibit the attachment of many bacteria and viruses to human cells.[4]

GLYCOBIOLOGY AND MEDICINE

Clinicians are widely aware of the abnormal glycation of hemoglobin in diabetes, which is the basis of a useful test to track the control of this disease. Glycation refers to addition of sugars to molecules that does not involve enzymes, whereas glycosylation involves enzymes. Glycation of proteins other than hemoglobin is believed to be implicated in some of the damage to tissues that occurs in diabetes mellitus. Abnormal glycosylation is involved in a number of other diseases, among these being certain congenital types of muscular dystrophy, many cancers, autoimmune arthritis, and rheumatoid arthritis. Diseases due to abnormal catabolism of the sugar chains of glycoproteins (eg, the mannosidoses) and glycolipids (eg, Gaucher and Tay-Sachs disease) are also well recognized.

Drawing some points from a theme issue on the science of carbohydrates and glycobiology in the prestigious journal *Science* stimulates some interesting prospectives about the utility of glyconutrients in medicine.[5] Examples of genetic diseases for which glyconutrients are useful are two different types of congenital disorders of glycosylation (CDGs). These diseases generally involve mutations in genes directing the synthesis of various enzymes involved in the synthesis of the glycans of glycoproteins. The CDG1b glycosylation disorder causes chronic gastrointestinal, hematological, and neurological problems, for which adding mannose to the diet can be lifesaving. Fucose supplementation can be useful for another CDG (leukocyte adhesion deficiency II) affecting the immune system via defective leukocyte function.

Another example of the application of glycobiology in medicine is the *Haemophilus influenzae b,* or *Hib* vaccine, which is a sugar-based vaccine. The sugar component helps to improve the antigenicity of the vaccine. Another potential application is in the development of cancer vaccines. By manipulating tumor antigens through altering glycoforms, they become visible to the immune system. The immune system can then better recognize, attack, and destroy the tumor. Commercial development of new sugar-based delivery systems for such chemotherapeutic agents as 5-fluorouracil are proposed and are undergoing phase I and phase II studies.

Another application under study is viral deconstruction. Alterations of the sugars on viral coats (eg, those of the viruses causing hepatitis B and C, and also human immunodeficiency virus [HIV]-1) may be useful in preventing viral replication.

A major role of glycosylation is in the structure and function of T-cell antigen presentation, the major histocompatibility complexes, and immunoglobulin glycoform synthesis, stability, and recognition. Also, ABO blood types are based on differences in sugar composition (eg, blood group A contains a terminal *N*-acetylgalactosaminyl moiety, whereas blood group B contains a terminal galactosyl moiety).

Another review of glycobiology by researchers at the Massachusetts Institute of Technology[6] is also of interest. They noted, as described above, that many carbohydrates exist as glycans, rather than as simple sugars. Some of these glycans coat cellular membranes as proteoglycans, a number of which are involved in cellular signaling and interaction with the extracellular matrix. The extracellular matrix is intimately involved in transmitting important biochemical signals into and between cells. Glycan-protein interactions can be structurally very selective, for example, heparin binding to antithrombin III to inhibit blood coagulation. Furthermore, such signaling is critical to multiple biochemical pathways and disease processes: cancer, angiogenesis, tissue repair, skeletal development, cardiovascular disease, and microbial infection.

Glycosaminoglycans such as heparan sulfate–which is related to heparin–also interact with proteins and regulate them. When abnormal, these can result in loss of a protective barrier, contributing to the development of inflammatory disease of the gut and bladder. As noted above, carbohydrate-based drug therapies are being researched. Carbohydrate-containing molecules may be targets for drugs, or may be used as drugs, or as conjugates with cancer drugs.

EVOLUTION OF GLYCOMICS

The sum total of sugars and sugar-containing molecules in an organism is called its glycome. Glycomics is a new area of science, closely allied to glycobiology. It basically arose as an extension of the Human Genome Project, in which the structure of most of our genome (containing approximately 25,000 genes) was elucidated. Human glycomics seeks to determine the complete structures and functions of sugar-containing molecules found in our cells and tissues. This is no easy task; it has been estimated that approximately one half of the proteins found in humans are glycoproteins. Thus, humans may contain a minimum of approximately 12,000 different glycoproteins. However, advances in analytical methodology (eg, nuclear magnetic resonance spectroscopy, mass spectrometry, and other techniques) have greatly accelerated the characterization of glycoconjugates. Alterations of sugar-containing molecules in health and disease will also be studied, as will genetic aspects. It is anticipated that information afforded by such comprehensive studies will offer new insights into our understanding of wellness and disease, and also to the development of new nutritional and drug approaches.

In an era when proteomics and genomics form the cutting edges of molecular biology, the field of glycomics is expanding rapidly with improved isolation, characterization, and also manufacturing of complex carbohydrates. Such efforts, as previously noted, have been limited by the complexity of many glycoconjugates, which had until recently proven difficult to characterize.

A biannual symposium, the Jenner Glycobiology and Medicine Symposium[7] brings glycoscientists together to examine and describe the pivotal role of glycosylation from embryogenesis to immune function. They recently examined the impacts of sugar metabolism on the morphogenesis of viruses (hepatitis C, bovine diarrhea virus, HIV, and Ebola). One of the Symposium's lead researchers, Dr. John Axford, St. George's Hospital Medical School, University of London, predicted that immune mechanisms will be a major focus of clinical intervention in upcoming decades. His laboratory has a study underway to "fingerprint" a number of immunoglobulin glycoforms related to autoimmune disease.[7]

Thus, the range of glycomics and glyconutrient-related scientific studies, the increased sophistication of analytical and manufacturing processes for carbohydrates, and the understanding of the functions of carbohydrates in disease and health continue to expand.

COMMON GLYCONUTRIENTS

Most physicians practicing integrative medicine, and also other healthcare practitioners, are well aware of a common glyconutrient, glucosamine. This is widely used by the public for osteoarthritis and has been found to have not only analgesic but possibly disease-modifying benefits in this condition.[8,9] A large NIH study comparing it with chondroitin sulfate, or a combination of the two (as commonly marketed), and with placebo and a COX-2 inhibitor, was recently published.[10] Glucosamine hydrochloride and chondroitin sulfate alone, or in combination, did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. Exploratory analyses suggested that the combination of glucosamine hydrochloride and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain. This study, however, utilized glucosamine hydrochloride, rather than glucosamine sulfate, which has been the standard form studied in previous trials, so the results may have been confounded by the preparation. Also, the very high placebo response of over 60% affected the interpretability of all arms of the trial.

Aloe vera is a cactuslike succulent that has wide application in skin and tissue healing. It is also used internally for gastric and esophageal problems and as a laxative. The central pulp of the plant is an important source of mannose, one of the important saccharides described below. Its active constituent is in fact a polymannose.

Another important group of glyconutrients are the complex polysaccharides contained in a variety of medicinal mushrooms. Extracts of Reishi, maitake, cordyceps, and shiitake are used for immune support, in hepatitis, and in traditional Chinese medicine used for cancer treatment.

The most common sources of glyconutrients are:

- *Aloe vera*
- Arabinogalactans (gum sugars) from corn, wheat, leeks, carrots, radishes, pears, red wine, coconuts, tomatoes, curcumin and Echinacea
- brans from brown rice, slow-cooked oatmeal, whole barley
- breast milk
- mushrooms, especially reishi (ling zhi), maitake, cordyceps and shiitake
- pectins from apples, citrus fruits

Summaries written primarily for a lay audience but with literature references give an overview of the glyconutrients in health and disease.[11,12]

Mondoa and Kitei[11] describe the eight major saccharides present in glycoconjugates, and some of their uses as listed below. Many of the clinical uses described are from preclinical and animal studies and very few from randomized controlled trials, so evidence levels are often low for human applications.

The eight major saccharides, sources, and their imputed benefits are as follows:

- *Xylose*–antibacterial and antifungal, cellular communication, prevention of cancer of the digestive tract, does not promote caries, tolerable for diabetics, decreased in colitis.
- *Fucose*–long-term memory (animal studies), immune modulator, protection against upper respiratory infection and allergic reactions; metabolism is abnormal in cystic fibrosis, diabetes mellitus, cancer, and shingles; abundant in human breast milk and certain mushrooms.
- *Galactose*–inhibition of tumor growth, especially liver (animal studies), enhanced wound healing, antiinflammatory, enhanced cellular communication, radiation protection, long term memory, low in rheumatoid arthritis, juvenile rheumatoid arthritis, lupus patients; abundant in dairy products.
- *Glucose*– ubiquitous; table sugar (sucrose) contains glucose and fructose; rapid source of energy, raises level of insulin, and linked to obesity and diabetes, low levels found in Alzheimer's

patients; disturbed metabolism of glucose associated with depression, manic-depression, anorexia, bulimia.

- *Mannose*–tissue remodeling and cellular communication, inhibition of tumor growth, antibiotic properties, anti-inflammatory (lupus, rheumatoid arthritis), reduction of blood sugar and triglycerides in diabetics.
- *N-acetylgalactosamine*–inhibits tumor spread, cellular communication; low serum levels in patients with heart disease.
- *N-acetylglucosamine*–immune modulator, antitumor properties; glucosamine for osteoarthritis is closely related to it and is useful for reducing pain and inflammation; vital to learning, essential to mucosal defensive barrier (GAG layer), and important in inflammatory bowel disease, interstitial cystitis.
- *N-acetylneuraminic acid*– brain development and learning, immune modulator affecting mucus viscosity, antiviral, affects blood coagulation and lipid levels– disturbed metabolism in Sjogren's and alcoholics; decreased tissue levels with age; abundant in breast milk.

2nd Generation Glyconutrients:

- acemannan from Aloe has been used to treat infection with HIV
- active hexose correlated compounds (AHCC) from shiitake–liver cancer from hepatitis C
- alpha and beta glucans from mushrooms, yeasts, oat, barley, rice bran–lipid-lowering
- bovine tracheal cartilage–improve immune response to tumors, skin healing topically
- chitin and chitosan from shellfish–reduce allergic reactions in animals
- inulin and oligofructose (prebiotics)– gut health
- lentinan from shiitake has been used in venereal warts, chronic fatigue syndrome, infection with HIV, cancer (injectable)
- ling zhi 8 from reishi may be useful in leukemia (rodent model)
- maitake D-fraction, a beta-glucan for reducing side-effects of chemotherapy (nausea, vomiting, diarrhea, hair loss, low white blood cell) and inhibiting cancer and its spread
- polysaccharide K and polysaccharide P from *Coriolus versicolor* mushroom for cancer treatment

In summary, a number of glyconutrients have found their way into integrative practices, and some, for example, glucosamine, mushroom extracts, and certain polysaccharides, have found application in conventional therapeutics. Clinical science still lags behind, however, as is often the case in the translation of nutritional science to clinical care.

CLINICAL STUDIES OF GLYCONUTRIENTS

Asthma

A randomized double-blind placebo-controlled trial was performed using glyconutrients and/or phytonutrients in 87 children with asthma (7-17 years old, mean age, nine).[13] The glyconutritional group trended toward fewer exercise-induced asthma symptoms. The group taking glyconutritional as well as phytonutritional supplements demonstrated significant improvement in change in peak flow variability.

This six-month study did not show improvements in the primary outcome measure of quality of life nor in any of the other secondary measures, which included emergency room visits, missed school days due to asthma, night-time symptoms, nebulizer treatments required, rescue medication treatments required, or days of allergy symptoms.

The patients were all stable on medications for mild to moderate asthma for at least one year prior to the study; the medications were maintained throughout the study period along with rescue medications as indicated. The study was well designed to capture data by using patient and parent logs, monthly clinical assessments, and examined a wide variety of clinical measures and quality of life measures. The study was underpowered to measure significant changes in children already stable on medication.

The authors concluded that quality of life scores were high at baseline, leaving little room for improvement. Further, they suggested that glyconutrients and phytonutrients may improve symptoms and peak flow variability in some asthmatic children who are on stable asthma medications. They called for future studies to involve larger numbers of patients who have more severe disease.

At best, this study suggests glyconutrients may have a marginal benefit for asthmatic children.

Cystic Fibrosis

A retrospective study was performed of confirmed cystic fibrosis patients taking glyconutritional supplements for at least three successive months.[14] The patients were all on standard medical therapy with age range from six months to 50 years old. The objective of the study was to evaluate the potential benefits of glyconutritional supplementation in cystic fibrosis patients.

Evaluation was through questionnaires completed by patients or parents, who were asked to rate respiratory/digestive involvement prior to supplementation (mild, moderate, or severe) and also to rate symptom changes after supplementation (worsening, no change, improvement [mild, moderate, great])

There were 108 respondents, of whom 90.7% reported positive changes in cystic fibrosis symptoms; 70.4% reported improved pulmonary symptoms, 28.7% reported reduced chronic cough, and 15.7% reported less nebulizer use. Seventy-seven percent reported improved digestive function, and 33.3% reported less difficulty in gaining weight.

The authors concluded that glyconutrients appear to enhance pulmonary and/or digestive functions in some cystic fibrosis patients. While this study was promising, such retrospective analyses are well known to be confounded by recall bias, placebo effect, and patient/parent expectations. A prospective blinded placebo-controlled randomized controlled trial of glyconutrients coupled with clinical measures of response would be necessary to validate this preliminary report.

Myasthenia Gravis

The purpose of this pilot study was to examine micronutrient supplementation as an aid in support of various innate physiological mechanisms involved in myasthenia gravis (MG).[15]

Nineteen patients with symptomatic MG were assigned in an open-label, matched-crossover pilot study to either a nutritional intervention group or a control-crossover group. The age range of the patients was 18-81 for 12 females and 15-84 for seven males. Patients were started on a fixed serving of nutraceutical supplements, and servings were to be increased as needed to support a response rate of approximately 75%. The nutritional intervention administered was one teaspoon glyconutritional powder three times daily in food or juice; 1/4 teaspoon phytonutritional powder three times daily in food or juice; one plant phytosterol complex three times daily; and one vitamin and mineral supplement three times daily.

The study design used the standard quantitative myasthenia gravis score taken from the Recommendations for Clinical Research Standards developed by the Myasthenia Gravis Foundation of America. Quantitative myasthenia gravis measurements were taken initially and at two weeks, followed by one-month and two-month intervals. Patients were also queried with regard to their subjective rating scale–initially, at 10 weeks, and at the end of the study.

Results demonstrated a decrease in quantitative myasthenia gravis scores of 72.3%; $P < .001$. Subjective scores improved in several areas: activity of daily living, 43.9%; energy, 44.8%; endurance, 44.3%; productivity, 48.1%; and quality of life, 47.0% ($P < .001$).

There were no reported adverse reactions or worsening of MG symptoms from any patients in the study over the 52-week period. The authors concluded that a sharp contrast rapidly developed between intervention group versus controls. Similar rapid improvement was seen in the control group after crossover to intervention protocols mirroring the initial intervention group. They hoped that this kind of response in MG patients might be seen in other autoimmune diseases from such a nutritional intervention.

This was a small though nicely designed, crossover pilot study. Utilization of several nutritional supplements at the same time introduced difficulty in interpreting the results. Because multiple products were used simultaneously, neither mechanisms of action, nor cause and effect of the individual supplements, nor the combination could be clearly determined. This is a limitation of the study but may be a whole science, complexity theory issue as the combination of products may be synergistic. Given the objective and subjective improvements in this pilot study, larger studies with higher power are indicated.

SUMMARY

The glyconutrients are simple sugars that are best described as foods and nutritional supplements derived from foods or other plant sources. As such, no therapeutic claims can be made that they prevent or treat specific diseases, as specified by Food and Drug Administration regulations. Companies marketing such products must be careful not to overstate the potential of these products, particularly in relation to disease treatment. Biological effects of glyconutrients are described including biochemical, immunological, and medical areas.

Much of the literature on the clinical use of glyconutrients, such as illustrated by the three studies above, has been inconclusive and preliminary. A number of case reports and small pilot studies for conditions such as Tay-Sachs disease,[16] chronic fatigue syndrome and fibromyalgia,[17] attention deficit hyperactivity disorder,[18] diabetes,[19] autoimmune disease,[20] inflammatory bowel disease and interstitial cystitis,[21] and others have been reported. These provide intriguing leads for the future. Yet, the clinical science of glyconutrients is clearly in its infancy. Many studies suffer from methodological and statistical problems as well as the concerns that industry support may unduly influence researchers interested in this field. Publications are often in industry-sponsored journals, websites,[22] specialized symposia,[23] and other rather narrow scientific venues, which are helpful in an emerging science but do not reach a broad audience of clinicians and scientists.

That being said, we predict that the gap in the clinical translation of the basic science of glycobiology will narrow as more high-quality research is conducted and is published in peer-reviewed journals, and innovative, safe, and effective glyco-therapies for difficult-to-treat and/or chronic conditions is introduced.

Further, as respected scientists increase their interest in the associations of oligosaccharides with disease mechanisms, substantial advances will occur in the design of carbohydrate-based therapies and diagnostic techniques. This will promote the expansion of future clinical research.[24,25] For now, what can clearly be stated is that the safety of these products is high. Their effectiveness in the prevention and treatment of disease remains promising, yet unproven. As the fields of glycobiology and functional glycomics evolve, we expect to see more evidence for a wide variety of clinical applications, as well as wellness support by glyconutrients.

REFERENCES

1. Varki A, Cummings R, Esko J, Freeze H, Hart G, Marth J, eds. *Essentials of Glycobiology*. Cold Spring Harbor, MA: Cold Spring Harbor Laboratory Press, 1999.
2. Taylor ME, Drickamer K. *Introduction to Glycobiology*. Oxford, UK: Oxford University Press, 2003.
3. Murray RK, Mayes P, Rodwell V, Granner D. *Harper's Illustrated Biochemistry*. 27th ed. St. Louis, MO: McGraw-Hill, 2006.
4. Sharon N, Ofek I. Safe as mother's milk: carbohydrates as future anti-adhesion drugs for bacterial diseases. *Glycoconj J*. 2000;17:659-664.
5. Carbohydrates and glycobiology. *Science*. 2001;291:2337-2378.
6. Sasisekharan R, Myett JR. The Sweet Science of Glycobiology. *American Scientist Online*. 2003;91:432. Available at: http://www.americanscientist.org/template/IssueTOC/issue/400. Accessed October 11, 2006.
7. Axford J. 7th Jenner Glycobiology and Medicine Symposium. Sept 5- 8, 2004. *Adv Ex Med Biol*. 2005;564:v-viii.
8. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA*. 2000;283:1469-1475.
9. Richy F, Bruyere O, Ethgen O, et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Int Med*. 2003;163:1514-1522.
10. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Eng J Med*. 2006;354:795-808.
11. Mondoa E, Kitei M. Sugars that Heal: The New Healing Science of Glyconutrients. New York, NY: Ballantine; 2001.

12. Elkins R. *Miracle Sugars*. Pleasant Grove, Utah: Woodland Publishing; 2002.
13. Pippenger CE, VanderWal MC, Kurlandsky LE, et al. Evaluation of the Potential Efficacy of Glyconutrient and Phytonutrient Supplementation in the Clinical Management of Asthma. Presented at the 7th Jenner Glycobiology & Medicine Symposium, Sept 5-8, 2004, Exeter College, Oxford, UK. Published in Proceedings of the Fisher Institute for Medical Research. Available at http://www.FisherInstitute.org. Accessed October 11, 2006.
14. VanderWal MC, Pippenger CE, A Retrospective Post-Marketing Survey of Clinical Symptom Changes in a Cystic Fibrosis Population Voluntarily Supplementing Their Diets with Glyconutrition: Clinical Symptom Changes Presented at the 7th Jenner Glycobiology & Medicine Symposium, Sept 5-8, 2004, Exeter College, Oxford, UK Published in Proceedings of the Fisher Institute for Medical Research. Available at http://www.FisherInstitute.org. Accessed October 11, 2006.
15. Randell DJ, Byars, A, Williams F, Miller L. The Effects of Nutraceutical Dietary Intervention in Myasthenia Gravis. Presented at Annual Meeting of Myasthenia Gravis Foundation, Sept 24, 2005, San Diego, CA. Published in Proceedings of the Fisher Institute for Medical Research. Available at http://www.FisherInstitute.org. Accessed October 11, 2006.
16. Arcadi VC, Dykman K. Case study: Tay-Sachs disease improvement during nutritional supplementation. *JANA*. 1997;(S)1:26-27.
17. Dykman K, Gardiner T, Ford CR, Horn E. The effects of long-term supplementation on the functionality and use of non-drug therapies in patients diagnosed with fibromyalgia and chronic fatigue syndrome. Presented at: Experimental Biology 2001; March 31-April 4, 2001; Orlando, Fla.
18. Dykman KD, Dykman RA. Effect of nutritional supplements on attention-deficit hyperactivity disorder. *Integr Physiol Behav Sci*. 1998;3:49-60.
19. McDaniel CF, Dykman K, McDaniel HR, Ford CR, Tone CM. Effects of nutraceutical dietary intervention in diabetes mellitus: a retrospective survey. Proceedings of the Fisher Institute for Medical Research. Available at http://www.FisherInstitute.org. Accessed October 11, 2006.
20. Axford JS. Review of glycosylation and rheumatic disease. *Biochim Biophys Acta*. 1999;1445:219-229.
21. Russell AL. Glycosaminoglycan (GAG) deficiency in protective barrier as an underlying primary cause of ulcerative colitis, Crohn's disease, interstitial cystitis and possibly Reiter's syndrome. *Med Hypoth*. 1999;52:297-301.
22. GlycoScience. Available at: http://www.glycoScience.org. Accessed October 11, 2006.
23. The Proceedings of the Fisher Institute for Medical Research. Available at http://www.FisherInstitute.org. Accessed October 11, 2006.
24. Axford J. Glycobiology and medicine: an introduction. *J R Soc Med*. 1997;90:260-264.
25. Maeder T. Sweet medicines. *Scientific American*. July 2002:41-47.