U.S. WHEY PROTEINS AND HIV/AIDS

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As donor-funded initiatives expand in developing countries, it has become clear that improving nutrition quality must be addressed in the treatment of HIV *disease and* AIDS. *When considering nutritional intervention to improve the health of those with* HIV *infection, it should be remembered that whey proteins provide a number of unique advantages; a range of protein fractions and growth factors with established immune-enhancing properties; and an amino acid profile that exceeds world health standards.*

HIV (Human Immunodeficiency Virus) is the virus that causes AIDS (Acquired Immune Deficiency Syndrome), a disease that has no precedent in medical history. HIV attacks the immune system, primarily, the white blood cells (the T-lymphocytes or CD4 cells) and macrophages of the body. These cells play a key role in maintaining a person's immunity to disease. As a result, HIV-infected people become susceptible to illnesses caused by the collapse of the body's immune system. HIV-infected individuals can remain physically well for many years after initial infection. However, over time, the virus overwhelms the immune system, symptoms manifest and, at a critical point, AIDS develops.

Malnourishment is thought to exacerbate the incidence and severity of opportunistic infections that HIV manifests, which in turn accelerate the progression of this disease.[29] Therefore, HIV infection is having a devastating impact in developing countries,[2] where malnutrition is more prevalent. A vicious cycle has been envisaged in which undernourished HIV-infected persons have nutrient deficiencies, leading to further immunosuppression and oxidative stress and subsequent acceleration of HIV replication and CD4+ T-cell depletion.[36]

The devastation of this cycle is thought to be reduced significantly by improving nutritional quality.[2] However, it is clear that even in the asymptomatic individual, HIV creates intense metabolic demands that lead to the depletion of specific biochemical components.[16] A reduction in these components is thought to forecast immune dysfunction and wasting.[16] It is also clear that the requirements of this highly specific biochemical environment that maintains immune competence and prevents wasting are not met simply by increasing caloric intake alone.[28]

This review of the relevant literature suggests that, more than many other nutritional material, the incorporation of whey proteins into the diet would help meet the intense metabolic demands created by HIV and improve the health of people living with this virus. Whey proteins are the soluble protein fractions and growth factors found in dairy milk. Whey protein products such as whey protein concentrate (WPC, ≥80% protein) and whey protein isolate (WPI, 90-95% protein) are pure sources of high quality proteins that contain minimal fat, carbohydrate and lactose. They also contain a range of protein fractions that are implicated in an array of immune-enhancing and bioactive functions that promote the maintenance of intestinal health, destruction of pathogens and elimination of toxins.[35,52] Most importantly, WPC and WPI contain a high concentration of the indispensable biochemical constituents thought to maintain immune competence that helps to prevent HIV-related wasting.

WHAT IS HIV-RELATED WASTING?

Wasting is simply the unintentional loss of life-supporting body cell mass (BCM) that underlines mortality in HIV/AIDS.[28] BCM comprises all metabolically-active cells in organs and tissues, the highest proportion of BCM residing in skeletal muscle.[54] HIV infection causes a depletion in BCM but also a redistribution in body composition (increased fat accumulation in the torso and a reduction of muscle mass in the limbs, particularly in men).[10] In the initial stages, a reduction in BCM often occurs without detectable weight loss.[28] However, a reduction in BCM is associated with immunological dysfunction, a progression in this disease.[16] Most patients (and many clinicians) do not have access to equipment that can assess alterations in BCM. Therefore, interventions that focus specifically on maintaining muscle mass are tangible objectives that may help control the progression of HIV.

WHAT CAUSES HIV-RELATED WASTING?

HIV-related muscle wasting is basically the result of an unrelenting attack by this virus on a failing immune system. Although its pathology is multifaceted, HIV-related wasting is driven essentially by inadequate energy intake and the body's chronic, systemic inflammatory response to this virus.[30,33,43] The constant immune response to HIV creates a dramatic increase in whole body protein turnover that leads to excessive breakdown of muscle tissue in an attempt to provide the chemical energy required to fight this virus and its related infections.[21] Specifically, the demand is for muscle glutamine, the indispensable fuel that powers immune function[46,59] (see: Muscle, HIV and the Immune System). However, the mechanisms that underline HIV-related wasting are thought not to reside exclusively within muscle.

HIV-related wasting is thought to originate from a breakdown in the precise regulatory network between muscle, blood (plasma) and the liver.[18] In particular, the concentration of the amino acid cysteine in the blood appears pivotal in the prevention of HIV-related immunological dysfunction and wasting.[21] An abundant supply of cysteine in the blood appears essential for the necessary metabolism of this amino acid within the liver; a textbook biochemistry process that down-regulates urea formation (protein loss within the body).[18] Low plasma cysteine concentrations and a high rate of urea production are the metabolic "symptoms" that forecast wasting before the condition becomes evident.[18] However, an adequate supply of cysteine to the liver not only inhibits the loss of body proteins but it also boosts glutathione production (an important antioxidant in fighting HIV infection) and shifts whole body nitrogen disposal towards preservation of the muscle glutamine reservoir.[16] Therefore, nutritional interventions that focus specifically on providing an abundance of cysteine to the liver and substrates that boost muscle glutamine production would help maintain immune competence and BCM, and control the progression of the disease.[5,16,49]

PROTEIN BASICS AND HIV

All proteins are constructed of linear chains of amino acids (the building blocks of protein). The quality of a protein is generally reflective of its concentration in essential amino acids; those that must be derived from the diet to maintain health. WPC and WPI contain a higher concentration of essential amino acids than other high quality protein sources such as soy and casein.[8] Therefore, whey proteins score the highest ratings in most methods that determine protein quality (Table 1). Assessments of protein quality also provide a relative measure of a protein's ability to satisfy specific requirements related to health. Whey protein's amino acid profile meets or exceeds all of the essential amino acid requirements set by the Food and Agriculture Organization/World Health Organization (FAO/WHO).

As whole-body protein turnover is markedly increased from HIV infection,[59] people living with this virus are thought to have an increased dietary requirement for protein.[47] The results of cross-sectional studies in HIV-infected people demonstrate that the preservation of BCM is highly correlated with dietary protein intake.[55] Consequently, a high protein intake appears to be an important dietary factor in maintaining BCM. However, obtaining an adequate protein intake on a daily basis is often difficult for HIV-infected individuals due to oral infections and/or compromised digestion capabilities associated with HIV. Thus, individuals with HIV infection must ensure that the protein they consume is of the highest nutritional value.

THE BENEFITS OF WHEY PROTEINS IN HIV

When untreated, HIV infection depletes BCM which leads to mortality.[28] Highly active anti-retroviral therapy (HAART) reduces viral load and therefore improves protein metabolism.[57] However, it is important to understand that these drug therapies (including protease inhibitors) do not correct the underlying abnormalities in protein metabolism that HIV creates.[57] Weight is regained with HAART but the weight gain is primarily visceral adipose tissue.[37]

Many clinically unrelated conditions that create wasting (cachexia) reveal conspicuously similar biochemical symptoms.[16,27] When combined, the results of these studies have also identified an optimal biochemical environment that appears essential to maintaining immune competence and preserving/restoring BCM.[16] When designing a nutritional intervention that may help meet the intense metabolic demands of conditions that cause wasting, it should be remembered that in comparison to other dietary protein sources, whey proteins such as WPC and WPI provide a higher concentration of all the indispensable constituents that create and maintain the optimal biochemical environment that helps to maintain/restore immune proficiency and BCM.

Table 1. Protein Quality Comparison Chart

Protein Type	PDCAAS	AAS	PER	BV	NPU
Whey Protein Concentrate	1.14	1.14	3.2	100–104	99
Whole Egg	1.00	1.21	3.9	88–100	98
Casein	1.00	1.00	2.5	77–80	99
Soy Protein Concentrate	1.00	0.99	2.1	61–74	95
Beef Protein	1.00	0.94	2.9	80	98
Wheat Gluten	0.25	0.47	0.8	54	91

Source: Protein Quality Evaluation, Report of the Joint FAO/WHO Consultation; Reference Manual for U.S. Whey Products, 2nd Edition, U.S. Dairy Export Council

PDCAAS—Protein Digestibility Corrected Amino Acid Score*: The PDCAAS is the current accepted measure of protein quality as it closely compares to determinations done with animals. Values greater than 1.0 for both the AAS and the PCDAAS are considered to indicate that the protein contains essential amino acids in excess of the human requirements.

AAS—Amino Acid Score: A chemical technique considered fast, consistent and inexpensive. It measures the indispensable amino acids present in a protein and compares the values with a reference protein. The protein is rated based upon the most limiting indispensable amino acid.

PER—Protein Efficiency Ratio: Measures the ability of a protein to support the growth of a weanling rat. It represents the ratio of weight gain to the amount of protein consumed.

BV—Biological Value: Measures the amount of nitrogen retained in comparison to the amount of nitrogen absorbed. The BV and the NPU methods reflect both availability and digestibility and they give an accurate appraisal of maintenance needs.

NPU—Nitrogen Protein Utilization: The ratio of the nitrogen used for tissue formation versus the amount of nitrogen digested.

- Whey proteins encompass a range of protein fractions including α-lactalbumin, β-lactoglobulin, serum proteins, lactoferrin and a series of immunoglobulins. Individually, these fractions are established immune-enhancing constituents that are implicated in a range of bioactive functions such as prebiotic effects, promotion of tissue repair, maintenance of intestinal integrity, destruction of pathogens and elimination of toxins.[35,52] Collectively, whey proteins are also one of very few nutritional materials shown in research to modulate both specific and nonspecific aspects of immune function using proven in vitro and in vivo models. Often, these improvements are correlated with measurable improvements in immune-meditated health.[7,19,22,32,48]

- HIV retards the cellular mechanisms that build and restore muscle protein.[57] Whey's amino acid profile is almost identical to that of skeletal muscle; it provides all of the correct amino acids in approximate proportion to their ratios in skeletal muscle.[20] Compared to other protein sources, WPC and WPI contain a higher dose (per 100 g) of the essential amino acids.[8] The essential amino acids are indispensable for activating the cellular mechanisms that promote protein accretion within muscle.[51]

- In comparison to other high quality proteins such as casein and soy, WPC and WPI contain at least a 4-fold higher concentration of the amino acid cysteine.[8] The concentration of cysteine within the body is one of the key components in the optimal biochemical environment that builds/maintains muscle mass and immune competence.[18] The concentration of this amino acid in the blood (plasma) is one of the factors thought by some scientists to regulate whole body protein metabolism, particularly in conditions that promote wasting.[21] An adequate supply of cysteine in plasma and tissues is essential to maintaining a high ratio of active glutathione (GSH) in cells, which protects against oxidative stress.[5,26] Enhanced GSH status is also associated with improved immune function[42,50] and the preservation of lean body mass, mainly muscle.[27] In comparative studies with other protein sources, whey proteins are exclusive in their ability to boost GSH status. This is thought to be a result of whey protein's rich concentration of bioavailable cysteine.[6,26,31,34,40]

- Whey proteins are the richest, naturally occurring source of branched chain amino acids (BCAAs): leucine, isoleucine and valine.[52] For the person living with HIV, the BCAAs play a pivotal role in the preservation of BCM and the immune system (see: Muscle, HIV and the Immune System). The BCAAs serve as direct precursors for glutamine synthesis and energy production within muscle.[24] The BCAAs have also been identified as key components in activating the mechanisms that restore muscle protein.[3]

- Whey proteins are digested in a manner that is most suitable to those with compromised absorption capabilities. Whey proteins are soluble, do not clot in the stomach and are absorbed rapidly.[4] They deliver more essential amino acids to tissues that result in a higher net protein gain in both young and older adults.[15] When prescribed to clinically ill patients, whey proteins are shown to be nontoxic and free of adverse effects.[5] Therefore, whey proteins are a rich source of easily assimilated protein and of all of the amino acids that appear essential to preserving/restoring BCM and immune competence. Whey protein supplementation can be combined safely with antiviral therapy but also other therapeutics that aim to preserve or restore critical BCM.

MUSCLE HIV AND THE IMMUNE SYSTEM

Skeletal muscle and the immune system are intimately related. The glutamine synthesized in muscle is the primary fuel for immune activation in cells such as enterocytes, thymocytes and neutrophils but particularly, the lymphocytes and macrophages that play such a quantitatively important role in the immune response.[13] It is important to note that even in healthy individuals, the rate of uptake of glutamine by immune cells proceeds regardless of the body's present concentration. All immune cell replication requires glutamine, yet it cannot be synthesized by immune cells.[46] One of the key aspects thought to underline muscle wasting seen with HIV infection is an imbalance between rates of muscle glutamine production and the unrelenting demand for this amino acid by the immune system.[46] HIV is a traumatic condition that generates a constant immune response that can easily overwhelm the body's ability to produce enough glutamine. Numerous studies have demonstrated that the body's capacity to synthesize glutamine is insufficient when coping with metabolic stress created by conditions such as HIV.[13,46]

Commercially available whey protein formulations such as WPC and WPI are the richest known sources of the constituents used exclusively for glutamine synthesis in muscle.[24] These constituents are the BCAAs (26%) and glutamate (6%).[8] Therefore, over one-third of whey proteins' entire amino acid profile is devoted to preserving the muscle glutamine reservoir. On a gram for gram basis, whey proteins are an economical source of BCAAs, which are indispensable to the maintenance of immune competence and the preservation of muscle tissue.

GLUTATHIONE AND HIV

The GSH antioxidant system is the principal cellular mechanism that protects tissues against oxidative stress.[56] An integral role of the immune system is to reduce oxidative stress.[17] Therefore, GSH is also indispensable to many aspects of the immune function such as lymphocyte proliferation, antibody-dependent and cell-mediated cytotoxicity, and protection of lymphocytes against superoxides produced to destroy invading pathogens.[49,56] In fact, immune competence is correlated with the concentration of GSH in the lymphocytes (T-cells).[42]

The critical importance of GSH in HIV has been confirmed in a report that demonstrated poor survival rate of HIV-infected individuals with low GSH levels in immune cells.[23] Specifically, GSH deficiency in CD4+ T-cells is associated with death within 2-3 years after baseline data collection. Conversely, the chance of survival improves when GSH is replenished and maintained.[23]

The progression of HIV infection is characterized by a systemic depletion of GSH which can develop only weeks after infection.[39] Even symptom-free HIV-positive individuals show a significant decline in GSH concentrations over a 12 month period.[41] This decline in GSH is exacerbated by oxidative stress generated by HIV and its related illnesses.[39] The GSH deficiency caused by HIV infection is thought to be due to a decrease in synthesis capacity that is secondary to a shortage of its rate-limiting precursor, cysteine.[25] Unfortunately, very few clinical trials have examined the effects of whey protein supplementation on GSH status in HIV-infected people.[39] However, whey protein supplementation has been shown to augment GSH or antioxidant status under a variety of unrelated conditions.[6,11,26,31,40,53] In comparison to other protein sources, whey proteins are exclusive in their capacity to boost GSH status and/or maintain concentrations of active GSH during conditions of intense metabolic stress.[5,6,22,26,38,40,53]

INCORPORATING WHEY PROTEINS INTO THE DIET FOR BEST RESULTS

Whey proteins are one of very few nutritional supplements that have been shown, in well-controlled studies, to enhance GSH status and/or improve other physiological parameters that promote health. However, not all types of whey proteins are the same. The beneficial effects obtained in clinical trials utilized WPC or WPI formulations that met the following criteria by: the maintenance of low temperature and a neutral pH during processing as well as a significant degree of enzyme-specific hydrolysis (selectively cleaves the protein into smaller peptide chains) to extract the whey protein fractions in their natural, intact state.

Nutritional guidelines for HIV disease support the intake of high quality proteins.[29] Despite the literature documenting a variety of benefits from supplementation with whey proteins, very few clinical trials have examined the effects of whey proteins on the health of HIV-infected patients.[1,39] More clinical trials need to be completed before clear recommendations regarding dosages can be made. However, the following suggestions are research-based guidelines on how to incorporate whey proteins into the diet to improve the health of people living with HIV.

Studies that have assessed the digestion-absorption characteristics of whey proteins show that, generally, a dose of whey protein is absorbed rapidly and provides dramatic but transient (2 hour) increase in blood amino acid concentrations.[4] Therefore, a single dose may not provide a net gain in protein within the body over the long term (4-7 hours).[14] However, a higher gain of protein within the body is obtained when whey proteins are consumed as part of a mixed-macronutrient meal, one containing carbohydrates and a small amount of fat, compared to other high quality proteins such as casein.[15]

Based on this information, it appears that to maintain or increase body protein stores, a person with HIV should take small servings of WPC or WPI (10-40 g) in small, mixed-macronutrient meals, every 3 to 4 hours. Obviously, digestion ability and food allergies will dictate nutritional choices. However, this mixed macronutrient meal profile can be easily achieved by mixing a serving of WPC or WPI in dairy, soy or almond milk. Conversely, a serving of whey protein could also be mixed in water and consumed with or soon after a regular meal. These simple strategies would enable the individual to obtain the most benefits from whey protein consumption.

Whey proteins are unique in that they are absorbed rapidly, even when consumed with other nutrients. Therefore, combining whey with other high quality proteins that are more slowly absorbed, such as casein, may provide the best overall results in body protein accretion. Combining whey proteins with casein may prolong amino acid absorption for several hours, helping to reduce protein break-down and replenish body protein stores.

Regular, moderate exercise is important for longevity in people with HIV infection. However, the ability to recover efficiently from exercise is equally as important. Whey proteins' immune-enhancing properties, excellent amino acid profile and rapid digestion kinetics make it the ideal protein to consume after exercise. To promote efficient recovery from any type of exercise, the HIV–positive individual should aim to consume a 10 to 40 g dose of WPC or WPI combined with an easily absorbed carbohydrate source (such as glucose), mixed in plenty of water immediately after exercise. The all-important post-workout meal should be consumed soon after supplementation to maintain steady insulin, glucose and amino acid levels in the blood to improve net protein gains.

Although information points to a potential beneficial effect of whey protein consumption by HIV-infected individuals on BCM preservation and immune function, much still remains to be determined on the appropriate doses and timing of intake. Clinical studies with a control group consuming an alternate protein source should be done to determine the exact effects of whey proteins, compared to other protein sources, on body composition and immune function in the HIV-infected individual. A combination of exercise and adequate or supra-optimal protein intake may be most appropriate intervention for this population group. Again, the correct amount and type of both exercise and protein intake remain to be determined.

THE IMPORTANCE OF EXERCISE IN HIV

HIV promotes muscle wasting which dramatically increases the risk of mortality. HIV impairs the cellular mechanisms that restore muscle protein so that even when body weight is regained, muscle mass is not restored.[57] Therefore, progressive resistance exercise (PRE) (the use of weighted machines, or any type of free weights) is indispensable to people with HIV. It is the most effective activity to stimulate the cellular mechanisms that restore muscle protein.[44] A small number of trials have concluded that PRE is a safe and effective strategy to increase lean muscle mass in HIV-infected patients.[1,45,58] However, exercise without the correct nutritional intervention can cause immune dysfunction and a reduction in BCM, even in individuals who do not have HIV. Therefore, the exercise program must be tailored to the health status of the individual. Particularly, when it comes to PRE prescription, more is not necessarily better. The optimum frequency of exercise for individuals who are not infected with HIV is only 3-4 PRE workouts per week. For individuals who exhibit wasting, 1 or 2 brief (10-15 minute) bouts of PRE per week will result in beneficial effects.

Whey proteins may be particularly useful to enhance the effects of PRE. They are rapidly absorbed and present a high concentration of all the essential amino acids to muscle tissue.[15] The combination of PRE and these amino acids is shown to dramatically enhance the anabolic (building) stimulus of PRE in healthy individuals.[44] Therefore, a dose of whey protein (10-40 g) should be taken just before and after each workout to boost the acute muscle building effect of PRE. As a single bout of PRE stimulates cellular anabolic mechanisms for up to 48 hours, the frequent consumption of whey protein in mixed-macronutrient meals is thought to optimize muscle tissue accretion during a PRE training program.[9,12]

This enhancement of anabolism via a combination of whey protein consumption and PRE has, however, not yet been shown in HIV patients. Only one study has specifically studied PRE and whey protein consumption to date, and found that BCM was not increased to a greater extent than with PRE alone.[1]

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