Protease and the Modulation of Inflammation

COMMENTS AND DISCUSSION BY

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Transformation Professional Protocol (TPP) Protease:
An Inflammation Modulation Product As Evidenced by an Independent Study Conducted at Baylor University by Buford et al., 2008

Transformation Professional Protocol (TPP) Protease is a unique formulation of Transformation Enzyme Corporation. It is used to enhance blood rheology, enhance the digestion of proteins, control inflammation, and help remove protein debris from the circulatory system. TPP Protease is comprised of several proteolytic enzymes (enzymes able to hydrolyze proteins) blended to provide unique benefits and able to sustain the acidic environment of the stomach (Mamadou et al., 2005) without addition of any excipients or coating agents. This particular enzyme product has been used in various areas of health and wellness including cardiovascular support, inflammation control, support of all major organ systems, sports activities, wound healing, detoxification, and as an adjunctive to chemo and radiotherapies as well as many other health or metabolic disorders. The results obtained with TPP Protease, based on many clinical observations, are remarkable and beneficial.

RECENTLY, IN AN EFFORT to specifically determine some of the biochemical characteristics involved in the action of TPP Protease as it relates to inflammation, a randomized, double-blinded, and placebo-controlled study was conducted at Baylor University (Buford et al., 2008, in preparation for publication) under the direction of Dr. Willoughby.

The specific objectives of the study were to determine the effect of TPP Protease on muscle function after strenuous exercise and on inflammation control. However, Transformation's objective was to corroborate some of the clinical observations imparted by this product, i.e., improvement in various health challenges that are characterized by inflammation.

While the present study by Buford et al. (2008, manuscript in print) focused on inflammation caused by strenuous exercise and the effect of TPP Protease to alleviate any potential damage, the overall ramifications can be extended to many other health challenges.

Physical activity, especially intense athletic or sports activities, involves increased:

- Heart activities
- Respiration: oxygen uptake and demand as well as carbon dioxide removal
- Blood circulation and load on the vascular system
- Muscle contractions, i.e., induction of "micro-injuries" within the myofibrils in an adaptation response
- Increased need of nutrients to support glycolysis, oxidative phosphorylation, and control of free radical damage
- Higher metabolic rate to meet the bio-energetic and bio-synthetic demands
- Faster rate of kidney function as well as elimination of metabolic wastes through lungs and skin

The clinical applications of TPP Protease have shown benefits in supporting the above conditions related to intense activities. More specifically, TPP Protease has been used to improve blood circulation and control inflammation.

What is inflammation? Biochemically, physiologically, or clinically, inflammation can be defined as the biological reparation response following any disruption of the cell's structural or functional integrity by injurious agent(s) (internal or external) to the body. Based on this definition, the injury brought about by the sports or athletic activities will trigger a biological reparation response. Any therapeutic agent or dietary supplement that could enhance this biological reparation response would not only be helpful in athletic events but also in healthcare, as inflammation remains a common denominator to any health challenge.

Moreover, where there is life, there is inflammation. On a biochemical level, one does not need to feel pain to be under an inflammatory condition. Pain always results from inflammation, but inflammation can occur without pain sensation. Also, based on the above definition, inflammation implies cellular injury, immune response for correction, pain sensation, and reparation and recovery. Usually when referring to exercise—especially strenuous exercise—people don't think about the inflammatory process that takes place. But inflammation occurs.

The mere fact of subjecting muscles, connective tissue, tendons, ligaments, and bones to intense activities leads to "micro-injuries" within the musculoskeletal system often characterized by the disruption of cell structures and the leaking of proteins such as myoglobin. Thus, whether a cellular/tissue injury is induced by trauma, invading microorganisms, toxins, tumor cells, or by increased load on the muscles as in intense exercise, the biological response is the same—inflammation.

Another point worth mentioning is the fact that inflammation as a trigger response for biological reparation *must* occur—this initial inflammatory process helps the body in the healing process. As it is occurring, inflammation involves various systems and resources in the body. The goal is for inflammation to take its timely course but not to persist within the body, as "uncontrolled inflammation" or chronic inflammation leads to the weakening of the whole body and the progressive onset of degenerative diseases. Thus, timely and controlled inflammation upon cellular injury must occur, however chronic inflammation must be avoided.

Many studies (Blonstein 1967, 1969; Goldberg, 1992; Howat et al., 1972) have demonstrated the role of proteolytic enzymes in modulating inflammation and in helping expedite recovery of the body from injury. Furthermore, some of the studies have indicated that although proteases do not prevent the synthesis and secretion of key cytokines involved in the inflammatory process, they do control their persistence (Desser et al., 1993, 1994; LaMarre et al., 1991).

This specific action on the cytokines is very beneficial and helps prevent the negative effects of chronic inflammation. Most of the enzymes used in those studies were animal derived and require extensive gastric acid protection by various excipients. Recent concerns on animal health and the ingestion of some of the enteric coating agents have pushed for development and use of effective and naturally gastric-stable enzymes. TPP Protease is not animal-derived and has been shown to sustain gastric acidity following oral administration, thus ensuring its beneficial effects (Mamadou et al., 2005).

It is also important to note that although oral enzymes are exogenous to the body, they do not elicit any harmful allergenic or antigenic reactions. In this particular case of oral supplemental protease, alpha-2 macroglobulin has been thought to serve as a "carrier" of oral proteases. Its coupling with some proteases allows the catalytic function to take place yet "hide" the protease from the immune system.

Study Protocol

This study, as mentioned above, was conducted in a randomized, double-blinded, placebo-controlled manner. Basically, the study was carried with 29 healthy, physically active males with an approximate average age of 22. Their selection was by consent and upon approval of the study guidelines by the University of Baylor Institutional Review Board for Human Subjects.

Following the baseline testing (**T1**), the participants were divided into two groups: one group of 14 received TPP Protease, whereas the other group of 15 received a placebo made up of cellulose. The participants received and took their respective supplements for 21 days. On day 21 the participants were subjected to another series of tests (**T2**) and underwent an intense physical exercise regimen. Immediately following exercise, the tests were performed again (**Post**) as well as at **3**, **24**, and **48** hours. The participants continued taking the supplement until all testing had been completed. Specific details of the study protocol are described in the full article.

The data collected during the study include:

- Force production
- Determination of circulating leucocytes: neutrophils, monocytes, lymphocytes, eosinophils, and basophils
- Determination of the key immunoglobulins: IgA, IgG, and IgM
- Determination of creatine kinase
- Cytokine and inflammation mediator assays: IL1, IL6, IL8, IL10, IL12, COX2, PGE2, and 8-iso-prostane
- Determination of the serum level of Superoxidase dismutase (SOD)
- Determination of the expression of some genes such as COX2, IL6, IL8, NFkB, IL12, TNFα, IL1β, IL8
- Average daily nutritional intake based on some key nutrients: caloric intake, fats, proteins, carbohydrates, and the vitamins E and C

Discussion of Study Results

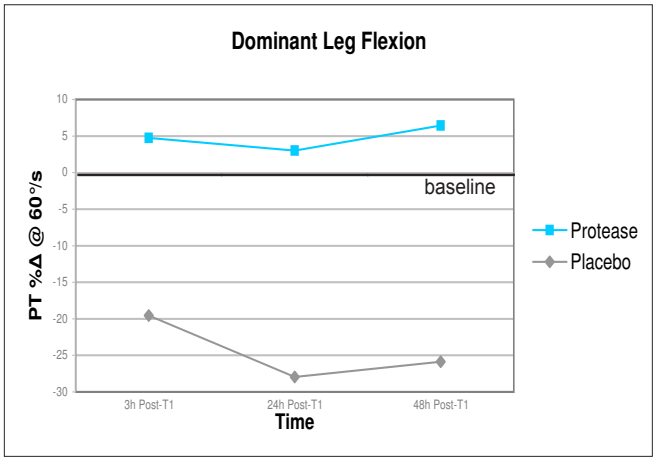

***Figure 1**: Dominant leg flexion*

In the above graph (Figure 1) depicting the force production during flexion, the protease group showed increased force production from baseline as compared to the placebo group. In the Figure 2 below, both groups showed decreases in force production during the extension movements. However, despite the decreases in force, the protease group performed better than the placebo as shown in the figures. These results indicate that TPP Protease improves force production and will help in athletic performance.

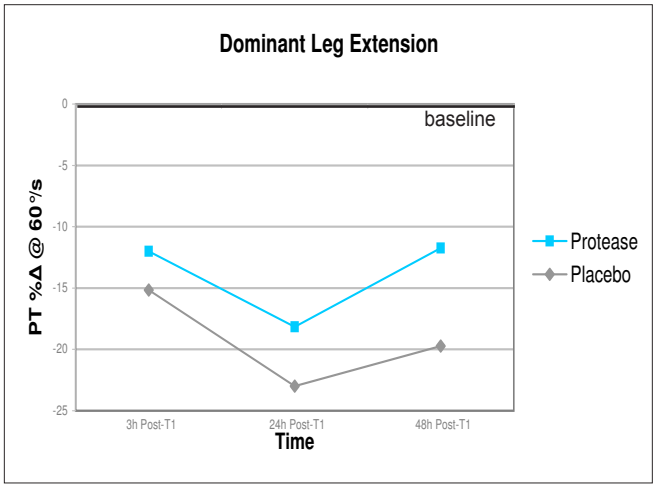

***Figure 2**: Dominant leg extension*

Figure 3 depicts the levels of creatine kinase in both groups and as a function of various times. As creatine determination is indicative of muscle damage, this study showed that no significant differences were observed between the two treatments. As the authors indicated, the TPP Protease did not prevent the damage. Both groups had a similar pattern of creatine kinase levels as a function of time, although the levels seen in the TPP Protease group appeared higher though not statistically significant.

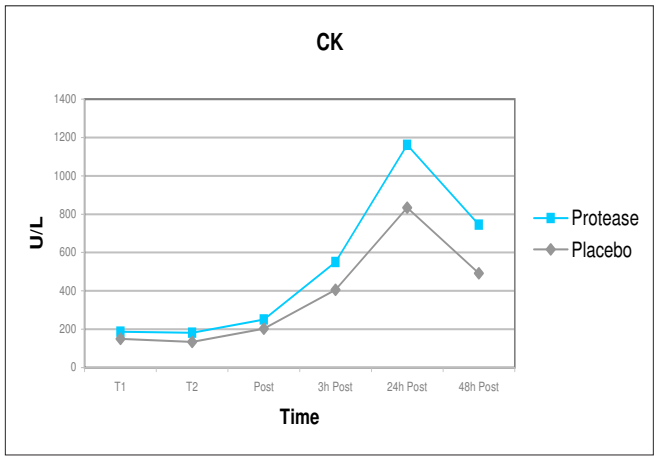

***Figure 3**: Creatine kinase concentration in serum as a function of treatment and at different times post-exercise*

This observation may also be indicative of the capacity of the muscles in the protease group to take more load, as noted in the force production Figures 1 and 2. That increased force may lead to more myofibril adaptation response, thus more creatine kinase release. In fact, one positive outcome is to induce more adaptation response, thus enhancing muscle growth and bioenergetics capability. As the protease group produced more force, it could also be conceivable that the injury/pain sensation was more tolerable despite the increased cellular impact, as evidenced by its creatine kinase levels. This result supports the use of TPP Protease as part of routine athletic/sports supplementation.

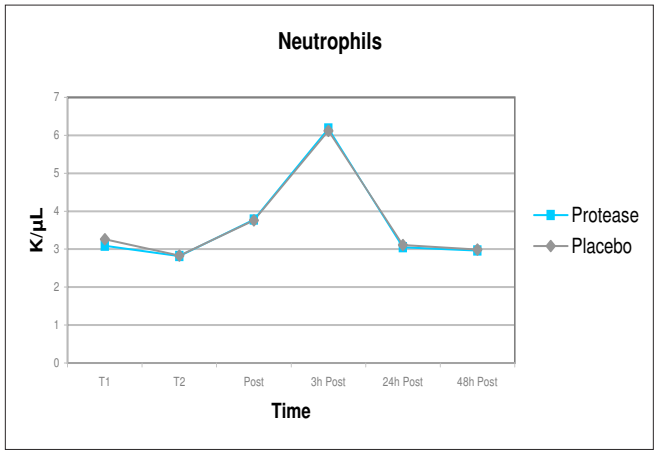

***Figure 4**: Neutrophil count as a function of treatment and at different times post-exercise*

Neutrophils are white blood cells that are abundant at the site of inflammation within a short time after cell/tissue injury. The data in Figure 4 showed that the neutrophil accummulation profile was basically the same between the two groups and also in a time-dependent manner following the strenous exercise. By 24 hours

post-exercise, the levels returned to baseline. From immediately post-exercise to 24 hours later, the neutrophil population pattern was the same in the two groups. However, it is not clear whether that pattern is identical through that time period. A closer interval of sampling and analysis may reveal a different pattern between the two groups.

It is possible that TPP Protease helped control the inflammatory process by returning the levels to baseline much faster than in the placebo group. Clinically, this will indicate an acceleration in tissue recovery from any damage. Future studies may fully address that point and determine the mechanisms of action involved. In either case, the fact that neutrophils showed this pattern indicates that the supplement did not prevent an inflammatory response to the tissue "injury" caused by the strenous exercise.

This data in correlation with the force production data indicate that not only does TPP Protease not prevent tissue adaptation to muscle growth but it does increase force production. Thus, this is another benefit for athletic performance as well as to other conditons such as repair after surgery or radiation.

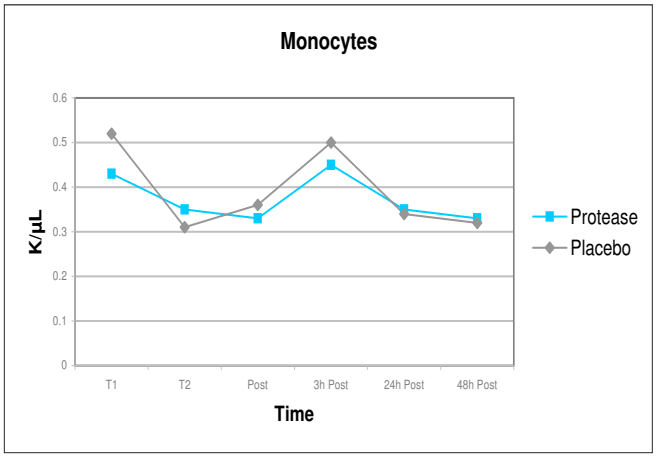

***Figure 5**: Monocyte count as a function of treatment and at different times post-exercise*

Monocytes are types of white blood cells that are released at sites of tissue injury and help supply macrophages and dendritic cells to help control the inflammatory process. Although Figure 5 showed a time effect in the numbers of the monocytes as a result of the strenous exercice, there was no statistical difference between the two treatment groups. This observation also indicates that tissue injury was not prevented by the TPP Protease.

As stated above, an initiation of the inflammatory process helps the reparation process and should not be prevented. It is very important to emphasize the fact that inflammation should take place and the role of TPP Protease is both to modulate that inflammation when it does occur as a result of any injury and to control it from being chronic. On a larger scale of application, this result serves to emphasize the benefit of TPP Protease in the treatment of many health challenges.

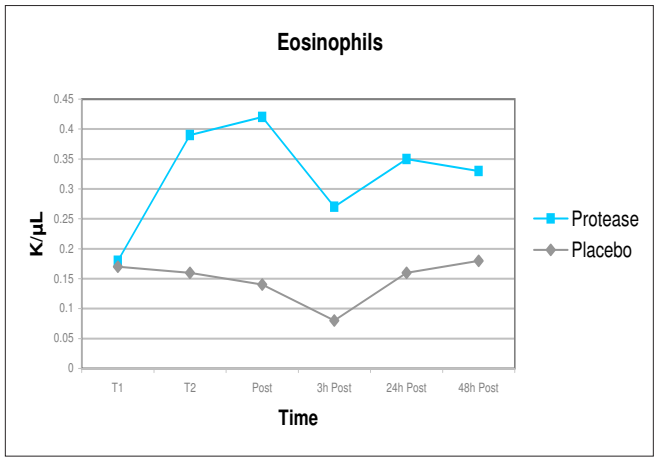

***Figure 6**: Eosinophil count as a function of treatment and at different times post-exercise*

Another group of white blood cells involved in inflammation control is the eosinophils. The data in Figure 6 showed a time-dependent population change as a result of the physical exercise endured by the subjects. However, contrary to the other white blood cells discussed above, the eosinophils showed a treatment response in their numbers when comparing the protease group and the placebo.

The increase of the various white blood cells, especially in response to the ingestion of TPP Protease without adverse allergic or hypersensitive effect, may be attributed to the interaction with alpha-2 macroglobulin and also to the tissue damage induced by the strenuous exercise rather than the supplement. The placebo is made of a cellulose molecule, a relatively "simple molecule in its repeating composition" and usually not antigenic.

This time-dependent increase in the eosinophil population in response to the exercise and to the TPP Protease administration is an indication of a normal functioning and controlled immune response as seen by the numbers of the eosinophils returning to normal levels.

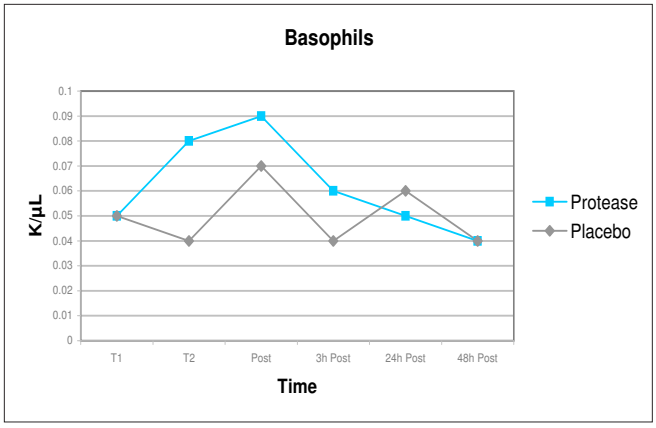

***Figure 7**: Basophil count as a function of treatment and at different times post-exercise*

Basophils are white blood cells that respond mostly to agents that can trigger an allergic reaction. The numbers of basophils as shown in Figure 7 were time-dependent and a function of the exercise activity. Furthermore, their relative high numbers in the protease group compared to the placebo group may be a result of the fact that the supplement contains a blend of enzymes that are exogenous proteins to the body. Although they could trigger an immune reaction, the oral immune tolerance as well as the biochemical action of alpha-2 macroglobulin help prevent a negative action on the body. However, as the data indicated, the levels of basophils, although high in the early phases of supplement administration, started to decline post-exercise and the levels then returned to baseline level.

This initial high number in the basophil should not be of concern, but rather an indication of a responsive immune function. It should also be noted that any elevation of the immune cells may be resulting from the exercise-induced micro-injuries within the muscle fibers and not from the supplementation. This actually seems to be the case as the data on the immunoglobulins (Figures 8, 9, and 10) did not show any statistical difference between the supplement group and the placebo group.

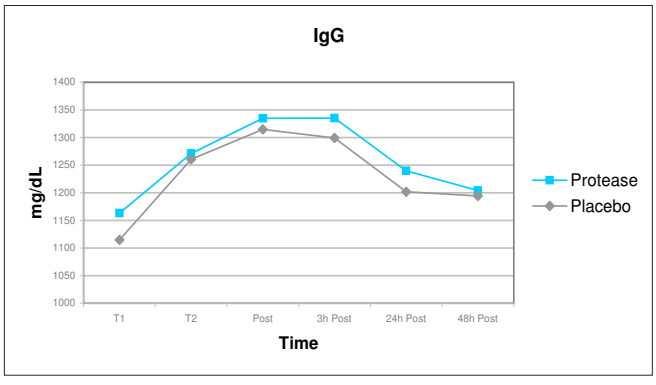

***Figure 8**: Serum concentrations of IgG as a function of physical exercise and protease supplementation*

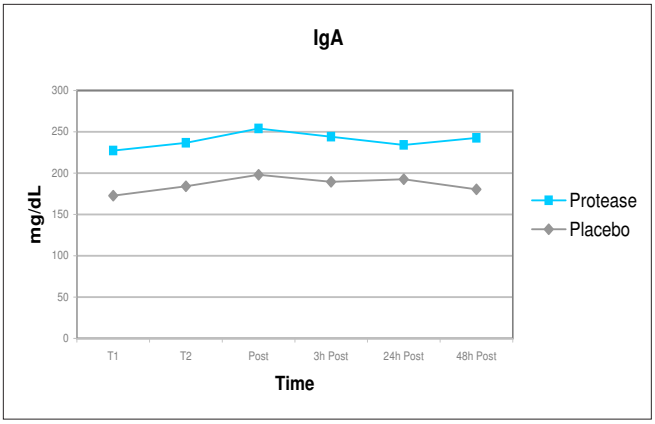

***Figure 9**: Serum concentrations of IgA as a function of physical exercise and protease supplementation*

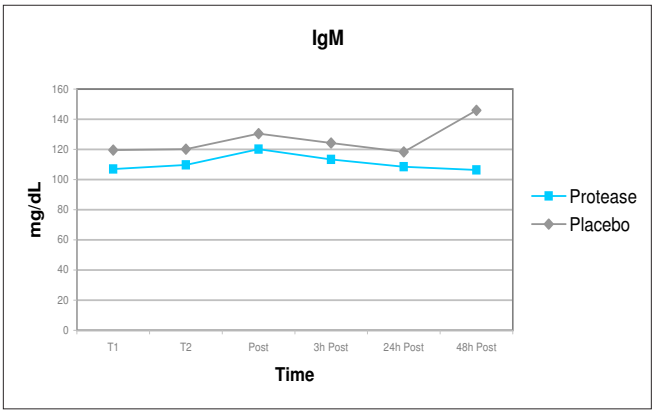

***Figure 10**: Serum concentrations of IgM as a function of physical exercise and protease supplementation*

The data in Figures 8, 9, and 10 represent the serum concentrations of IgG, IgA, and IgM—antibody classes secreted by B cells in response to antigens encountered by the body. There were no differences between the treatment groups, although some time-dependent numbers post-exercise were different. The fact that there were no differences in immunoglobulins may just indicate a normal response to the oral intake of some components of the TPP Protease and their interactions with the gut immune system. This is actually a normal response to help build oral tolerance. Also, the immunoglobulins were not specific, so it is difficult to determine the antigen(s), if any, that triggered the antibody increases.

Cytokines are small polypeptides with hormone-like function acting primarily on immune cells. They are tightly regulated in their synthesis, secretion outside of the cells, and lifespan within circulation (Arai et al., 1990). This tight regulation is to prevent an overacting of the immune system and inflammatory response. However, in an unhealthy system with chronic inflammation, there is continuous synthesis and secretion of various cytokines that ultimately undermines health.

The 3 cytokines TNF, IL1β, and IL6 together trigger the synthesis of acute phase proteins, including C-reactive protein and alpha-2 macroglobulin. For instance, IL6 induces formation of fibrinogen in an attempt to control bleeding. In addition, the role of alpha-2 macroglobulin is to protect against tissue injury by controlling the effects of endogenous proteases (see *Oral Enzymes: Facts and Concepts* by Dr. Mamadou).

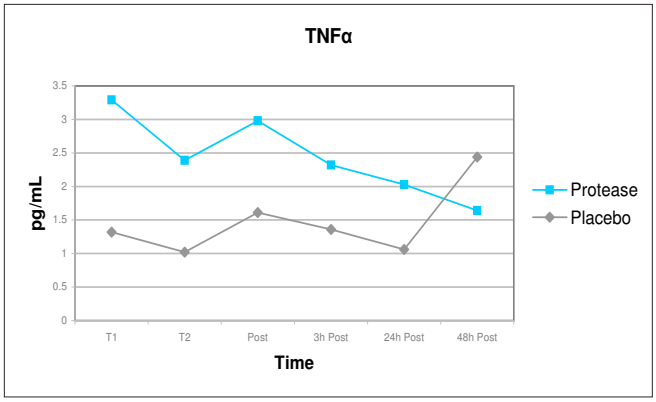

***Figure 11**: Serum concentrations of TNFα as a function of physical exercise and protease supplementation*

TNFα (tumor necrosis factor alpha) is another cytokine that plays an important role in inflammatory response. It actually stimulates the secretion of IL1 and IL6. The secretion of TNF needs to occur in any type of inflammation or disease condition. However, it is its persistent secretion and long-term effect on the body that could be harmful. Therefore, a controlled synthesis and secretion of TNF is beneficial.

In Figure 11 above, TNFα levels were high in the early phases of the study, but as a result of the intake of the supplement, the levels came down below baseline while the placebo group showed increases. This is an exemplary observation of what has been attributed to oral proteases during inflammation control: oral proteases induce the synthesis and secretion of TNFα, and in a timely manner reduce the levels of that cytokine to normal level. The data in the study confirmed that observation! However, in the placebo group, it can be noted that the TNF levels are increasing 24 hours post-exercise: that is not a desirable condition.

The contrast between the effect of the supplement and that of the placebo is remarkable: the protease supplement controls inflammation while the placebo may continue the inflammatory process. As TNFα modulates many other cytokines and immune cells, it can be seen that by modulating TNFα, TPP Protease controls inflammation. This particular observation is fundamental in the use of TPP Protease as an adjunct therapeutic agent for any health disorder.

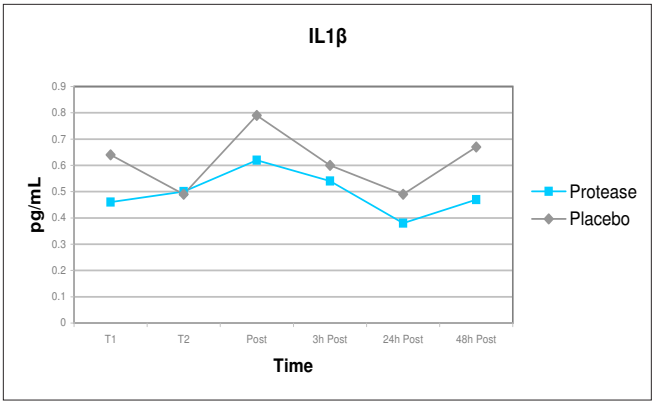

***Figure 12**: Serum concentrations of IL1β as a function of physical exercise and protease supplementation*

Interleukin 1β is a mediator of inflammatory response and is mostly synthesized by activated mononuclear phagocytes but also by epithelial cells and endothelial cells. In high concentrations within the blood circulation, IL1β induces fever which triggers the inflammatory response of the liver including a blood pro-coagulation effect and also promotes catabolism. The levels of IL1 were relatively lower in the supplement group than the placebo group. This trend helps control the persistence of pro-inflammatory conditions in the body and alleviates the onset of chronic inflammation and its negative impact on the body.

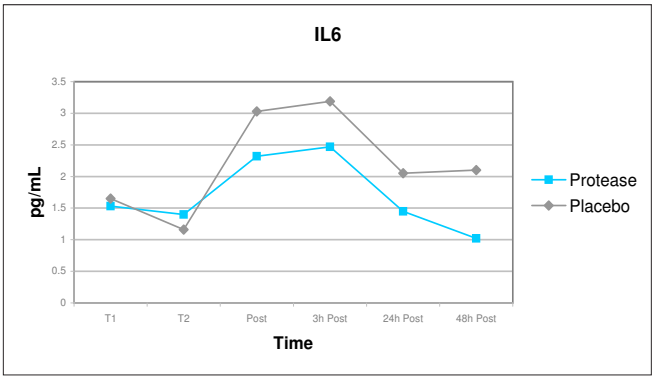

***Figure 13**: Serum concentrations of IL6 as a function of physical exercise and protease supplementation*

IL6 is another cytokine involved in the inflammatory process and is synthesized in response to IL1β and TNF by immune cells. The serum concentrations of IL6 were not statistically different between the treatment groups. However, the protease group had much lower serum concentrations of IL6 than the placebo group, indicating a good inflammation control benefit, as IL6 is a major pro-inflammatory cytokine promoting fever and high levels of acute phase liver proteins. Its persistence is not desired, and TPP Protease controls its synthesis and secretion by reducing the levels when needed. Further studies may need to be conducted to determine the mechanisms of TPP Protease's effect as

well as the impact of this supplement on the various acute phase proteins such as C-reactive proteins and levels of fibrinogen, for instance.

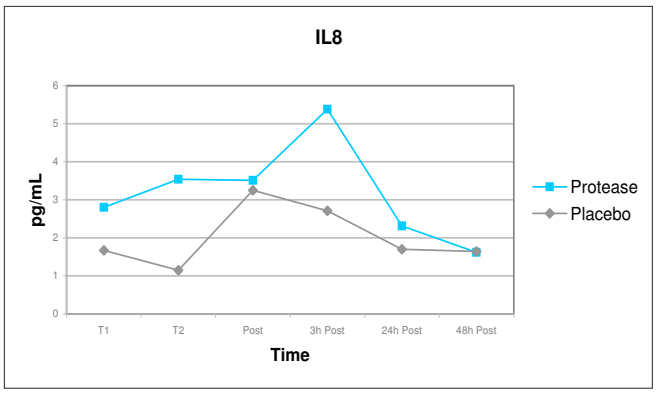

***Figure 14**: Serum concentrations of IL8 as a function of physical exercise and protease supplementation*

IL8 is a cytokine with a chemo-attractant role. Basically, it promotes the migration of various immune cells to the site of injury, thus playing a key role in mediating inflammation. The fact that there was an increase in IL8 in the protease group may be an indication that TPP Protease increased the migration speed to repair any damage inflicted by the strenuous exercise. Thus, upon exposure to TPP Protease, although the protease molecules may be "carried" by alpha-2 macroglobulin, there may be some triggering of the macrophages releasing IL8 which in turn attracts the neutrophils to the inflammation site(s). This migration of neutrophils could also be induced by TNFα, or the effect may be due to the exercise but enhanced by the supplement.

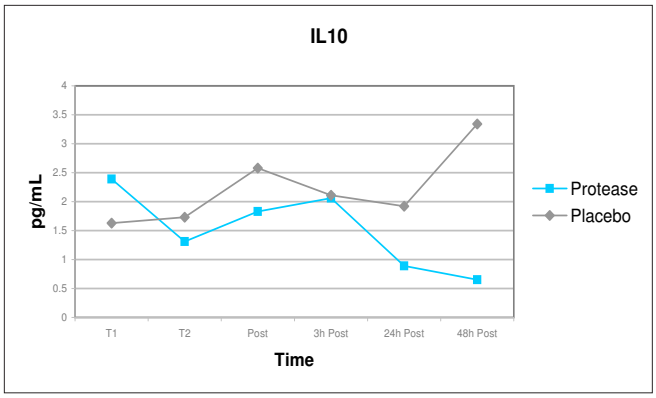

***Figure 15**: Serum concentrations of IL10 as a function of physical exercise and protease supplementation*

IL10 is an anti-inflammatory cytokine that is involved in controlling the synthesis/secretion of some pro-inflammatory cytokines such as TNFα. The study indicated that there were no statistical differences between the treatment groups. However, there was a time-dependent effect related to the physical activities of the subjects in the study. The exact reasons for the IL10 pattern in this study are not known. However, it could be speculated that the relative lower concentrations of IL10 in the protease group allowed the initial increase of TNF in the protease group to mediate the inflammation process.

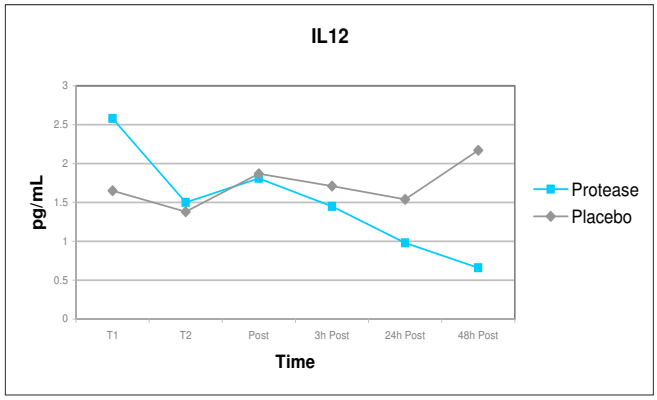

***Figure 16**: Serum concentrations of IL12 as a function of physical exercise and protease supplementation*

IL12 is another cytokine that is involved in controlling inflammation. It is particularly known to stimulate natural killer cells, control angiogenesis, and stimulate the production of TNFα. Based on the study results, there were no significant differences between the two treatment groups. The levels of IL12 continued to drop post-exercise—a benefit that could be attributed to TPP Protease. This decrease may also be involved in reducing the levels of TNF after an initial triggering of its production. Studies have shown that decreased levels of IL12 help control some auto-immune disorders. Thus, based on these results, TPP Protease should be considered as a good candidate in the management of auto-immune disorders.

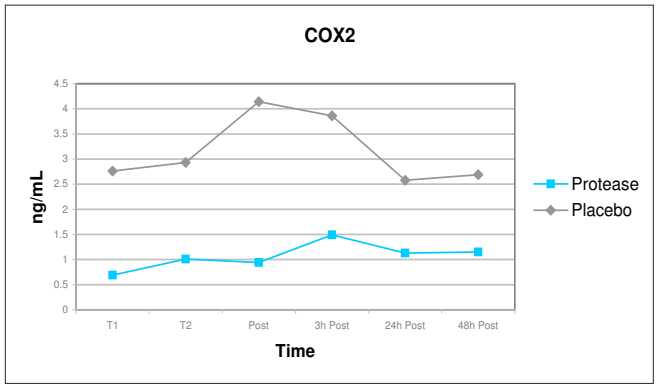

***Figure 17**: Serum concentrations of COX2 as a function of physical exercise and protease supplementation*

COX2 (cyclooxygenase 2) is an enzyme involved in pain and inflammation. Several pharmaceutical drugs are in use to help control its activity to alleviate pain. However, those drugs are not without major side effects. Alternative treatments are continuously being sought to

provide pain relief without harmful effects on the body. The study revealed that COX2 activity was higher in the placebo group compared to the protease group where the levels of COX2 activity were significantly lower, thus alleviating the pain sensation in those subjects. This finding may also explain the tolerance of that group in sustaining the load and performing better, as shown in Figures 1 and 2. The role of TPP Protease in alleviating pain has been noted by many athletes, clinicians, and patients. This finding by the group at Baylor lends more scientific basis to the clinical observation that TPP Protease is an effective pain management product.

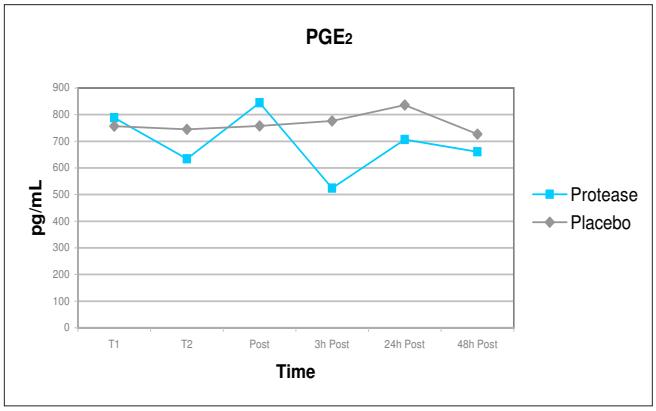

***Figure 19**: Serum concentrations of PGE2 as a function of physical exercise and protease supplementation*

PGE2 is a prostaglandin that provides vasodilation and can also induce fever. In the Baylor study, it appeared that the levels of PGE2 in the protease group were lower than in the placebo control group. The data here indicate that TPP Protease may help in alleviating further inflammatory damage to the tissues.

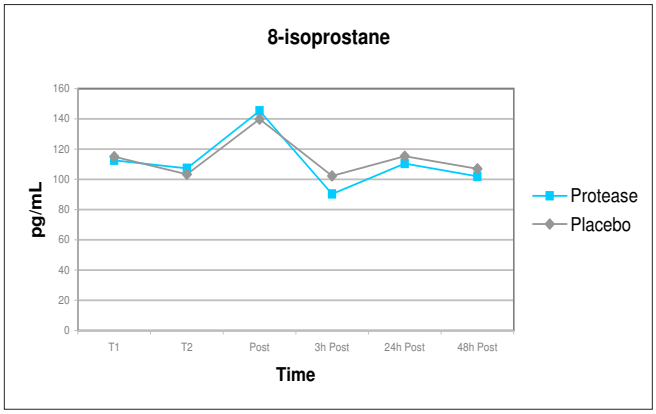

***Figure 18**: Serum concentrations of 8-isoprostane as a function of physical exercise and protease supplementation*

Isoprostane is a good marker of oxidative stress. As a result of the physical exercise and increased demand in oxygen supply as well as the oxidative phosphorylation process of the bioenergetics involved, there will be excessive formation of reactive oxygen species (ROS).

The levels of isoprostane were increased in both groups. The differences between the groups were not statistically significant although there were significant differences due to times post-exercise. Although the profile of isoprostane variation is similar in both treatment groups, it may be interesting to determine how quickly the protease blend will help reduce those levels by managing the overall oxidative stress through removal of oxidized proteins and improvement in blood circulation and inflammatory control. This aspect could be studied in future research.

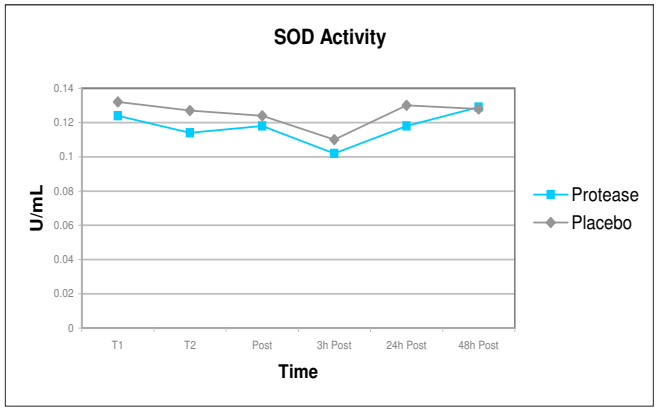

***Figure 20**: Serum activity level of SOD as a function of physical exercise and protease supplementation*

Another molecule with good antioxidant activity in the body is superoxide dismutase (SOD). Its level of activity was assayed in the Baylor study. The levels of SOD activity are indicative of intense free radicals in the body as a result of the physical activity and the generation of the ROS. The fact that the supplement group had a relatively lower level of SOD may indicate a lesser generation of ROS or a faster reduction of the oxidized molecules, thus reducing the need for SOD. In either case, TPP Protease is a good supplementation in controlling free radical-damaged proteins.

Conclusion

Inflammation is a common denominator to any pathological condition and occurs as long as the body is functioning. The causative agents may be varied, but the body's basic response is the same (see *Dr. M's Science Notes, v11 and v12: Cellular Injury*).

While the Baylor study used strenuous exercise to induce inflammation, the data points are characteristic of any pathological condition such as trauma, microbial infection, tumor growth, etc. Thus, the effect of TPP Protease on the treatment and influence on the various data points could be extended to many other health challenges.

One of the functions of orally administered proteolytic enzymes used as adjunct therapeutic agents is to trigger the inflammatory response but also control it. That function has been verified in many studies. TPP Protease as a unique dietary supplement has also been shown in the Baylor study (Buford et al., 2008) to enhance muscle performance but also control inflammation.

Contrary to other studies that have used animal-derived enzymes that require enteric coating, this study has used a fungal/plant enzyme blend that was shown to be gastric acid-stable and functional—TPP Protease is not animal-derived and does not need enteric coating for stability and activity (Mamadou et al., 2005). As these enzymes maintain their structure and function in the gastrointestinal tract, they are also absorbed and impart their systemic benefits as shown in the data.

One important aspect in triggering an inflammatory response is the synthesis and secretion of the various cytokines. As stated, it is important to secrete the cytokines, but their persistence in the system must be avoided to prevent chronic inflammation of various diseases. The levels of the various cytokines and mediators observed in the study contribute in proving that TPP Protease does not prevent the defensive benefit of inflammation in mobilizing the body's reparation process. Furthermore, TPP Protease helps control the cytokines to prevent the onset of chronic inflammation and its negative impact on the body.

This study is the first in its scope in delineating some of the mechanisms by which the clinical observations made by healthcare professionals, athletes, and patients could be explained scientifically.

Transformation's Professional Protocol (TPP) Protease is a unique proteolytic blend formulated to enhance blood circulation, control pain, and modulate inflammation. It is a valuable dietary supplement to be used as an adjunct therapeutic agent to manage pain and control the debilitating effects of inflammation. Inflammation occurs as long as there is life. An objective of any wellness plan is to control it directly or indirectly. TPP Protease is a proven candidate in helping achieve that needed inflammation control.

For additional information, please refer to *Stability and Activity of Supplemental Digestive Enzymes in a Simulated Gastric Fluid Environment: Quantitative Evidence Proving the Efficacy of Supplemental Enzymes*, a research brief by M. Mamadou, Ph.D.

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