The Clinical Relevance of *Bioimpedance Analysis (BIA)*

Jeffrey Bland, Ph.D.
President and Chief Science Officer
Metagenics, Inc.

Recently it has been demonstrated that body fat is more than just the storage of excess Calories. Body fat stored within the adipocyte cell has been shown to be metabolically active and a component of the neuroendocrine immune system. As such adipose tissue produces messenger substances such as the inflammatory cytokines IL-1 and TNF-α that may contribute to the origin of heart disease, insulin resistance/Type 2 diabetes and other chronic illness associated with obesity (1). The production of cytokines may also contribute to the loss of muscle protein through an accelerated catabolic process.

Analysis of body composition over time in the adult may then provide for an indirect marker of inflammation-related chronic disorders associated with increased body fat and reduced body protein stored in muscle and organs (2).

The Lean Body Mass Connection to Inflammation

This emerging story suggests that body fatness that is associated with increases in the levels of inflammatory cytokines can have adverse impact on protein synthesis and muscle function.[i] Recent studies have shown that cytokines can directly influence skeletal muscle contractility independent of changes in muscle protein content.

In situations in which there is an increase in inflammatory signals, production of IL-1, IL-6, and TNFα in white cells is enhanced, as is that of nuclear factor kappa B (NFκB). NFκB has been implicated in autoimmune

and inflammatory disorders, and infection. Its production is increased as a consequence of an inflammatory event that shifts toward the proinflammatory cytokines.[ii] In situations of increased expression of NFκB and downstream elaboration of proinflammatory cytokines, there is alteration in muscle protein metabolism and function.

Nutritional factors, per se, cannot fully explain these conditions. Humoral mediators, including the TH1 cytokines, appear to influence protein nutritional status by directly impairing the regulation of skeletal muscle protein turnover. Extensive research is currently ongoing in an effort to identify specific nutritive factors that can influence cytokine production and promote regular catabolic activity on the muscle cell.

Under conditions of physiological stress and increased body fatness, there is increasing production of proinflammatory mediators and loss of muscle, which has been called sarcopenia (*sarc*-flesh, *penia*-loss of).[iii]

Obesity and the Relationship to Inflammatory Mediators

As was mentioned previously the adipocyte cell produces inflammatory cytokines. **Obesity, therefore, may be viewed as a low-grade systemic inflammatory disease**.[iv] Overweight and obese children and adults are well known to have elevated serum levels of high-sensitivity C-reactive protein, interleukin-6, TNF, and leptin, all of which are known markers of inflammation closely associated with cardiovascular risk factors.

Extreme obesity is known to be associated with heart failure. It has recently been found that lesser degrees of obesity also increase the risk of heart failure. The risk of heart failure increases with increases in body mass index.[v] The most interesting observation from this research is that obesity may result from an underlying disturbance in physiology through the altered neuroendocrine-immune function that in turn produces heart failure.[vi]

The problem may not be obesity itself, but a shared mechanism mitigated through inflammatory processes resulting in heart failure. This

hypothesis may shed important light on the increased risk of diabetes, heart disease, and other chronic diseases in the obese individual as it relates to inflammatory potentiation.

It is important to recognize that loss of muscle and replacement by body fat occurs well before an individual exhibits a significant alteration in body mass index. (Body mass index equals height in meters squared divided by weight in kilograms).

Sarcopenic Obesity and Disease Risk

Heber and his colleagues at the Division of Clinical Nutrition of UCLA School of Medicine evaluated body composition using bioelectrical impedance analysis (BIA) in 233 females and 73 males. The surprising result of this study was that the BIA showed a high prevalence of sarcopenic obesity in 28 out of a subgroup of 30 premenopausal women who were at increased risk to breast cancer. These were women who had normal body height-to-weight ratios, but who, upon analysis of body composition by BIA, had increased levels of body fat and decreased muscle. Heber uses the term "sarcopenic obesity" to describe this condition, meaning loss of muscle and replacement by body fat.[vii]

This study points out the need to determine the metabolic and clinical significance of sarcopenic obesity and the potential influence of various factors pertaining to the modulation of inflammatory cytokines on this condition. Sarcopenia is related to altered functional capacity of the individual. **The symptoms found in those patients included sarcopenic obesity were weakness, fatigue, depression, immune hypersensitivity, and inflammation.** Altered aerobic capacity, altered immunological function, and altered hormone levels are commonly associated with sarcopenic obesity and may represent a physiognomy associated with altered biotransformation and changes in cellular signaling.[viii]

Bioelectrical Impedance Assessment as a Clinical Tool

BIA is an important clinical tool for any clinician in evaluating the metabolic status of patients. It is inexpensive and noninvasive, and it provides useful information concerning altered body composition and membrane potential at the tissue level measured by phase angle. Phase angle is defined as the relationship between the two vector components of impedance: resistance and reactance. Phase angle has been used as another way of interpreting BIA (3). **As the resistance decreases, there is a breakdown in membrane compartmentalization of cells with a loss of electrolyte balance, which reduces the phase angle.** A reduction in phase angle when measured serially in a patient has been associated with states of chronic or acute illness.

Both percent body fat and phase angle can be useful tools in defining aspects of the overall cell signaling process and physiological status in the "whole organism," which represents a balance between muscle and fat cell physiology. A number of studies looking at BIA of individuals from young to older ages have shown a general trend toward lower fat-free mass after the age of 50.[ix] A recent study used BIA to assess body composition of 995 acutely or chronically ill patients at hospital admission and found that the fat-free mass was significantly lower and fat mass was significantly higher in the patients, as compared to 995 healthy age- and height-matched controls.[x]

An understanding of the amount of fat-free mass of an individual and the relative phase angle can be useful for assessing imbalances related to chronic health problems that may derive from endocrine disturbances, oxidative stress, imbalances in biotransformation, or poor nutritional status.

Phase Angle as a Prognostic Indicator

A study comparing 131 patients on chronic hemodialysis with 272 age- and sex-matched healthy controls found a change in phase angle was the strongest predictor of poor prognosis in the hemodialysis patients. It seemed to be a reliable detector of clinically overt depletion of lean body mass and

changes in intracellular electrolyte and fluid balances.[xi] **The strong association of phase angle with patient survival in this study suggests that bioimpedence index reflects a dimension of the illness beyond deranged nutritional status.** This concept suggests phase angle is a potentially important clinical tool in assessing the trajectory of general health of the individual.

Another study demonstrated that patients with both overt and subclinical thyroid disease had altered phase angle and bioimpedence values. This study suggests it may be a useful tool in the management of patients with complex endocrine metabolic dysfunctions.[xii] **Phase angle, in a sense, might be thought of as an indirect measure of cellular redox potential.** As the phase angle decreases, there is the loss of electrochemical gradient and lowered bioenergetics at the cellular level.

Sarcopenia and Basal Muscle Protein Synthesis

It has become more apparent that loss of muscle mass and replacement by body fat result from more than a poor-quality diet and lack of exercise. Instead, this shift in physiognomy appears to be the result of a complex interaction between cellular physiology and cellular messengers that may induce loss of muscle function and integrity, resulting in a reduced fat-free mass. A study by Volpi et al. demonstrates this concept.[xiii] **Using a sophisticated amino acid double-labeling technique, these investigators found the presumption of a decreased protein biosynthetic rate in old versus young men does not appear to be true.** They found net muscle protein balance was similar in young and old men, and only very small differences were found in mean muscle protein synthesis or mean muscle protein breakdown in a comparison of older and younger men.

The most important result, however, was that differences in basal muscle protein turnover between younger and older men do

not appear to explain the muscle loss that occurs with age. Instead, other secondary factors influence the physiology of the muscle cell that may contribute to loss of muscle protein with age. In a companion editorial titled "Sarcopenia—Understanding the Dynamics of Aging Muscle," Roubenoff and Castaneda describe this process.[xiv] In commenting on the Volpi paper, the authors wrote:

> "These observations strongly suggest that sarcopenia is not due to inadequate basal (fasting) protein synthesis. More likely, aging muscle fails to respond to stimuli that are anabolic to young muscle – e.g., diet and exercise -- perhaps because of hormonal or immunological changes that occur with age and no longer favor anabolism... Taken together, these two studies [this study and an earlier one by Volpi's group] implicate insulin resistance or immune factors, such as catabolic cytokines or other hormonal or immunological factors, acting primarily in the postprandial state as an important cause of sarcopenia."[xiv]

The objective in this study was to determine why older men tend to lose muscle mass as contrasted to younger men. The long-held belief has been that older men lose muscle principally as a consequence of lowered protein biosynthetic capability. For that reason, most people have felt there is little an individual can do about that loss.

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Sarcopenic obesity triggers the release of the inflammatory mediators create a cellular environment in post-mitotic tissue The messenger molecules that stimulate this particular process are alarm molecules associated with physiological, chemical, traumatic, and psychosocial stresses. The biotransformation of these molecules associated with stress and sarcopenic obesity and their resulting accumulation or elimination from the body is therefore critically important in determining the signals the genes receive to alter cellular function.

Phosphorus 31 Nuclear Magnetic Resonance Spectroscopy (NMR) and Bioimpedance Analysis

Phosphorus 31 nuclear magnetic resonance spectroscopy (NMR) has been used to evaluate mitochondrial function in muscle. In a study of individuals who were suffering from disorders associated with malnutrition and increased levels of proinflammatory cytokines, Khursheed Jeejeebhoy and colleagues found phosphorus 31 NMR was capable of detecting bioenergetic changes in muscle.[xv]

Phosphorus 31 NMR analysis of the patients was used to evaluate the ATP dynamics in muscle because it can evaluate the presence of ATP, ADP, AMP, and inorganic phosphorus, as well as phosphocreatine in muscle. Therefore, it can be used as a noninvasive tool to look at aspects of mitochondrial bioenergetics. **The results of this research indicated a correlation between changes in body composition as measured by BIA and muscle energy dynamics.**

Using this same Phosphorus 31 analysis technology, Dr. Robert Hackman and colleagues evaluated modestly overweight women who were placed on a medical food intervention program, along with a regular walking regimen. After following this program for several weeks, phosphorus 31 NMR revealed that the women had significantly improved body composition, lowered body fat and increased fat-free mass (muscle mass gain), as well as increased bioenergetics.[xvi] **The program resulted in preservation of muscle energy function, loss of fat mass, and preservation of lean muscle mass with improved phase angle on the BIA.**

A companion study used the same nutritional supplement that is high in soy protein with phytonutrients, vitamins, and minerals in another group of modestly overweight women. This program resulted in a reduction in blood cholesterol, increased muscle mass, and lowered body fat. This study compared the nutritional supplement to an over-the-counter weight-loss

product. Although the two programs resulted in the same weight loss over 12 weeks, most of the weight lost using the commercially available, over-the-counter product came as muscle loss and not as fat loss.

The nutrient-dense, phytonutrient-rich product, in contrast, resulted not only in the loss of weight as fat, but also in a reduction in blood cholesterol.[xvii] At the close of the study, the authors stated, "This difference (between the two products) may be due to endocrine-modulated effects associated with differential aspects of nutritional quality between the two programs."

Increasing evidence indicates that altered body composition, as seen with obesity, overweight, and sarcopenia is a consequence, at least in part, of nutritional, environmental and lifestyle changes that result in early changes in body composition as measured by BIA.

Given these associations between health and body composition, BIA represents a primary tool for assessing the trajectory of health of the individual and should be a component of every patient evaluation. Longitudinal studies of a patient's body composition over time by BIA is an invaluable tool in personalizing a program to the individual needs of the patient.

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