Editorial

Rheumatoid Cachexia: What Is It and Why Is It Important?

Rheumatoid cachexia (RC) is common, probably underappreciated, and incompletely understood. It is important to recognize this, because these patients can often be helped.

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease affecting more women than men, with a prevalence of 0.5%–1% in the United States[1,2]. Nearly two-thirds of patients with RA have a metabolic abnormality accompanied by wasting of muscle mass, with the presence of stable or even increased fat mass[3]. This is referred to as RC. This condition is seen without any evidence of malabsorption or impaired renal or liver function.

RC was first described by Sir James Paget over 100 years ago. It is derived from the Greek word meaning "bad condition"[4]. It is a major cause of weight loss and increased mortality and morbidity in patients with RA.

While cachexia generally reflects advanced malnutrition and wasting, we now know that this term more specifically refers to a loss of body cell mass (BCM). BCM is clinically relevant as loss of more than 40% of baseline BCM is associated with death[5]. With even as little as 5% loss of BCM, there are demonstrable changes in morbidity, including reduced muscle strength, altered energy metabolism, and increased susceptibility to infections[6]. The average loss of BCM among patients with RA is 13%–15%, about one-third of the maximum survivable loss of BCM[3].

Patients with RA have a 2-fold to 5-fold higher mortality rate than the general population because of increased risk of infections[2]. Thus, RC should be viewed as an important contributor to increased morbidity and premature mortality in RA. Understanding the metabolic abnormalities and mechanisms involved in the development of RC may help to identify potential new therapeutic targets.

Three weight-losing syndromes, associated with different disease states, have been defined. These are cachexia, starvation, and sarcopenia[7]. In cachexia, lean body mass (LBM) is lost while fat mass tends to be maintained or even increased so that body weight, at least in the early stages, can remain stable. Cachexia, which occurs in the context of a chronic inflammatory response in diseases such as RA, cancer, acquired immunodeficiency syndrome, cardiac failure, tuberculosis, inflammatory bowel disease, and chronic lung disease, is always associated with a poor prognosis and cannot be treated with protein-energy repletion alone. BCM is the most metabolically active component that determines energy expenditure, protein requirements, and the metabolic response to physiological stress. BCM consists primarily of muscle mass, with visceral mass (serum proteins, erythrocytes, granulocytes, lymphocytes, liver, kidneys, pancreas, and heart) and immune cell mass. Fat mass, extracellular water, connective tissue (cartilage, fibrous tissues, and skeletal tissues), and bone account for the remaining components.

The etiology and consequences of loss of BCM can be variable. Frank wasting involves loss of body weight (fat mass) and BCM. This is typically due to inadequate dietary intake. Cachexia, however, refers to loss of BCM without loss of weight; in fact, loss of BCM is at times accompanied by increased fat mass and stable body weight. In patients with RA, these changes predispose to a condition called rheumatoid cachectic obesity[8], which, although seemingly contradictory, appears to be a common metabolic consequence of RA.

The exact pathophysiological mechanisms underlying the development of RC are not fully understood. But several potential mechanisms have been investigated. The etiology is probably multifactorial. It includes excessive cytokine production, physical inactivity, and reduced peripheral insulin action.

The inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin 1ß (IL-1ß) are thought to be centrally involved in the pathogenesis of RA[9]. Both cytokines are produced primarily by monocytes and macrophages, but they are also produced by a variety of other cells including B lymphocytes, T lymphocytes, and skeletal muscle[10]. Concentrations of TNF and IL-1ß are high in patients with active RA; these substances act by stimulating the release of tissue-destroying matrix metalloproteinases as well as by inhibiting the production of endogenous inhibitors of these metalloproteinases, the net result being joint damage.

Not only are TNF-α and IL-1ß centrally involved in causing joint damage in RA, but these cytokines also exert a powerful influence on whole-body protein and energy metabolism. The so-called sarcoactive ("muscle-active") cytokines include IL-6, interferon-γ, and transforming growth factor-ß, in addition to TNF-α and IL-1ß. Although the specific mechanism(s) by which TNF-α and IL-1ß exert their catabolic effect is not known, it has been shown that subjects with RA have higher rates of whole-body protein breakdown compared with young and elderly healthy subjects, and TNF-α is thought to stimulate muscle catabolism[11].

It has been demonstrated that patients with RA have low

physical activity. Many factors contribute to reduced physical activity among patients with RA, including joint pain and stiffness, metabolic changes leading to loss of muscle mass and strength, and simple disuse, perhaps related to general caution regarding physical activity. Physical inactivity is associated with changes in normal physiological processes leading to muscle atrophy and insulin resistance. Lack of effective muscle stimuli decreases the turnover rates of muscle and whole-body proteins with inhibition of protein synthesis. These factors also lead to the initiation and progression of RC[12].

Studies have shown that in normal aging there is an association between loss of lean mass and decrease in activity of the growth hormone (GH)/insulin-like growth factor (IGF)-1 axis. Therefore it raises the question of whether GH is reduced in patients with RA and whether it may contribute to loss of BCM. Studies have found no differences in the amount of GH between patients with RA and healthy controls. These findings suggest that persistent GH deficiency does not appear to be the cause of RC. However, lower serum IGF-1 levels have been noted in patients with RA; this may contribute to RC[13].

Peripheral insulin action is reduced in patients with RA. Insulin acts to inhibit muscle protein degradation, thus making it a potent anabolic hormone. Therefore, decrease in insulin action causes muscle loss in RA[14]. The etiology of reduced peripheral insulin action in RA is not known, but TNF-α may interfere with insulin receptor signaling and may be a contributing factor[15].

Three approaches have been found to be effective: exercise, and dietary and pharmacological interventions.

Studies have demonstrated significant improvements in strength and pain in patients with RA without exacerbating disease activity or joint pain. High-intensity strength training is feasible and safe in patients with well controlled RA[16]; studies have shown that regular progressive resistance strength training is the best way to improve muscle strength and physical functioning in patients with RA and is one of the best nonpharmacological treatments. It should be routinely prescribed and maintained[17].

Patients with RA appeared to have adequate dietary intake in terms of calories and protein. Because the total energy expenditure was reduced in these patients (despite their elevated resting energy expenditure), they were most likely prone to fat accretion over time. Clinicians should not recommend increased caloric intake to patients with RA. Some studies have shown that increased protein intake would be helpful for overcoming the catabolic process in RA, particularly when combined with an exercise intervention[18]. Many dietary suggestions have been made for RA, ranging from fasting or vegetarianism to supplementation with various fatty acids or protein supplements, but none of these various diets have proven to be effective.

TNF-α has a central role in the pathogenesis of joint inflammation and destruction in RA. RC is thought to have the same pathogenesis as joint inflammation and it would be anticipated that TNF blockers would result in significant improvements in body composition[19].

It is known that RC increases morbidity and mortality in patients with RA. It is therefore important to prevent or at least slow the advance of this complication. Available therapeutic methods include increasing physical activity and maintaining a diet adequate in protein and energy. Anti-TNF-α therapy is an intervention that seems to improve RC, but more investigation is needed to prove its efficacy and safety.

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