EDITORIAL (SEE PARK ET AL., P. 1993)

Diabetes, Muscles, and the Myth of Ulysses' Bow

At the end of Homer's *Odyssey*, after 20 years of adventurous traveling, the goddess Athena brings Ulysses back to Ithaca disguised as an old man. With little hope for Ulysses' return, his faithful wife Penelope has reluctantly agreed to marry whoever wins a contest using Ulysses' bow. In spite of his infirmed appearance, Ulysses is the only contestant strong enough to string the bow and shoot an arrow through 12 axe-handles. Thus, the image of a hero as the "only one who can string the bow" has been embedded in civilization since before the beginning of written history and suggests that from time immemorial, people have equated strong muscles with youth and good health. Thousands of years later, we are beginning to understand exactly how health and age affect muscle, and we are now on the cusp of translating that knowledge into medical research and practice.

In this issue of *Diabetes Care*, Park et al. (1) from the Health, Aging, and Body Composition Study group report that in individuals aged 70–79 years, a diagnosis of diabetes is associated with accelerated decline in muscle mass, especially in women and in subjects with undiagnosed diabetes. These longitudinal findings open an important chapter in our understanding of the complications and consequences of diabetes and its effect on physical function. However, to fully understand the relevance of these findings, we should interpret them in the context of the known effects of age on body composition and of diabetes on muscle strength and physical function (2,3).

The aging process is associated with consistent changes in body composition in all animal species, from worms to rodents to primates, with few exceptions (4–6). With increasing age, lean body mass decreases and fat mass (and possibly connective tissue mass) increases. These changes are almost always associated with a reduction in vitality, expressed as poor mobility and physical function (7). In humans, individuals tend to build muscle mass over the first two decades of life, begin to lose muscle mass and strength between the third and fourth decade, and the decline accelerates during the sixth decade (8). This age trajectory of muscle mass and function is universal, but the interindividual heterogeneity in rates of decline is so striking that some individuals reach extreme age with little functional consequences while others become weak, disabled, and die decades earlier.

The source of this heterogeneity is likely a mix of individual genetic factors, health behaviors, and the effects of discrete diseases. Behavioral factors have powerful effects on muscle mass and strength. A sedentary state is by far the strongest risk factor for accelerated decline of lean body mass with aging. Inactivity impairs the balance of muscle protein synthesis and degradation and influences muscle-cell regeneration. Inactivity is also a strong predisposing factor for many chronic diseases. The role of nutrition as a behavioral influence on muscle is more controversial and has focused mostly on proteins and antioxidant micronutrients (9,10).

Recently, many common and disabling chronic diseases have been shown to be associated with excessive decline in lean body mass and muscle strength. The contribution of diabetes, as shown in the article by Park et al., is perhaps the most clearly established, although little is understood about the underlying biological mechanisms (11). Accelerated loss of muscle mass now has also been found in congestive heart failure, obstructive pulmonary disease, rheumatoid arthritis and other autoimmune diseases, chronic kidney disease, peripheral artery disease, cancer, HIV, and many others (12–17).

The relationship between body composition, strength, and function is so intimately intertwined with the relationship between health, aging, and disease that low muscle mass, increased fat mass, and poor muscle strength are more robust predictors of disability and mortality than factors related to disease diagnosis, disease severity, or biomarkers (18,19). While observational studies have documented the relative magnitudes of risk among these factors, it is not clear whether they act via distinct, shared, or even cumulative biological mechanisms. Thus, it is possible that each disease acts through a unique pathophysiologic mechanism that is superimposed on the independent process of body composition change with aging. Alternatively, multiple diseases and even aging may share a common mechanism that accelerates the loss of muscle mass. Studies conducted in animal models suggest that multiple conditions, including experimentally induced diabetes, may share an underlying regulatory process that is characterized by the activation of specific atrogenes that upregulate protein catabolism (20). It is not yet known whether atrogenes play a role in age-related muscle impairment or whether animal models accurately reflect the process that occurs in humans. As the search for potential therapeutic targets accelerates, it is essential to build an understanding of the biological mechanisms underlying the loss of muscle mass and strength that can integrate the contributions of aging, behavior, and disease. Interestingly—and particularly relevant here—the biological pathways that modulate the expression of the atrogenes are strongly affected by the IGF-I/insulin signaling pathway that has been shown to influence age-related changes in body composition, strength, and disability.

To add to the complexity of the issues, there is more to muscle strength than just muscle mass. There is strong evidence in the literature that the decline in muscle strength that occurs with aging results from a combination of muscle mass shrinking and the deterioration of muscle "quality." Deterioration of muscle quality appears to be critical. In fact, muscle strength is a much stronger predictor of disability and mortality than muscle mass (19). We are just beginning to explore the multiple additional factors that affect muscle quality, including intracellular influences on energy metabolism and interfaces with critical systems such as the neuromuscular junction (21). The biological pathways that affect muscle mass and quality have both distinct and shared components that likely influence each other.

The findings reported by Park et al. lead to exciting new questions: Does optimal glycemic control in diabetic patients prevent the loss of muscle mass and strength? This possibility is implied in the

finding that undiagnosed diabetes, compared with diagnosed diabetes, is a stronger predictor of the accelerated decline of muscle mass. Does loss of mass and strength affect the clinical evolution and prognosis of diabetes? Should interventions to prevent loss of mass and strength in diabetes be similar to those used in the general population such as behavioral strategies that promote physical activity, or do they also require a disease-specific component? We simply do not have enough data to respond to these questions. Real clinical benefit will require us to link pathophysiology and molecular mechanisms with clinical diagnosis and treatment. To understand what is happening, we need new, in vivo measures of muscle protein metabolism that can be repeated over time in well-characterized patient populations. We also must identify the signaling pathways that modulate protein anabolism and catabolism and muscle-cell differentiation in the presence of relevant pathologic conditions, as well as behavioral states such as physical activity during the aging process.

Finally, the work by Park et al. leads us to consider the need for a screening test for the accelerated loss of muscle mass and strength as a component of good diabetic care. Surprisingly, we still do not know what criteria to use to detect the problem or how to best implement such a screening. There are not yet standard, population-based normative data on muscle strength and muscle mass. While longitudinal studies of multiple populations have reported on muscle strength and muscle mass, they have not shared similar measurement technology or operational definitions. In the case of diabetes, databases on body composition, strength, and function in large clinical series of patients are greatly needed and might be feasible ancillary studies to the many existing multicenter observational and intervention programs. Since muscle mass may be only one important indicator of the problem, muscle strength is probably the most relevant clinical indicator. In patients who screen positive for "low strength," it would be important to determine whether this condition is attributable to a reduction in mass, a deterioration of muscle quality, or a combination of both. Understanding whether diabetes primarily affects muscle mass, muscle quality, or both is a first step in understanding the pathophysiology of diabetic muscle impairment. Research within the field of diabetes could lead the way and serve as the model for the many other disease, behavioral, and age-related factors that affect muscle.

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