The underappreciated role of muscle in health and disease[1–3]

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ABSTRACT

Muscle plays a central role in whole-body protein metabolism by serving as the principal reservoir for amino acids to maintain protein synthesis in vital tissues and organs in the absence of amino acid absorption from the gut and by providing hepatic gluconeogenic precursors. Furthermore, altered muscle metabolism plays a key role in the genesis, and therefore the prevention, of many common pathologic conditions and chronic diseases. Nonetheless, the maintenance of adequate muscle mass, strength, and metabolic function has rarely, if ever, been targeted as a relevant endpoint of recommendations for dietary intake. It is therefore imperative that factors directly related to muscle mass, strength, and metabolic function be included in future studies designed to demonstrate optimal lifestyle behaviors throughout the life span, including physical activity and diet. *Am J Clin Nutr* 2006;84:475–82.

KEY WORDS Strength, muscle, protein metabolism, sarcopenia, dietary requirements

INTRODUCTION

The importance of muscle mass, strength, and metabolic function in the performance of exercise, as well as the activities of daily living (ADL), has never been questioned. Perhaps less well recognized, muscle plays a central role in whole-body protein metabolism, which is particularly important in the response to stress. Furthermore, abundant evidence points to a key role of altered muscle metabolism in the genesis, and therefore prevention, of many common pathologic conditions and chronic diseases. This review discusses the various roles of muscle metabolism in health and disease, including consideration of possible solutions to muscle loss. Particular emphasis will be given to the notion that increasing protein or amino acid intakes may optimize muscle strength and metabolism and thereby improve health.

CENTRAL ROLE OF MUSCLE PROTEIN IN WHOLE-BODY METABOLISM

Maintenance of the protein content of certain tissues and organs, such as the skin, brain, heart, and liver, is essential for survival. In the postabsorptive state these essential tissues and organs rely on a steady supply of amino acids via the blood to serve as precursors for the synthesis of new proteins to balance the persistent rate of protein breakdown that occurs in all tissues. It has been recognized since the early 1960s that, in the absence of nutrient intake, muscle protein serves as the principal reservoir to replace blood amino acid taken up by other tissues (1–3). In the fasting state, blood amino acids serve not only as precursors for the synthesis of proteins but also as precursors for hepatic gluconeogenesis (4). Consequently, the protein mass of essential tissues and organs, as well as the necessary plasma glucose concentration, can be maintained relatively constant despite the absence of nutritional intake, provided muscle mass is adequate to supply the required amino acids.

The demands for amino acids in most organs and tissues do not vary significantly from the fed to the postabsorptive state because little surplus protein is accumulated. Furthermore, the hepatic uptake of gluconeogenic amino acids decreases with nutrient intake (5). Consequently, the primary fate of ingested amino acids is incorporation into muscle protein to replete the reserves of amino acids lost in the fasting state. Under normal conditions, gains in muscle protein mass in the fed state balance the loss of muscle protein mass in the postabsorptive state.

The ability of net muscle protein breakdown to maintain plasma amino acid concentrations is remarkable, provided adequate muscle mass is available. For example, obese individuals (with increased muscle mass) were able to maintain normal concentrations of plasma amino acids after ≥60 d of fasting (6). In contrast, depletion of muscle mass is incompatible with life. For example, there is a strong association between the depletion of body cell mass (presumably reflecting depletion of muscle mass) and the length of survival of seriously ill patients with AIDS (7). Studies performed by Jewish physicians in the Warsaw ghetto suggest that death from starvation, uncomplicated by critical

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illness, occurs when muscle protein breakdown becomes inadequate to maintain the necessary supply of gluconeogenic precursors (8). The extensive work by Keys et al (9) also concludes that the depletion of muscle mass is the cause of death in human starvation.

MUSCLE AND THE ACUTE RESPONSE TO CRITICAL ILLNESS

The stressed state, such as that associated with sepsis, advanced cancer, and traumatic injury, imposes greater demands for amino acids from muscle protein breakdown than does fasting (10). Physiologic responses necessary for recovery may include the accelerated synthesis of acute phase proteins in the liver, synthesis of proteins involved in immune function, and synthesis of proteins involved in wound healing. The demands for precursor amino acids for the synthesis of these proteins are significant. For example, quantitative studies of wound healing suggest that a protein intake of >3 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1} is required to provide the necessary precursors for the synthesis of proteins required for normal healing of a burn injury to 50% of the body (11). Coupled with the continued amino acid requirement of most tissues and accelerated requirements for tissues such as immune cells and liver, actual utilization of protein in severely burned individuals may exceed 4 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1}. This represents $\approx$4 times or more the normal daily intake of protein. In addition, stimulation of hepatic gluconeogenesis in stressed states further increases the demand for amino acids (12). Net breakdown of muscle protein is stimulated to provide abundant amino acids to meet these increased demands. This response is not readily reversed, even by aggressive nutritional support (10). Not surprisingly, individuals with limited reserves of muscle mass respond poorly to stress. For example, survival from severe burn injury is lowest in individuals with reduced lean body mass (13). Loss of muscle mass is also known to be detrimental to survival from cancer. For example, in patients with lung cancer receiving radiation therapy, the amount of body protein (measured by in vivo neutron-activation analysis) predicted recurrence. In those in whom body protein decreased, recurrence and, ultimately, survival was worse than in patients who were able to maintain or increase muscle mass (14). Although it is possible that muscle loss occurs because of impaired appetite and, thus, reduced protein intake in those more susceptible to recurrence, the relation between muscle mass and recurrence is nonetheless striking.

Whereas muscle mass plays a key role in recovery from critical illness or severe trauma, muscle strength and function is central to the recovery process. The extent and duration of the debilitation resulting from critical illness is dramatic; $<50\%$ of individuals employed before entering an intensive care unit return to work in the first year after discharge (15). Extensive losses of muscle mass, strength, and function during acute hospitalization causing sustained physical impairment were likely contributors to the prolonged recovery. If there is a preexisting deficiency of muscle mass before trauma, the acute loss of muscle mass and function may push an individual over a threshold that makes recovery of normal function unlikely to ever occur. For this reason, $>50\%$ of women older than 65 y who break a hip in a fall never walk again (16).

ROLE OF MUSCLE IN CHRONIC DISEASE

Chronic diseases related to poor lifestyle behaviors account for more than two-thirds of deaths in the United States (17). Population-based studies assess diet and physical activity and measure indexes such as blood lipids, body mass index, and bone biomarkers to predict risk of disease. Few if any population-based studies have assessed muscle mass or physical or metabolic function to understand the role of muscle in these conditions. However, alterations in muscle play an important role in the most common diseases and conditions. Heart disease and cancer are the major chronic diseases suffered in the United States (17). Both cardiac failure and cancer are often associated with rapid and extensive loss of muscle mass, strength, and metabolic function (cachexia). With cardiac and cancer cachexia, the loss of muscle mass is an important determinant of survival (14, 18). Sarcopenia, the progressive loss of muscle mass and function that occurs with aging, is a widespread syndrome that has a devastating effect on quality of life and ultimately survival (19). Progressive sarcopenia is ultimately central to the development of frailty, an increased likelihood of falls, and impairment of the ability to perform ADL (19). The logical endpoint of severe sarcopenia is loss of quality of life and ultimately institutionalization.

OBESITY AND MUSCLE

Whereas the role of muscle is central and obvious in syndromes such as sarcopenia and cachexia, which are defined—at least in part—by loss of muscle mass and strength, the potential role of muscle in the prevention of obesity is less well appreciated. The development of obesity results from an energy imbalance over a prolonged time, which means that energy intake exceeds energy expenditure. An effect on energy balance can therefore be achieved by altering either energy intake or energy expenditure. Total energy expenditure is the sum of resting energy expenditure (REE), the thermic effect of food, and the energy expenditure related to activity. Under most circumstances, REE is the largest component of total energy expenditure (20). The energy expenditure related to muscle metabolism is the only component of REE that might vary considerably. The resting metabolic requirements of splanchnic tissues, brain, and skin vary little under normal conditions because of relatively constant tissue mass and protein turnover rates (21). In contrast, large variations in muscle mass are possible, and the rate of muscle protein turnover (ie, muscle protein synthesis and breakdown) may vary as well. The synthesis and breakdown of muscle protein are principally responsible for the energy expenditure of resting muscle. Whereas the precise in vivo energetics of muscle protein turnover are uncertain, a conservative estimate can be made on the basis of muscle protein synthesis. The average 24-h (including response to meal feeding) fractional synthetic rate (FSR) of muscle protein is $\approx$0.075%/h (22). The absolute synthetic rate can be calculated as the product of the FSR and muscle mass. We have found the average muscle mass of young, healthy males to range from 35 to 50 kg (22). In contrast, an elderly woman may have $\leq$13 kg muscle. Thus, muscle protein synthesis ranges from $\approx$0.23 to 0.90 kg/d, depending on the amount of muscle mass. Because 4 mol ATP is utilized per mole of amino acids incorporated into protein (21), and because the hydrolysis of 1 mol ATP releases 20 kcal energy (23), the energy released per day as a

result of muscle protein synthesis may range from ≈485 kcal/d in a well-muscled young man to ≈120 kcal/d in an active elderly woman. These estimates are consistent with the observed increase in REE during an infusion of amino acids at a rate known to stimulate muscle protein synthesis (24). Extremes in muscle mass, eg, young male body builders to frail elderly, would be even greater. In terms of whole-body energy balance, a difference in REE of ≈365 kcal/d, stemming from a difference in muscle protein turnover, would lead to a gain or loss of 47 g fat mass/d because 1 kg of fat stores 7700 kcal. If activity and diet remained constant, this would mean a gain or loss of ≈1.4 kg fat mass/mo. This effect on energy balance is particularly striking when it is realized that the estimate given above for the energy expenditure associated with muscle protein turnover is likely an underestimate, because protein breakdown also requires the hydrolysis of ATP, and the energy released in this process is above and beyond the contribution of muscle protein synthesis to energy production. It is evident from these estimations that, when a long-term perspective is considered, even relatively small differences (eg, 10 kg) in muscle mass could have a significant effect on energy balance. Every 10-kg difference in lean mass translates to a difference in energy expenditure of ≈100 kcal/d, assuming a constant rate of protein turnover. In considering the magnitude of energy imbalances leading to obesity, it is reasonable to view the situation over long periods of time, because obesity often develops over months and even years. A difference in energy expenditure of 100 kcal/d translates to ≈4.7 kg fat mass/y. Consequently, the maintenance of a large muscle mass and consequent muscle protein turnover can contribute to the prevention of obesity.

Regardless of the energetics of muscle protein turnover, obesity can develop if energy intake is great enough. Obesity is clinically characterized by a disproportionate increase in fat mass. Less appreciated is the fact that muscle mass in obesity is also increased (25). Although the energy expenditure associated with larger muscle mass in obesity is insufficient to offset the excessive energy intake, the expanded muscle mass can be capitalized on to facilitate weight loss. It is evident from the calculations presented above that a stimulation of muscle protein turnover in the setting of increased muscle mass could have a significant effect on REE and, thus, energy balance. This can potentially be accomplished through nutrition, because increasing amino acid availability increases muscle protein turnover (26). Furthermore, the energy to provide the ATP for muscle protein turnover is largely derived from the oxidation of fat, because this is the preferred energy substrate of resting muscle (27). Thus, when muscle protein synthesis was increased by testosterone injection in hypogonadal elderly men, the increase in lean body mass over time was accompanied by a decrease in fat mass (28). Extending this notion to the situation of a hypocaloric diet for weight loss, a high percentage of protein in the diet would therefore be expected to effectively repartition nutrient deposition from fat to muscle. Recent reports of improved body composition during weight loss with high-protein, hypocaloric diets support the notion of repartitioning of nutrient intake when protein turnover is stimulated (29). It has yet to be determined whether the same repartitioning occurs when the proportion of protein intake is increased in the circumstance of energy balance (ie, caloric intake = caloric expenditure), but the same rationale should apply.

MUSCLE IN INSULIN RESISTANCE AND DIABETES

Type 2 diabetes develops in stages. The onset of the process involves a decreased ability of insulin to stimulate muscle to clear glucose from the blood. So-called "insulin resistance" of muscle is a hallmark of the metabolic syndrome, which is considered to be a precursor of frank diabetes (30). Insulin secretion is amplified in the initial phase of insulin resistance to enable muscle to clear glucose from plasma adequately to maintain normal glucose concentrations. As the metabolic syndrome progresses to diabetes, increased insulin secretion is unable to effectively counterbalance the ineffectiveness of insulin to stimulate muscle glucose uptake, and glucose intolerance ensues. Only in the later stage of diabetes does the pancreas lose the ability to secrete extra insulin in response to hyperglycemia. Disruption of the normal rate of muscle glucose uptake by muscle is thus central to the onset and progression of diabetes (31).

A relative increase in body fat is an appealing explanation for the decline in insulin sensitivity in both obese and elderly individuals. A higher percentage of body fat generally translates to a higher rate of appearance of free fatty acids (FFAs) in plasma (32), and a relation between an elevated availability of FFAs and insulin resistance has been recognized since the "glucose–fatty acid cycle" was proposed by Randle et al (33) in 1963. However, over the past few years it has become evident that changes in the metabolic function of muscle itself plays a more direct role in the genesis of insulin resistance than previously appreciated. The central thesis of the glucose–fatty acid cycle is that elevated plasma FFA concentrations limit glucose uptake in muscle by inhibiting the oxidation of glucose (33). Thus, according to this theory, the genesis of insulin resistance lay entirely with the increased availability of FFAs, and the muscle responded normally to that signal to limit glucose uptake and oxidation. However, research done in our laboratory (34), as well as in others (35), has shown that the glucose–fatty acid cycle″ was inadequate to explain regulation of muscle glucose uptake in a physiologic setting. Rather, alterations in metabolic function within the muscle are more likely at the heart of the genesis of insulin resistance.

Recent studies that used new applications of magnetic resonance spectroscopy to quantify triacylglycerol deposition in muscle have revised thinking about possible mechanisms by which alterations in lipid metabolism may affect insulin sensitivity in muscle. Triacylglycerol deposition in muscle has been found to be associated with insulin resistance in a variety of circumstances (36–39), whereas obesity without insulin resistance is not associated with increased triacylglycerol deposition in muscle. Increased triacylglycerol deposition in muscle has been interpreted to be an indicator of dysfunctional muscle lipid metabolism that is likely related to insulin resistance by mechanisms independent of total body fat mass (40). An accumulation of intracellular triacylglycerol results from an imbalance between tissue fatty acid uptake and fatty acid disposal. Fatty acid uptake by muscle is directly proportional to delivery in a wide variety of circumstances (27). Although fatty acid delivery to muscle is generally elevated in obesity (because of a large fat mass), triacylglycerol deposition in muscle is not elevated in obese subjects who are not insulin resistant (35). It is becoming clear that, rather than an increased delivery of FFAs to muscle, it is more likely that impaired disposal via oxidation is the principal basis for accumulation of triacylglycerol deposition in muscle

and other potentially active products of fatty acids. In vivo capacity to oxidize fatty acids is reduced in insulin-resistant individuals (35). This deficiency may be more evident during exercise (41). It is likely that this deficiency in fatty acid oxidation is due to a decline in mitochondrial oxidative function (42). There are many potential causes of decreased mitochondrial oxidative capacity, including genetics; a lack of physical activity is most likely a major factor in patients with type 2 diabetes. Mitochondrial oxidative capacity is decreased by inactivity (43), and as little as a single bout of exercise [thereby stimulating triacylglycerol deposition in muscle intramuscular triacylglycerol (IMTG) oxidation] can transiently reverse insulin resistance (44).

It is possible that IMTG does not exert a direct effect on insulin sensitivity, but that accumulation of IMTG represents a dysregulation of normal tissue lipid metabolism and that other intracellular lipids or lipid products actually induce insulin insensitivity. Fatty acids entering the cell are converted to their corresponding fatty acyl CoAs before being transported across mitochondrial membranes for oxidation. Fatty acyl CoAs that do not enter mitochondria are substrates for the synthesis of triacylglycerol and phospholipids. Diacylglycerol is a second messenger product in the pathway of triacylglycerol synthesis and can also induce insulin resistance by impairing the intracellular insulin signaling cascade (45). There are other potentially active products of fatty acyl CoAs. Thus, palmitoyl CoA is rate-limiting in the de novo synthesis of ceramide (46). Ceramide can also induce insulin resistance in vitro (45), although in vivo data are not yet available.

The exact mechanisms by which disruptions in intramuscular trafficking of fatty acids in muscle are linked to impaired insulin signaling are under current investigation. One proposal is that elevated intracellular concentrations of diacylglycerol activate protein kinase C, which in turn is an inhibitor of insulin signaling transduction (40). Regardless of the specific intracellular mechanisms at the molecular level, it is clear that insulin resistance is not simply the result of increased fat mass and release of FFAs into plasma at an accelerated rate, with the muscle responding to elevated plasma FAA concentrations. Rather, alterations in the metabolic function of muscle are central to the development of insulin resistance and ultimately diabetes.

MUSCLE AND OSTEOPOROSIS

Mechanical force on bone is essential for modeling and remodeling, processes that increase bone strength and mass (47). Whereas body weight and weight-bearing exercises provide a direct mechanical force on bones, the largest voluntary loads on bone are proposed to come from muscle contractions (47). Correlations between grip strength and bone area, bone mineral content, and bone mineral density in both healthy athletes (48) and stroke patients (49) support the notion that muscle contractions play a significant role in bone strength and mass. Even the correlation between body weight and bone mass (47) can be explained on the basis of the force exerted on bone by muscle contractions, in that it takes more force per unit area to move heavier bodies. Furthermore, changes in bone mass and muscle strength track together over the life span (47). Although it is debatable whether it is muscle strength or simply muscle mass that is important in determining bone strength and mass, it is significant that skeletal muscle mass was correlated positively with bone mineral content and bone mineral density in MINOS (Mediterranean Intensive Oxidant Study), a prospective study of osteoporosis and its determinants in men (50). Men with the least skeletal muscle mass also had increased risks of falls due to impaired static and dynamic balance, presumably at least in part because of a decrease in muscle strength (50).

Thus, maintenance of adequate bone strength and density with aging is highly dependent on the maintenance of adequate muscle mass and function. The relative importance of muscle compared with normal hormonal and nutritional effects on bone may be argued. Because some of the factors, such as dietary protein, insulin growth factor, and testosterone (51), that are proposed to affect bone directly also affect muscle, it is impossible to distinguish in vivo whether these factors directly affect bone if their effects on bone are the consequence of increased muscle strength, which putts greater mechanical force on bone. Regardless, the importance of muscle in prevention of osteoporosis is clear.

SOLUTIONS TO MUSCLE LOSS

There are 3 potential approaches to maintaining or increasing muscle mass and function: hormonal therapy, exercise, and nutrition.

Hormonal therapy

There are 3 general approaches to hormone therapy. Hormones can be given to replace a deficiency, hormones can be given to raise the concentration above the normal value, and agents can be given to block hormone action by either reducing the rate of secretion or blocking their action. All approaches may have a role in maintaining or increasing muscle mass. Replacement of testosterone in hypogonadal elderly men has successfully increased both muscle mass and strength (28). Administration of insulin at rates sufficient to raise plasma concentrations above the naturally occurring value has been shown to have an anabolic effect on muscle in severely burned patients (52). In the stressed state, the catabolic hormones cortisol and epinephrine are counterregulatory hormones, the effects of which can be minimized by either blocking receptors, in the case of epinephrine (53), or blocking secretion, in the case of cortisol (54). Thus, there clearly is a role for hormone therapy in maintaining and increasing muscle mass and function. New advances in synthetic hormones provide promise for expanded applications in the future. For example, the synthetic steroid oxandralone stimulates muscle growth, possibly without the same magnitude of androgenizing effects of testosterone (55). At the same time, there are limits and dangers of hormonal therapy caused by unexpected, unwanted, and often unrecognized complications. For example, it is well known that large doses of testosterone increase muscle mass and function, particularly when given in conjunction with exercise training. However, many undesirable side effects may accompany the use of testosterone or any of its many synthetic analogues, thereby limiting its clinical use on a widespread or unsupervised basis.

Exercise

Exercise improves muscle function and, in some circumstances, increases muscle mass as well. Improved function may not be limited to the contractile properties of muscle but also muscle metabolism. For example, exercise training improves insulin sensitivity (56). It appears that exercise is more effective

at preventing loss of muscle than of restoring lost muscle mass. Whereas exercise interventions in individuals with sarcopenia can successfully improve functionality (57), the reversal of the loss of muscle mass with aging has been more problematic. Further gains in physical strength and function resulting from exercise programs are often less effective in the elderly than would be expected in younger subjects undergoing the same training protocol (58). The diminished responsiveness of frail elderly to the beneficial effects of exercise probably stems from the restrictions imposed by the initial sarcopenia or lack of muscle mass and strength. Elderly individuals, particularly women, are often too weak to perform the intensity of exercise necessary to induce the same magnitude of physiologic adaptations that occur in younger subjects. Rather than initiate practices to reverse sarcopenia, it would be more effective to prevent its development. Progressive loss of muscle mass (59) and strength (60) occurs throughout adult life, and in middle age the rate of loss is accelerated and maintained until old age (61). Intervention in middle age or younger ages is therefore necessary to offset the deleterious effects of sarcopenia in old age.

There is little debate regarding the beneficial effects of exercise on muscle, whether it be to maintain or attempt to restore muscle mass and function. The most practical issue from a public health standpoint is motivation. In that light, it is important to identify the minimal exercise regimen to achieve desired results, including maximizing the interactive effects between nutritional intake and exercise on muscle protein synthesis. Furthermore, the desired result should be identified in terms of outcomes on muscle mass, strength, and metabolic function, as opposed to traditional measures of exercise training, such as the maximal oxygen consumption, which have little direct relation to health outcomes.

Nutrition

The previous sections have documented the varied and essential roles that muscle mass and physical and metabolic functions play in health and disease. Regardless, these factors have rarely, if ever, been targeted as relevant endpoints of studies on which dietary recommendations are based. For example, in the extensive section on recommendations for adult protein intake in the recently published Dietary Reference Intakes (DRIs) (62), there is no consideration in which muscle mass, physical, or metabolic function are endpoints. Rather, the determination of the recommended protein intake for adults in the DRIs relied entirely on a meta-analysis of nitrogen balance measures(62). Use of nitrogen balance may well be appropriate for establishing the nitrogen or amino acid requirements necessary to prevent deficiency, but it is likely inadequate to establish intakes that are optimal for maximizing muscle mass, strength, and metabolic function. This is because individuals can adapt to suboptimal protein intakes by reducing nitrogen excretion. In the extreme example of starvation in the Warsaw ghetto, grossly depleted individuals were basically able to maintain nitrogen balance until shortly before death by greatly reducing their nitrogen excretion, yet obviously neither their intake of energy substrates nor of protein were close to optimal (8). Thus, there is no necessary relation between nitrogen balance and any variable of muscle mass or function. The recommended daily intakes of individual amino acids were also considered in the DRIs. These recommendations were based on studies of the metabolic fate of individual amino acids. Although this approach may yield accurate values for specific amino acid requirements, these values have little relevance to total protein intake. This is because the recommended intake of the most limiting amino acid can be achieved with a protein intake well below the estimated average requirement (EAR) of protein ($0.66\ g \cdot kg^{-1} \cdot d^{-1}$) (62).

There are direct measures of body composition, such as total body potassium or measurement of lean body mass by dual-energy X-ray absorptiometry that are better reflections of muscle mass than are nitrogen balance studies because nitrogen balance only measures change or stability of muscle mass and not whether total mass is functionally optimal. Nonetheless, body-composition studies have not been utilized to formulate dietary recommendations for protein intake. In any case, knowledge of the effects of diet on muscle mass is less important for adults than are dietary effects on the physical and metabolic functions of muscle. The absence of a direct relation between muscle mass and strength has been shown in a variety of studies (63). As described above, only in severe cases of cachexia or sarcopenia does loss of muscle mass, per se, directly affect health. Rather, the physical and metabolic functions of muscle are more important in normal day-to-day life. For example, in a longitudinal study of 1071 men, lower and declining strength was most closely associated with survival (64). The importance of the physical function of muscle as an indicator of nutritional status is well established. A series of studies that used electrical stimulation of the adductor pollicis muscle showed that, in malnutrition, increased fatigue and altered patterns of muscle contraction precede changes in body weight and composition (65). Although the physical function of muscle has been assessed in isolated circumstances to determine the adequacy of dietary intake in hospitalized patients (65), this variable has never been targeted as a relevant endpoint for dietary recommendations in the population at large.

Dietary recommendations in the United States have relied heavily on epidemiologic studies such as the Nurse's Health Study (66) and the Physicians' Health Study (67). These studies have not directly considered any variable of muscle mass or function to be a relevant endpoint. Rather, recommendations arising from these studies have been predicated on minimizing the risk of diseases that, in many cases, affect only a small percentage of the population. Thus, although heart disease, cancer, stroke, and diabetes account for a high percentage of death by disease in persons younger than 65 y, >82% of persons in the United States live beyond this age (68). Therefore, when expressed as the percentage of persons per year younger than 65 y that die of particular diseases, the values are small. In fact, only 0.11% of persons younger than 65 y die of cancer, heart disease, stroke, and diabetes combined (69, 70). Furthermore, in many cases, conclusions have been based on surrogates such as lipid concentrations that may predict, with varying precision, the development of disease rather than the actual occurrence of disease. This point is particularly relevant to recommendations for protein intake. Because dietary recommendations are heavily weighted toward lowering saturated fat intakes, recommended intakes of protein sources, such as meat, have decreased because of the association between protein and saturated fat intakes (71). Thus, recommendations to reduce protein intakes have been made apparently without consideration of the effects on muscle mass and function.

Consideration of factors that might lead to the development of major diseases is reasonable when formulating dietary recommendations. At the same time, it is also reasonable to consider the welfare of most Americans, who do not contract these diseases before the age of 65 y. Beyond the age of 65 y, a depletion of mass, strength, and metabolic function of muscle is clearly important endpoints to consider when developing diet and lifestyle recommendations. Sarcopenia is estimated to occur in 30% of individuals over the age of 60 y (72). Furthermore, many of the diverse functions of muscle described above are central to overall health at all ages. It is not impractical to consider muscle mass, strength, and metabolic function in the development of future diet and physical activity guidelines. Mass can be reasonably estimated from determinations of lean body mass (eg, by using dual-energy X-ray absorptiometry) and strength can be directly measured. The metabolic function of muscle can be assessed by determining insulin sensitivity from an oral-glucose-tolerance curve (73).

Implicit in the argument that maintenance of muscle mass and, in particular, optimization of the physical and metabolic functions of muscle should be considered in formulating dietary guidelines is the notion that recommendations would be changed if these factors were to be considered. Available evidence to directly support this notion is limited because of the lack of studies specifically addressing this postulation. However, there are ample relevant studies of the metabolism of muscle protein that support the concept that increasing protein intakes above current guidelines would benefit muscle. Muscle protein is directly affected by protein intake in the diet. High dietary protein intakes increase protein synthesis by increasing systemic amino acid availability (74). The amino acids absorbed as a result of the digestion of protein stimulate the synthesis of muscle protein and promote muscle protein synthesis in a dose-dependent way (75–77). This metabolic response is reflected physiologically. For example, children given high protein intakes grow faster (78) and have greater muscle mass (79). The anabolic effect of exercise is amplified by amino acids or protein (80, 81). Protein intake above the currently recommended EAR of 0.66 mg $\cdot$ kg^{-1} $\cdot$ d^{-1} stimulates the FSR of muscle protein (82), and muscle FSR has been shown to be positively correlated with strength (61). Although the basis for the relation between FSR and strength is not certain, it is likely that a higher muscle protein turnover rate replaces older myofibrillar proteins with newer and better functioning proteins. Both muscle mass and strength are improved by increased availability of amino acids, even in the complete absence of activity in healthy young subjects confined to bed rest (63).

Recent studies in free-living elderly individuals indicate that an increased intake of amino acids improves the physical function and strength of muscle (83, 84). It is likely that the metabolic function of muscle is also improved by greater than recommended protein intakes, because amino acids not only stimulate the synthesis of myofibrillar proteins but also the synthesis of mitochondrial proteins needed to metabolize substrates (76). The recent finding that daily supplementation of type 2 diabetic subjects with amino acids improves metabolic control and decreases hemoglobin A_{1c} concentrations (85) is consistent with the expected benefits of stimulating muscle mitochondrial protein synthesis, for the reasons discussed above. Also, type 2 diabetic subjects maintained on a high protein intake had improved glycemic control (86). Insulin sensitivity was also improved by amino acid supplementation above recommended protein intakes in healthy elderly subjects with varying degrees of insulin resistance (87); both plasma and intrahepatic lipid concentrations were reduced as well (88).

The studies cited above provide adequate rationale for exploring the possibility that historical protein intake recommendations should be revisited. However, the recent DRIs (62) and the 2005 *Dietary Guidelines for Americans* (89) have retained historical recommendations. Not only has account not been taken of the issues raised in this article, but these recommendations have been retained despite new evidence obtained with the use of classic techniques that indicate the inadequacy of previous recommendations. For example, the recommended dietary allowance of 0.88 $\cdot$ kg^{-1} $\cdot$ d^{-1}, which is the EAR + 2 SDs, was directly shown to be inadequate to maintain lean body mass in individuals older than 65 y (90). Furthermore, the amount of protein needed to maintain lean body mass is likely below that needed to optimize physical and metabolic functions of muscle.

The optimal intake of protein is uncertain, but one can derive estimates from acute metabolic studies of muscle metabolism. Thus, the maximal response of muscle protein synthesis can be attained with intake of $\approx$15 g essential amino acids (EAAs) (91), which is approximately equal to the amount of EAAs in the EAR for a 55-kg woman (0.66 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1} $\times$ 55 kg $\times$ 0.42 EAA/g protein = 15.2 g protein). The response to a single dose of amino acids can potentially be achieved multiple times per day, with additive effects, with repeated meal ingestion (91, 92). Consequently, it would not be unreasonable to expect beneficial effects stemming from increased myofibrillar and mitochondrial protein synthesis to be achieved with the ingestion of 15 g EAAs at each meal rather than at only one meal per day. This would translate to a protein intake as high as 1.8 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1}. Although this amount may seem extreme in the context of the current recommendations, it is in line with the amount of protein in the average American diet, which was reported in the DRIs to be 1.5 g $\cdot$ kg^{-1} $\cdot$ d^{-1} for adults (62). Furthermore, detrimental effects of protein intakes $\geq$2.0 g $\cdot$ kg^{-1} $\cdot$ d^{-1} have not been documented (62).

The differences between the estimates given above, which are roughly consistent with the average American diet, and the EAR represent a physiologically important difference. There is not currently an adequate database with which to definitively resolve this discrepancy. The inadequacy of the means used to estimate the DRIs was tacitly acknowledged with the following statement: "While the N-balance method for estimation of protein requirements has serious shortcomings, this method remains the primary approach for determining the protein requirement in adults, in large part because there is not a validated or accepted alternative" (62). Whereas the studies cited above may give some reason to question this statement, it is nonetheless clear that further studies directly assessing the physical and metabolic functions of muscle in relation to protein intake in the context of other dietary nutrients are needed so that the next committee formed to produce the dietary guidelines to be published in the year 2010 will have a solid foundation on which to base new recommendations for protein intake.

CONCLUSIONS

The importance of maintaining muscle mass and physical and metabolic functions in the elderly is well-recognized. Less appreciated are the diverse roles of muscle throughout life and the importance of muscle in preventing some of the most common and increasingly prevalent clinical conditions, such as obesity and diabetes. It is therefore imperative that factors directly related to muscle be included in future studies designed to demonstrate optimal lifestyle behaviors throughout the life span, including physical activity and diet.

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