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Protein metabolism in women and men: similarities and disparities

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Abstract

Purpose of review—To provide an objective and comprehensive review of the recent literature addressing the effects of sex on protein metabolism. We also evaluate whether these differences can be attributed to physiology or methodology. Because of the developmental changes in hormonal milieu and body composition that occur across life, the literature has been examined in a longitudinal manner across the lifespan.

Recent findings—Throughout most points of life, men and women of similar health status and BMI display fairly similar protein turnover rates. However, some investigators have reported sexual dimorphism in protein metabolism, which may be partly attributable to differences in fat-free mass and/or methodology. In periods of significant changes in the hormonal milieu (puberty and menopause), sex differences may become more evident. Finally, anabolic stimuli such as feeding and exercise may help highlight any discrepancies in protein turnover between men and women.

Summary—Sex differences in protein metabolism, if any, are most evident during the main phases of hormonal changes, and may be also due to differences in body composition. However, methodological issues and sample size must be considered when designing and evaluating these studies.

Keywords

protein turnover; sex; stable isotope tracers

Introduction

Skeletal muscle is the major contributor to protein metabolism in the whole body. The obvious differences in muscle mass between adult women and men suggest the existence of significant sex disparities in protein metabolism initiating and sustaining such a discrepancy. However, research carried out over the past two decades has largely been unable to identify major differences in protein turnover between men and women across the lifespan [1,2••, 3,4••]. Nonetheless, some studies have reported small but significant differences between sexes [5•,6], but part of these differences may be attributable to methodological issues, such as subject selection and tracer technology employed to measure protein metabolism.

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The purpose of this paper is to provide an objective and comprehensive review of the recent literature addressing the effects of sex on protein metabolism, and evaluate whether these differences can be attributed to physiology or methodology. Because of the developmental changes in hormonal milieu and body composition that occur across life, the literature has been examined in a longitudinal manner across the lifespan.

Children

Few protein metabolism studies have been conducted in healthy children for ethical reasons. Much of the protein metabolism research has been done on children with diseases or disorders, such as malnutrition, obesity, and Crohn's disease [7–9]. Among the few studies on healthy children, one was performed on boys and girls 7–10 years old who consumed an oral dose of ^{15}N-glycine. Nitrogen balance was measured using the urinary excretion method. However, no direct comparisons were carried out or reported between normal boys and girls [10]. Schutz *et al.* [8] reported greater protein synthesis and breakdown in obese compared to nonobese children 7–10 years old, but, again, the authors did not address any sex-related differences. The fact that these studies in children did not directly address the issue of sex differences in protein turnover may be due to the assumption that prepubertal boys and girls have relatively similar hormone profiles [11] and muscle masses, and are not expected to display major differences in protein turnover.

Pubertal children

Despite the differing sex hormone concentrations through much of the postpubertal years, puberty may be the main point in which men and women differ in protein metabolism. Prior to puberty, boys and girls have similar body compositions. The onset of puberty is signaled by changes in hormone concentrations; accordingly boys will increase their muscle mass at a faster rate than girls and there does appear to be a difference in protein metabolism during this time.

However, scarce data are available also in this age group. A protein metabolism study in peripubertal children up to age 18 years (mean age 15.0 years) with Crohn's disease did not address the issue of sex differences. The wide range of ages and relatively small sample size (n = 15; nine girls, six boys) likely prevented any possible examination of sex-related differences [9].

Research in prepubertal children supplemented with testosterone (boys) and estrogen (girls) partially elucidates the effects of sex hormones on protein metabolism during the pubertal transition [12]. Healthy boys displayed an increased estimate of whole-body protein anabolism after intramuscular testosterone enanthate injections. In growth hormone-deficient boys, testosterone administration alone or with growth hormone resulted in lower leucine oxidation compared with pre-treatment values. However, estimates of whole-body proteolysis and whole-body protein synthesis (nonoxidative leucine disposal) were only increased when growth hormone was administered with testosterone. Testosterone plus growth hormone also increased absolute fat-free mass, which may at least partially account for the reported differences in metabolism [13]. Conversely, when pre-pubertal girls with hypogonadism were administered oral ethinyl estradiol (n = 5) or intramuscular depot estradiol (n = 2) there was no change in estimates of whole-body protein proteolysis, protein oxidation, or whole-body protein synthesis [14]. As researchers have previously demonstrated an increase in muscle mass associated with increased testosterone [15] and growth hormone during puberty, the results of the aforementioned research in children are not unexpected and can well explain the muscle gains that occur in boys during puberty [11].

However, after puberty the influence of hormones in men and women appears to be primarily limited to maintaining the muscle mass disparities, and differences in protein metabolism become less obvious and more difficult to detect.

Young adults

Generally, adult muscle mass is relatively stable, and in the absence of disease or exercise stimulation there are only small changes in muscle mass. The possible differences in protein metabolism some authors have reported during adult life may be due at least in part to the differences in body composition between men and women. Specifically, not only lean body mass but also the amount of body fat may influence protein turnover, as differences in protein metabolism between obese and nonobese people have been observed. Finally, it is possible that differences between men and women after puberty may be at least partially attributed to differing physical activity levels.

A recent study compared muscle protein metabolism in young men and premenopausal women after an overnight fast and during a hyperinsulinemic–hyperaminoacidemic state [4••]. In both the basal and hyperinsulinemia–hyperaminoacidemia states no sex differences were reported in mixed muscle protein fractional synthetic rate (FSR) or the RNA-to-protein ratio. These data are in agreement with our previous study showing no sex differences in mixed muscle protein FSR and in basal amino acid kinetics across the leg in young men and women when data were expressed relative to lean leg mass [1]. However, in the same study, we also highlighted the finding that when the leg kinetic data were adjusted relative to leg volume, men displayed a higher amino acid turnover rate. This is in agreement with an earlier study of forearm muscle protein kinetics in young men and women [3]. When expressed per unit of forearm volume men had greater net phenylalanine release and protein degradation and synthesis, but when expressed per unit of forearm muscle there were no sex differences. The results of these studies contribute to the hypothesis that potential sex differences in muscle protein synthesis are due to the absolute differences in muscle mass, rather than differences in intracellular protein turnover. While most studies conducted on young adults agree there are no differences in protein metabolism between adult men and women [1,2••], one recent study did find a sex difference between young men (mean age 23 years) and women (mean age 21 years). In this study, contrary to the previous reports, women were found to have higher lean body mass-adjusted whole-body proteolysis. In addition, mixed muscle protein FSR was also higher in women, but there was no sex difference in the relative contribution of muscle to whole-body protein synthesis or nonmuscle protein synthesis [5•]. However, it is noteworthy to underscore the significant methodological differences between this study and those previously mentioned above that did not detect any sex dimorphism in protein metabolism. Henderson *et al.* used a single-pool steady-state model with [^{15}N]phenylalanine and [$^{2}H_4$]tyrosine as tracers, whereas the other studies used two-pool or three-pool models with leucine, phenylalanine, or a combination of multiple amino acids as tracers [1,16]. These differences might have played a role, particularly with regards to whole-body protein kinetics, as the use of the single-pool model may lead to an overestimation of the precursor pool enrichment with consequent underestimation of the whole-body protein kinetic parameters.

It remains undetermined whether there are sex differences in nonskeletal muscle protein turnover. Several investigators have in fact reported a significantly higher whole-body leucine oxidation in men, both at rest and during aerobic exercise, even after correction of the data by lean body mass [6,16–19]. As the recent muscle kinetic data from most laboratories mentioned above show that protein turnover is not significantly different between the sexes once differences in body composition are accounted for, the greater whole-body leucine oxidation rates reported in men are likely due to sex differences in

leucine oxidation at the level of other tissues, for example, the splanchnic bed. Studies will be necessary to further address this point.

Adiposity is another potential contributor to protein turnover. The adipose tissue is now recognized as an independent endocrine organ, which secretes a number of hormones and cytokines that may influence protein kinetics [20,21]. In a study comparing nonobese, obese nondiabetic, and obese type 2 diabetic patients no sex differences in whole-body protein kinetics were found when data were adjusted for fat-free mass. However, in absolute terms, the obese type 2 diabetics had greater whole-body protein flux, synthesis, and breakdown than the nondiabetic obese and nonobese patients [22]. Additionally, the obese nondiabetics had greater whole-body protein flux, synthesis, and breakdown than the nonobese patients. In a separate study, leucine rate of appearance and nonoxidative leucine disposal (adjusted by fat-free mass) were higher in severely obese (BMI >35 kg/m^2) than moderately obese (BMI 30–32 kg/m^2) women [23•]. Similarly, obese men had a higher total protein and mitochondrial protein FSR than nonobese men [24•]. As a result of these studies, we can hypothesize that some of the differences previously reported between sexes and between studies may be due at least in part to the effect of different degrees of adiposity of the study subjects.

Physical activity is another potential major confounder that can artificially induce or mask sex differences in protein turnover. In general, the response of muscle protein metabolism to exercise is fairly similar in women and men [2••], although some minor differences have been reported in leucine oxidation during aerobic exercise [6]. However, the main difference between women and men may reside on the habitual level of exercise and nonexercise physical activity, particularly in nonathletes. Specific studies will be necessary to clarify this point.

Older adults

Aging induces significant loss of skeletal muscle mass, strength and function, termed sarcopenia [25], which increases the risk of disability, physical dependence, and also mortality [26]. Decreasing the rate of muscle loss, and, possibly, enhancing muscle function, are major goals for geriatricians and patients alike. Consequently, a considerable amount of protein metabolism research has been recently conducted in older adults to determine the mechanisms of muscle loss with aging, and find targets for interventions. Most investigators have focused on comparing protein turnover in young and older patients [27,28], sometimes including only one sex in the research design [28–31], and have not addressed sex differences [27,32,33]. Only a few papers have directly addressed the question of sex dimorphism in protein metabolism in older persons. Surprisingly, two of these papers reported a higher muscle protein synthesis rate in older women as compared to BMI-matched and age-matched men [5•,34], despite the women having approximately 25% less fat-free mass, total muscle mass, and leg muscle volume than the men. It is unclear, however, when these differences begin to manifest. One recent study suggests that such a sexual dimorphism does not occur until later in life, as muscle protein synthesis was reported to be similar in middle-aged women and men [4••]. However, another paper reported higher protein turnover rates in women throughout adult life [5•]. These latter whole-body protein turnover results obtained using phenylalanine and tyrosine tracers [5•] are in contrast with previous reports in which measures of whole-body protein breakdown relative to fat-free mass, as measured with a leucine tracer, were not found to be different between men and women [35,36]. As mentioned earlier, methodological issues and subject selection may have played a role in determining these discrepancies as the subjects were either morbidly obese [34] or overweight [5•], with women having between 25 and 40% more fat mass (relative to total body weight) than men. As adiposity can accelerate protein

turnover [22,23•,24•], it is possible that the reported differences between men and women, when present, could be mainly driven by differences in relative body fat mass rather than sex *per se*. Future studies are warranted.

Response to anabolic stimuli

The majority of research mentioned above was conducted under basal resting conditions. Several researchers have also examined the hypothesis that sex differences in protein turnover, which initiate and sustain the sexual dimorphism in muscle mass, may occur in response to anabolic stimulation, mainly nutrition and exercise.

In a recent paper, it has been reported that ingestion of a liquid meal increases mixed muscle protein synthesis in older men but not women. However, as fasting muscle protein synthesis was slightly but significantly higher in women, meal ingestion equalized the absolute protein synthesis rates between the sexes [4••]. Conversely, no sex differences were observed in the response of whole-body leucine turnover to feeding in these subjects. The same group also reported a lack of any sex differences in insulin-stimulated muscle protein synthesis in middle-aged persons [4••]. As these studies were all performed in a relatively small number of patients, it is still uncertain whether the response to feeding is truly different or not between women and men.

Resistance exercise has been shown to increase muscle protein synthesis equally in young men and women. Basal and postexercise mixed muscle protein FSR, intracellular phenylalanine concentration, and cell-signaling pathways involved in muscle protein synthesis were found to be not different between the sexes [2••]. However, postexercise differences in protein metabolism between women and men may exist when aerobic exercise is considered. For example, it has been shown that men oxidize more leucine than women during submaximal endurance exercise [6]. More recently, it has been shown that compared to a low-protein postexercise feeding, a high-protein postexercise feeding resulted in a better sprint performance 60 h later in young men cyclists [37]. When the same experiment was repeated in young women cyclists, sprint performance was independent of protein content of the previous meal [38]. It is well established that young men and women have different responses to fat metabolism during exercise and carbohydrate loading prior to exercise [39–42]; therefore, it is not surprising that protein dynamics in response to exercise may also be different. More research is needed to further clarify these apparent differences.

Conclusion

Throughout most points of the lifespan, men and women of similar health status and BMI display fairly similar protein turnover rates. However, some investigations have reported some minor sexual dimorphism in protein metabolism, which may be partly due to differences in fat-free mass and/or methodology. In periods of significant changes in the hormonal milieu (puberty and menopause), sex differences may become more evident. Finally, anabolic stimuli such as feeding and exercise may help highlight any discrepancies in protein turnover between men and women. However, given the limited sample size of most of these studies it is still not possible to draw a solid conclusion. Future studies are warranted.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 107).

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