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ORIGINAL RESEARCH

Alterations in IGF-I affect elderly: role of physical activity

Sagiv Moran · Yamin Chen · Amir Ruthie · Yenon Nir

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Abstract The growth hormone–insulin-like growth factor I (IGF-I) axis is an important physiological regulator muscle for development. Although there is evidence that aging muscle retains the ability to synthesize IGF-I, there is also evidence that aging may be associated with attenuation of the ability of exercise to induce an isoform of IGF-I that promotes satellite cell proliferation. However, it is clear that overexpression of IGF-I in the muscle can protect against age-related sarcopenia. Strength training appears to be the intervention of choice for the prevention and treatment of sarcopenia. IGF-I has been implicated in the loss of the muscle with age, and IGF-I expression levels change as a consequence of strength training in older adults. However, it seems that advancing age, rather than declining serum levels of IGF-I, appears to be a major determinant of life-time changes in body composition in women and men. We concluded that resistive exercise is a significant determinant of muscle mass and function. Elevated levels of IGF-I have been found in physically active compared to sedentary individuals. Recent work suggests that IGF-I as a mediator plays an important role in muscle hypertrophy and angiogenesis, both of which characterize the anabolic adaptation of muscles to exercise.

Keywords Aerobic exercise · Aging · Growth factors · Resistive training · Sarcopenia

Human muscle strength declines at the rate of 12–14% per decade after the age of 50 years [66, 68]. This loss of strength with age is due to many factors but is primarily attributed to a loss of muscle mass bringing to sarcopenia [30, 86]. Sarcopenia is related to a loss of functional abilities [82], dependency [83], increased risk of falls, fractures [5, 67], and decreased bone mineral density [94]. Thus, sarcopenia has negative consequences for the health status and functional abilities of older adults. Recent research has addressed the hypothesis that growth hormone (GH) and insulin-like growth factor I (IGF-I) have an anabolic effect in adults, including the elderly. These hormones stimulate whole-body and muscle protein synthesis, at least under some conditions. Serum IGF-I levels as well as GH secretion decline with advancing age [26, 92, 93]. The declining activity of the GH–IGF-I axis with advancing age may contribute to the decrease in lean body mass and the increase in mass of adipose tissue that occur with aging [17, 44, 100].

Mechanisms underlying age-associated change in body composition such as an increase in body fat and a decrease in bone mass are not fully understood. Decrease in GH secretion and serum IGF-I levels with aging may have some impact on these processes. IGF-I is predominantly synthesized in the liver, and serum levels of IGF-I are tightly regulated by GH release [79] and are indicated to reflect the integrated 24-h secretion of GH [15]. IGF-I is a trophic factor required for the proliferation of myoblasts, the proliferation of myogenic differentiation, and subsequent growth and hypertrophy of myofibers [27]. IGF-I has been identified as a potent regulator of gene expression in the skeletal muscle. Excitation–contraction uncoupling has been identified as a mechanism underlying sarcopenia in the skeletal muscle in aging mammals. The basic mechanism for excitation–contraction uncoupling is a larger number of ryanodine receptors uncoupled to dihydropyridine receptors [17]. In addition to effects on muscle development, IGF-I facilitates

S. Moran (✉) · Y. Chen · A. Ruthie · Y. Nir
Biogenetic Laboratory, The Zinman College of Physical Education and Sport Sciences,
1515 Holcombe Blvd.,
Wingate 42902, Israel
e-mail: moransag@012.net.il

skeletal muscle dihydropyridine activity via tyrosine kinase–protein kinase C-dependent phosphorylation [18]. It has also shown that IGF-I-dependent dihydropyridine modulation is impaired in aging skeletal muscles [87], which may explain, at least partially, the decline in muscle force with aging [79]. It has been established that high levels of GH and IGF-I increase body weight, bolster bone and muscle mass, and enhance immune function [64]. These hormones also modulate the onset of puberty and generally increase reproductive fitness. Furthermore, administration of GH or IGF-I to aged animals restores many of the deficits associated with age, including declines in immune function, bone mass, and skin thickness [16]. In addition to the attenuation of age-related physical deficits, administration of IGF-I to rodents prevents the development of age-related cognitive impairments [71]. These findings and others not detailed in this review provide evidence that the deficiency in GH and IGF-I contributes to the aged phenotype.

As described earlier in this review, GH and IGF-I are potent anabolic hormones that increase cellular metabolism and as a result enhance the function of numerous tissues. This effect is particularly important during development, when GH and IGF-I levels are high, and during aging, when these hormones' levels are low. It was propose that the GH–IGF-I-induced increase in metabolic activity results in increased glucose utilization, increased oxygen consumption, and increased oxidative stress [69].

In middle and late adulthood, all people experience a series of progressive alterations in body composition [93]. The contraction in lean body mass reflects atrophic processes in the liver, kidney, spleen, skin, bone, and skeletal muscle because of slower muscle protein synthesis. These structural changes have been considered unavoidable results of aging. It has recently been proposed, however, that reduced availability of GH in late adulthood may contribute to such changes [74, 93]. This proposal is based on two lines of evidence. First, after about the age of 30, the secretion of GH by the pituitary gland tends to decline [25, 92, 93]. Second, GH secretion can be measured indirectly by measuring the plasma concentration of IGF-I (also known as somatomedin C), which is produced and released in response to GH [14]. Because GH is secreted in pulses, mostly during the early hours of sleep, it is difficult to measure the 24-h secretion of the substance directly. There is little diurnal variation in the plasma IGF-I concentration, and measurements of it are therefore a convenient indicator of GH secretion [14]. Therefore, the atrophy of the lean body mass, its component organs, and the enlargement mass of adipose tissue, which are characteristic of the elderly, result at least in part from diminished secretion of GH [74, 93]. If so, the age-related changes in body composition may be correctable in part by the administration of human GH, now readily available as a biosynthetic product [50].

In healthy individuals, the anabolic GH–IGF-I axis maintains muscle mass by suppressing protein degradation, increasing amino acid uptake, and stimulating protein synthesis [89]. The bioavailability of IGF-I is dependent upon circulating IGF-I and IGF-I-binding protein (IGFBP) levels (fibroblast growth factor [FGF] 2). Like IGF-I, FGF-2 is ubiquitously distributed and is one of the most potent mitogens for myoblasts and plays a critical role in myogenesis and capillary angiogenesis during muscle development [4]. Furthermore, stress-induced muscle remodeling and repair after extensive pathological injuries are believed to be activated by FGF-2. It is also suggested that low levels of serum IGF-I may be involved in the progression of dementia in the oldest of the old [104]. An age-associated decline in serum IGF-I levels exist even in extremely old age, without being associated with lower body mass index, hypoalbuminemia, or poor functional status.

Less than 5% of the healthy men 20 to 40 years old have plasma IGF-I values of less than 350 U l^{-1}, but the values are below this figure in 30% of the healthy men more than 60 [92]. Likewise, the nocturnal pulses of GH secretion become smaller or disappear with advanced age. If the plasma concentration of IGF-I falls below 350 U l^{-1} in older adults, no spontaneous circulating pulses of GH can be detected by currently available radioimmunoassay methods [92]. The concomitant decline in plasma concentrations of both hormones supports the view that the decrease in IGF-I results from diminished GH secretion [26, 92]. Second, diminished secretion of GH is accompanied not only by a fall in the plasma IGF-I concentration but also by atrophy of the lean body mass and expansion of the mass of adipose tissue [93]. It may not be relevant to use the serum IGF-I level as an indicator of GH release in centenarians, but instead, the IGF-I level appeared to reflect its short-term nutritional status as a rapid turnover protein. Further longitudinal studies, including assessment of IGFBPs and the association of IGF-I with dementia, should be conducted in the future.

Physiological age-related muscle loss and weakness is referred to as sarcopenia. The etiology is multifactorial and not fully understood. However, during aging, there is evidence of declining activity of the GH–IGF-I axis, which is mainly dependent on age-related variations in the hypothalamic control of somatotroph function (somatopause). It has been reported that in older individuals, there is reduced GH production and attenuated IGF-I response to high-resistance exercise [39]. Furthermore, previous studies have demonstrated a delayed response to FGF-2 with aging satellite cells, most probably because of delayed expression of FGF-2 receptors and delayed binding of FGF-2 to the receptors [9].

The results of cross-sectional studies suggest that sarcopenia is a major determinant of aging-associated

decrements in strength [31, 84]. Sarcopenia involves significant alterations in the architecture of human muscles that stem from a loss of some myofibers and the remodeling of those that remain [77, 101]. It has been suggested that sarcopenia results from both a loss of myofibers and a decrease in type II fiber size [65]. In humans, age-related myofiber loss and myofiber atrophy generally involve type IIa and IIb fibers, with a greater impact seen in the IIb fibers [65, 76].

From results of epidemiological studies and interventional trials using recombinant human GH, serum IGF-I levels have shown a positive association with muscle strength, lean body mass [95, 96], and physical activity [62], and they have shown a negative correlation with body mass index and the body fat index [81, 93]. However, in the elderly population, serum IGF-I levels have been reported to have no association with body mass index, body fat, or lean body mass, but they have been significantly correlated with nutritional parameters and liver function [41]. Moreover, recent epidemiologic studies demonstrated that low serum IGF-I levels may be associated with increased cardiovascular risk [48] and cognitive impairment [3] in the elderly population. These data suggest that IGF-I values in elderly persons may not represent their GH activities and determinants of serum IGF-I levels may differ from middle-aged individuals.

IGF-I response to either acute or chronic physical activity remains unclear [59]. Based on several studies done in healthy young adults, there is an increase in circulating IGF-I in response to different types of exercise, either aerobic, resistance, or heavy ergometer cycling [10, 54, 58, 91], while exercise training improves local IGF-I expression without significant changes of systemic parameters of the GH–IGF-I axis. These findings indicate that exercise training has the therapeutic potential to attenuate peripheral skeletal muscle alterations in particular with respect to local IGF-I expression in patients with moderate cardiac heart failure [38].

Growing evidence suggest that IGF-I and FGF-2 play an important role in exercise-induced muscle hypertrophy and angiogenesis. Importantly, recent work suggests the possible synergism of local FGF-2 and circulating IGF-I in the regulation of the anabolic adaptation of muscles to exercise [103]. The mechanisms that mediate the functional adaptation of the skeletal muscle appear to reside, primarily, within the impacted muscle. This circumstance accounts for the specific adaptation of effected muscles. The skeletal muscle loading experienced as part of occupational and athletic activities often includes periods of loaded muscle shortening and lengthening as well as periods during which muscles are activated but no external length changes occur (isometric loading). The relative contribution of these three modes of loading to the processes that stimulate muscle adaptation is of great interest in the area of programmed resistance training. It is well known that resistance training paradigms that include sufficient intensity, frequency, and duration can induce skeletal muscle adaptations that include compensatory hypertrophy [57]. It has also become common for such programs to emphasize one particular training mode (e.g., lengthening, shortening, or isometric). Training programs that have employed relatively pure shortening, lengthening, or isometric loading have demonstrated that each of these three modes of loading can stimulate muscle adaptations, including hypertrophy, and strength gains [19, 32, 33, 42, 45, 51, 53, 60, 73, 75, 102, 105].

Muscle mass is arguably the most important determinant of functional capabilities and as such is an important consideration in a number of occupational and clinical settings. Load-bearing or resistance-type exercise is the primary method for the maintenance of, increase in, or recovery of muscle mass. This can be particularly important in settings where muscle atrophy is a risk such as bed rest or spaceflight [47]. It is well established that exercise is a significant determinant of muscle mass and function.

As mentioned previously, the GH–IGF-I axis and FGF-2 are important physiological regulators of fetal and postnatal growth and development [48]. Physical exercise has a significant impact on the GH–IGF-I axis. However, data from studies evaluating IGF-I response to exercise are controversial. Findings indicate that although both peak aerobic capacity and circulating IGF-I levels decline with age, aerobic capacity is not independently related to circulating IGF-I in healthy men and women across the adult lifespan [43].

Decline in muscle strength and muscle mass with age is well documented [50, 51] and is associated with a deterioration of health status and functional abilities [5, 47]. Strength training is thought to be an effective intervention against sarcopenia because it increases muscle strength and muscle mass in the elderly [22, 23, 29, 37, 46, 98]. Muscle mass and neuromuscular factors contribute to losses in strength with age [52, 63] and gains in strength with strength training [34, 37].

While some studies have demonstrated no change in circulating IGF-I levels, in many others, exercise induced a transient increase in IGF-I levels resulting from acute release of IGF-I from its binding proteins [59]. Furthermore, IGF-I response depends on exercise type, intensity, and duration as well as training status [88, 90]. However, Bermon et al. [8] investigated the effects of an acute bout of exercise on total and free IGF-I and IGFBP-3 plasma concentrations, 32 healthy elderly subjects (67–80 years, 16 men) performed a strength test. Subjects were then randomly assigned to habitual physical activity or to an 8-week strength-training program. After 8 weeks, both sedentary and trained groups underwent blood samplings

under the abovementioned conditions. The exercising group showed increased total and free IGF-I concentrations immediately (+17.7 and +93.8%, respectively) and 6 h (+7.5 and +31.2%, respectively) after the test, whereas no significant changes in IGFBP-3 concentrations were observed in either exercising or resting control groups. Strength training induced no significant changes in baseline IGF-I and IGFBP-3 concentrations. Trained and sedentary groups showed a similar hormonal response pattern to the strength test, which consisted of increased total and free IGF-I concentrations, indicating that strength exercise can induce an early and sustained IGF-I release, in elderly subjects, regardless of their training status. Resistance exercise is known to dramatically increase protein synthesis, accretion, and muscle hypertrophy [2, 21]. Whereas Adams et al. [2, 28] reported that muscle IGF-I is elevated early in the time course of myogenesis in overloaded skeletal muscle, the precise role that IGF-I plays in mediating this process (systemic vs local) is still poorly defined [21].

There are not many studies on IGF-I response to exercise in older age during which the activity of the GH–IGF-I axes declines. Specifically, the response of older individuals to acute all-out anaerobic exercise has not yet been investigated. In the few studies conducted to date in older individuals, controversial results have been obtained [36, 85, 97]. Most studies dealing with the acute response of IGF-I to resistance exercise have shown no change in serum IGF-I level [11, 55]. The chronic adaptation of circulating IGF-I in response to resistive training is controversial as well. While a few studies have reported no change in resting levels of IGF-I after short-term resistance training [40, 56, 99], other studies have shown elevations in IGF-I during short/long-term resistance-training programs [88, 91], particularly during high-volume training [61, 72]. Furthermore, IGF-I increased after endurance type physical training [94] and triathlon training [70]. The mechanism of this response has not been fully resolved and likely involves both increased skeletal muscle IGF-I release and increased clearance rate of IGF-I from IGFBP [59].

Anaerobic power is characterized by exposing subjects to a very high degree of sudden strenuous all-out exercise. Little data are available on changes in the levels of IGF-I and FGF-2 after sudden strenuous anaerobic exercise in healthy older subjects. Furthermore, the effect of fitness level on these responses has not been studied yet. It has been hypothesized [4] that aerobically trained older men would manifest greater alterations in serum IGF-I and FGF-2 levels after the Wingate anaerobic test, than the untrained men.

When evaluating the effect of fitness level on IGF-I and FGF-2 responses after all-out anaerobic exercise in healthy older men, suggested fitness level dependent alterations in the response of older individuals to the Wingate anaerobic exercise regarding the levels of IGF-I and FGF-2. The study demonstrates that trained compared to untrained older men had lower pre-exercise serum levels of IGF-I and higher pre-exercise FGF-2 levels. After the Wingate anaerobic exercise, there was a transient elevation in the level of IGF-I in both higher-fit and lower-fit individuals. However, IGF-I elevation was significant only in the trained individuals. Contrary to IGF-I, postexercise levels of FGF-2 decreased dramatically to almost undetectable levels in both groups and remained low for 50 min into recovery. The data of the study of Amir et al. [4] suggest that during aging, fitness level is an important determinant of growth factors responses to exercise.

By modulating the anabolic effects of growth factors, the fitness level may have positive effects on aging-associated skeletal muscle loss. This suggests that despite a decline in the GH–IGF-I axis in older age, IGF-I response to acute exercise improves among better-trained subjects. The exercise-induced anabolic adaptations of skeletal muscle are mostly attributed to IGF-I. Given that IGF-I regulation is involved in aging-associated sarcopenia and that anaerobic muscle activity is represented in many daily life activities of the elderly, these results highlight the clinical significance of IGF-I regulation during aging and further support the notion that exercise training especially for older individuals can be beneficial.

Surprisingly, Amir et al. [4] have suggested that at rest, circulating IGF-I in the trained were lower by 17% compared to the untrained older individuals. The discrepancy between higher levels of IGF-I in healthy young after 2 weeks of strenuous aerobic training [94] and this data showing lower levels of IGF-I in trained compared to untrained older individuals might be explained by the finding of higher IGFBP-1 levels in older age [7]. Unlike IGF-I response, pre-exercise FGF-2 was 14% higher in the trained compared to the untrained older individuals and decreased dramatically (75% reduction in the trained group and 93% reduction in the untrained group), in response to the all-out anaerobic exercise, remaining low for at least 50 min into recovery. Similar results have been obtained by Elyakim et al. [20, 78], who found a significant reduction in circulating FGF-2 in healthy young individuals after a single-wrist flexion exercise. Elyakim et al. [20] hypothesized that exercise promotes a marked reduction in circulating FGF-2 by inducing increased binding of FGF-2 to endothelial and muscle cells receptors resulting in redistribution and local capture. However, the effect of exercise training was evaluated in none of these studies. Previous studies employing either knee-extensor ergometer training or intense intermittent endurance training have analyzed the adaptation of human skeletal muscle to exercise training at the transcriptional level. Because there was a slight or no change in the level of skeletal muscle

FGF-2 messenger ribonucleic acid [49], increased synthesis does not seem to be the mechanism responsible for the elevation in pre-exercise circulating FGF-2. However, in vitro studies on differentiated human skeletal muscle cultures have demonstrated that mechanical load induces sarcoplasmic wounding and FGF-2 release from myofibers with a linear correlation between the degree of mechanical load and the amount of myofiber wounding and FGF-2 release [12, 13]. In light of these results, it is possible that prolonged resistive training imitates mechanical load by causing myofiber damage and FGF-2 release into circulation. The resulting increase in circulating FGF-2 might be an important compensatory mechanism during aging, in which the anabolic effects of FGF-2 are reduced by decreased binding affinity and by the delayed expression of local FGF-2 receptors [9].

It may be speculated that the changes in IGF-I and FGF-2 may have positive anabolic effects on the induction of muscle and capillary growth, resulting in muscle hypertrophy and angiogenesis. Thus, the fitness-induced alteration in IGF-I and FGF-2 levels may counteract the process of skeletal muscle loss, by modulating their positive anabolic effects, on skeletal muscle. This may have clinical implications during aging in which the declined activity of growth factors is a major determinant of the loss of muscle strength and function. Therefore, during aging, the fitness level can alter circulating levels of IGF-I and FGF-2 and can affect the response of both mediators to all-out anaerobic, resistive, and aerobic exercises. Future studies to elucidate the mechanisms behind these changes are desirable.

Conclusions

Exercise induce increases in IGF-I, IGF-I receptors, and IGF-I-activated signaling pathways. Although there is evidence that the aging muscle retains the ability to synthesize IGF-I, there is also evidence that aging may be associated with attenuation of the ability of exercise to induce an isoform of IGF-I that promotes satellite cell proliferation. Moreover, the aging muscle may be resistant to IGF-I, an effect that is reversed by exercise. However, it is clear that the overexpression of IGF-I in the muscle can protect against age-related sarcopenia [1]. Strength training appears to be the intervention of choice for the prevention and treatment of sarcopenia, based on efficacy and safety concerns with other interventions [6, 35]. IGF-I has been implicated in the loss of muscle with age [35], and IGF-I expression levels change as a consequence of strength training in older adults [24]. The literature has shown that in older adults, carriers of the 192 allele at the IGF1 locus have greater strength gains than noncarriers with strength training. However, it seems that advancing age, rather than declining serum levels of IGF-I, appears to be a major determinant of life-time changes in body composition in women and men [80].

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