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Insulin Resistance and Muscle Strength in Older Persons

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Background. The functional consequences of an age-related insulin resistance (IR) state on muscle functioning are unknown. Because insulin is needed for adequate muscle function, an age-related insulin-resistant state may also be a determining factor. We evaluated the relationship between IR and handgrip muscle strength in men and women from a large population-based study ($n = 968$).

Methods. The degree of IR was evaluated by the homeostasis model assessment (HOMA) and muscle strength was assessed using handgrip.

Results. Simple sex-stratified correlations demonstrated that, in men, body mass index-adjusted handgrip strength correlated positively with physical activity ($r = 0.321$; $p < .001$), muscle area ($r = 0.420$; $p < .001$), muscle density ($r = 0.263$; $p = .001$), plasma albumin ($r = 0.156$; $p = .001$), insulin-like growth factor-1 ($r = 0.258$; $p < .001$), calcium ($r = 0.140$; $p = .006$), and testosterone ($r = 0.325$; $p < .001$) concentrations, whereas a negative association was found for age ($r = –0.659$; $p < .001$) and myoglobin plasma levels ($r = –0.164$; $p = .001$). In women, body mass index-adjusted handgrip strength correlated positively with physical activity ($r = 0.280$; $p < .001$), muscle area ($r = 0.306$; $p < .001$), muscle density ($r = 0.341$; $p = .001$), plasma albumin ($r = 0.140$; $p = .001$), and insulin-like growth factor-1 ($r = 0.300$; $p < .001$), whereas a negative association was found for age ($r = –0.563$; $p < .001$), myoglobin levels ($r = –0.164$; $p = .001$), and IR ($r = –0.130$; $p = .04$).

Conclusions. Sex-stratified analyses adjusted for multiple confounders showed that the relationship between IR and handgrip strength was found significant in women, whereas it was negligible and not significant in men.

THE mechanisms and etiology responsible for age-related decline in muscle functioning are complex. A decline in muscle strength, a common phenomenon observed over the aging process, is attributable both to atrophy of the skeletal muscle mass fibers and to qualitative changes in muscle tissue that reduce the magnitude of generated force (1–4). However, the underlying mechanisms responsible for the age-associated muscle mass and function decline are still unknown. Several hypotheses have been proposed, such as: a) intrinsic biochemical and physical changes (1); b) reduced neuronal stimulation due to reduction in the number of α-motoneurons or their activity (5); c) oxidative damage of DNA (6); d) mitochondrial DNA mutations in muscle tissue (7); and e) influence of external factors such as nutrition, disuse, and disease typically observed in older persons (1,8).

It is interesting that there is growing evidence that age-related changes of hormonal regulation play an important role in most of the pathophysiologic mechanisms described above and, therefore, may be implicated in the pathogenesis of age-related impairment of muscle strength (9,10). In particular, insulin may also be an important determinant of muscle function, as glucose uptake is necessary for adequate muscle contraction. Another important role played by insulin is its ability to repress whole-body proteolysis, thus shifting total-body metabolism towards an anabolic state (11,12). Age-related insulin resistance (IR) has been shown to contribute to impaired glucose handling in elderly persons (13). Therefore, it is plausible that IR may be a determinant of poor muscle strength in older persons. Furthermore, a reduction of insulin peripheral activity may reduce the muscle tissue anabolic rate leading to a relative catabolic state and, in turn, contributing to the impairment in muscle functioning. Therefore, using data from a population-based study performed in Tuscany (Italy), we tested the hypothesis that IR is associated with reduced skeletal muscle strength in older men and women.

Methods

Participants

This study is part of the InCHIANTI Study, a prospective population-based study of older persons designed by the staff at the Laboratory of Clinical Epidemiology of the Italian National Research Council of Aging, (INRCA, Florence, Italy) and carried out in the Chianti geographic area of Tuscany, Italy. The InCHIANTI Study, which has been described in detail elsewhere (14) was performed in a representative sample of the Italian population. In brief, 1453 participants (age range 20–104 years, 91% of the eligible population) were selected from the residents in the two municipalities of Greve in Chianti and Bagno a Ripoli (14). Data collection started in September 1998 and was completed in March 2000.

Our study population consisted of 968 participants between 22 and 104 years of age, selected from the cohort from Greve and Bagno a Ripoli, excluding those affected by diabetes (diagnosed according to the criteria of the American Diabetes Association) (15) or alcoholism, participants who were taking drugs known to interfere with muscle strength, and those who

were affected by symptomatic osteoarthritis. All participants undergoing any pharmaceutical treatment were categorized into: drug intakers (participants currently in drug therapy) and not drug intakers (participants not undergoing any drug therapy). All participants gave their informed consent before participating in the study, which was approved by the ethical committee of our institution.

Anthropometric Determinations

Weight and height were measured using standard techniques. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. The waist circumference was measured at the midpoint between the lower rib margin and the iliac crest (normally umbilical level) and hip circumference at the level of the trochanters.

Metabolic Determinations and Analytical Methods

Blood samples were collected in the morning after the participants had been fasting for at least 8 hours. Using data on fasting glucose and insulin, we calculated the degree of IR according to the homeostasis model assessment (HOMA), which is a good index for assessing IR across a wide range of values and has a good correlation with insulin-mediated glucose uptake calculated by the euglycemic glucose clamp (16,17).

Baseline blood pressure was recorded by using a standard mercury sphygmomanometer. Three measurements were performed with the participant in supine position, and the average of the last two measures was used in the analysis.

Blood samples for the assay of insulin were collected in EDTA tubes, and the plasma was immediately aliquotted and stored at −80°C until assayed. Plasma insulin level was determined with a commercial double-antibody, solid-phase radioimmunoassay (intra-assay coefficient of variation = 3.1 + 0.3%; Sorin Biomedica, Milan, Italy). Cross-reactivity with human proinsulin was 0.3%.

Serum glucose level was determined by using an enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany) and a Roche-Hitachi 917 analyzer. Commercial enzymatic tests were used for determining serum total- and high-density lipoprotein (HDL) cholesterol and triglyceride (Roche Diagnostics, Mannheim, Germany) levels. Serum low density lipoprotein (LDL) cholesterol levels were calculated by the Friedewald formula (18). Total plasma insulin-like growth factor-1 (IGF-1) concentrations (Diagnostic System Laboratories, Milan, Italy) were determined by radioimmunoassay.

Serum albumin concentration was measured with an agarose electrophoretic technique (Hydragel Protein(E) 15/30; Sebia, Issy-les-Moulineaux, France). Plasma total testosterone level was assayed using commercial radioimmunologic kits (Diagnostic Systems Laboratories, Los Angeles, CA). Myoglobin was measured by sandwich enzyme-linked immunosorbent assay (ELISA) immunoassay using an anti-myoglobin monoclonal antibody and an anti-myoglobin polyclonal antibody (Roche Diagnostics).

Physical Activity

A modified version of the European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire was given to participants. This questionnaire has been validated with objective measures of energy expenditure in a large epidemiological study (19). All participants were asked to describe their physical activity over the past year. Their responses were combined to estimate their level of physical activity into 7 categories ranging from 1 (bedridden) to 7 (high intense physical activity).

Handgrip Muscle Strength

Isometric grip strength was assessed using a handheld dynamometer (Nicholas Manual Muscle Tester, model BK-5474; Fred Sammons, Burr Ridge, IL) following a standardized measurement protocol that has been shown to provide highly reliable data (20). Handgrip strength has a good predictive validity for disability (21) and mortality (22). In our study, handgrip was a good proxy measure of global muscle strength, as it significantly correlated with other muscle groups with correlation coefficients ranging from $r = 0.65$ with ankle flexion to 0.72 (hip adduction).

Muscle Area and Density

A lower leg peripheral quantitative computerized tomography (pQCT) was performed in all participants using a recent generation device (XCT 2000; Stratec, Pforzheim, Germany) to evaluate calf muscle cross-sectional area. Data were derived from standard 2.5-mm-thick transverse scans obtained at 66% of the tibia length. The cross-sectional images obtained from the scans were analyzed using BonAlyse software (Jyvaskyla, Finland). Different tissues in the analysis were separated according to diverse density thresholds. The average density of muscle tissue was also calculated and used in the analysis.

Osteoarthritis

Osteoarthritis was assessed using the Western Ontario McMaster Osteoarthritis (WOMAC) index (23).

Calculation and Statistical Analysis

All analyses were performed separately in men and women. Descriptive results of continuous variables' values are presented as means ± standard deviation or as means ± standard error. To approximate normal distributions, log-transformed values for plasma insulin concentration and degree of IR (HOMA) were used in the analysis and back-transformed for data presentation in Tables 1 and 2. Associations among variables were tested with Pearson product-moment correlations. The analysis of variance test was used to evaluate the differences in clinical and metabolic characteristics between men and women. To test the correlation between handgrip muscle strength and HOMA, mean scores were calculated according to IR tertiles and compared using analysis of variance-based tests for trend. To verify whether a certain degree of IR (HOMA) was significantly associated with handgrip muscle strength, we categorized participants into two categories of IR: high degree when the measure was >2 standard deviations above the mean, or low degree of IR (HOMA) when the measure was below that of the high degree definition (such dichotomous variable was then used as an independent variable in multiple linear regression models).

Multivariate linear regression models were used to

Table 1. Characteristics of Study Population ($N = 968$)

Characteristics	Women ($N = 500$)	Men ($N = 468$)	p
Age, y	68 ± 17	67 ± 16	NS
Sex, *n*	500	468	
BMI, kg/m^2	27 ± 4	27 ± 3	NS
Glucose, mmol/L	4.8 ± 0.6	4.9 ± 0.6	.018
Insulin, pmol/L	63 ± 37	64 ± 38	NS
Insulin resistance, HOMA	2.33 ± 1.53	2.31 ± 1.46	NS
Total IGF-1, ng/ml	123 ± 68	139 ± 65	<.001
WHR	0.89 ± 0.08	0.94 ± 0.07	<.001
Mean blood pressure, mmHg	103 ± 13	104 ± 11	NS
Systolic blood pressure, mmHg	145 ± 23	144 ± 19	NS
Diastolic blood pressure, mmHg	82 ± 10	83 ± 9	NS
Myglobulin, μg/L	51.4 ± 50.6	63.3 ± 53.1	<.001
Albumin, g/L	42 ± 3	43 ± 3	<.001
Calcium, mmol/L	2.37 ± 0.15	2.37 ± 0.16	NS
Drug intake, yes/no	360/162	318/150	
Physical activity score*	3.2 ± 1.0	3.7 ± 1.1	<.001
Testosterone, nmol/L		15.71 ± 4.37	
Handgrip strength, kg	23 ± 9	39 ± 14	<.001

Notes: Values are expressed as means ± standard deviation. Blood values were obtained on samples obtained after at least 8 hours of fasting.

*See Methods.

BMI = body mass index; IR (HOMA) = homeostasis model assessment; IGF-1 = insulin-like growth factor-1; WHR = waist–hip ratio; NS = not significant.

analyze the independent association of multiple confounders with BMI-adjusted handgrip muscle strength as dependent variable. BMI-adjusted handgrip strength was performed separately in men and women. Total plasma testosterone concentrations were added to the multivariate model fitted in men. Statistical analyses were performed using the SPSS software package (Chicago, IL).

Results

The characteristics of the study population are reported in Table 1. Simple correlations demonstrated that, in all participants ($n = 968$), BMI-adjusted handgrip muscle strength correlated positively with physical activity ($r = 0.405$; $p < .001$), muscle area ($r = 0.589$; $p < .001$), muscle density ($r = 0.263$; $p < .001$), plasma albumin ($r = 0.249$; $p = .001$), and IGF-1 ($r = 0.317$; $p < .001$) concentrations, whereas a negative association was found for age ($r = –0.510$; $p < .001$) and IR ($r = –0.131$; $p = .030$).

In men, BMI-adjusted handgrip strength correlated positively with physical activity ($r = 0.321$; $p < .001$), muscle area ($r = 0.420$; $p < .001$), muscle density ($r = 0.263$; $p = .001$), plasma albumin ($r = 0.156$; $p = .001$), IGF-1 ($r = 0.258$; $p < .001$), calcium ($r = 0.140$; $p = .006$), and testosterone ($r = 0.325$; $p < .001$) concentrations, whereas a negative association was found for age ($r = –0.659$; $p < .001$) and myoglobin plasma concentrations ($r = –0.164$; $p = .001$). No significant correlation was found between BMI-adjusted handgrip strength and IR ($r = 0.018$; $p = .719$).

In women, BMI-adjusted handgrip strength correlated positively with physical activity ($r = 0.280$; $p < .001$), muscle area ($r = 0.306$; $p < .001$), muscle density ($r = 0.341$; $p = .001$), plasma albumin ($r = 0.140$; $p = .001$), and IGF-1 ($r = 0.300$; $p < .001$) concentrations, whereas a negative association was found for age ($r = –0.563$; $p < .001$), myoglobin plasma concentrations ($r = –0.164$; $p = .001$), and IR (HOMA) ($r = –0.140$; $p = .02$).

BMI-adjusted average values of handgrip muscle strength were calculated according to IR tertiles in women. There was a progressive and significant decline in muscle strength across IR tertiles (Table 2).

The relationship between a high versus low degree of IR and BMI-adjusted handgrip muscle strength independent of age, sex, waist–hip ratio, mean arterial blood pressure, drug intake, level of physical activity, and plasma levels of albumin, myoglobin, and calcium was tested in a linear multiple regression model. In a model fitted on all participants, age, sex, high versus low degree of IR, muscle area, and physical activity were independent determinants of handgrip muscle strength. In sex-stratified multivariate analyses, we found that, in women, high versus low degree of IR, age, and muscle area were independently associated with BMI-adjusted handgrip muscle strength (Table 3). In a model restricted to men, only age, physical activity, testosterone levels, and muscle area were independently associated with BMI-adjusted handgrip muscle strength (Table 3).

Table 2. Clinical and Metabolic Characteristics Across IR Tertiles in Women ($N = 500$)

Characteristics	IR Tertiles			p for Trend*
	1st ($N = 187$)	2nd ($N = 177$)	3rd ($N = 136$)	
HOMA	1.2 ± 0.4	2.2 ± 0.3	4.1 ± 1.8	
Age, y	66 ± 19	68 ± 16	70 ± 13	NS
BMI, kg/m^2	25.6 ± 4.2	26.6 ± 4.1	27.8 ± 4.7	<.001
WHR	0.87 ± 0.07	0.89 ± 0.10	0.90 ± 0.07	NS
Insulin, pmol/L	40.9 ± 7.2	73.9 ± 12.2	126.8 ± 46.6	<.001
Glucose, mmol/L	4.57 ± 0.5	4.88 ± 0.6	5.16 ± 0.7	<.001
Total cholesterol, mmol/L	5.55 ± 1.00	5.79 ± 1.06	5.82 ± 1.09	.035
LDL cholesterol, mmol/L	3.51 ± 0.90	3.77 ± 0.96	3.80 ± 0.98	.009
HDL cholesterol, mmol/L	1.63 ± 0.40	1.55 ± 0.36	1.45 ± 0.38	<.001
Triglycerides, mmol/L	1.12 ± 0.48	1.31 ± 0.60	1.53 ± 0.78	<.001
Total serum IGF-1, ng/mL	123 ± 75	124 ± 67	135 ± 67	NS
Physical activity score	3.3 ± 1.2	3.1 ± 0.8	3.1 ± 0.9	NS
Mean arterial blood pressure	100 ± 14	102 ± 13	107 ± 13	<.001
BMI-adjusted handgrip, kg	11.7 ± 18.0	14.7 ± 18.1	17.1 ± 17.6	.038

Notes: Values are expressed as means ± standard deviations.

IR = insulin resistance; BMI = body mass index; HOMA = homeostasis model assessment; IGF-1 = insulin-like growth factor-1; WHR = waist–hip ratio; LDL = low-density lipoprotein; HDL = high-density lipoprotein; NS = not significant.

Table 3. Multivariate Linear Regression Model Predicting BMI-Adjusted Handgrip Muscle Strength According to Insulin Resistance, After Adjusting for Potential Confounders

	BMI-Adjusted Handgrip Muscle Strength		
	Beta	*SE*	*p*
All ($R^2 = 0.493$)*			
HOMA (high vs low)	−8.559	4.100	.038
WHR	−22.938	9.489	.016
Age, y	−0.779	0.079	<.001
Sex (female vs male)	−27.305	2.119	<.001
Muscle area	0.003	0.001	<.001
Physical activity score	2.901	1.067	.007
Women ($R^2 = 0.378$)*			
HOMA (high vs low)	−10.087	4.527	.027
Age, y	−0.593	0.095	<.001
Muscle area	0.002	0.001	.034
Men ($R^2 = 0.551$)*			
Age, y	−0.884	0.104	<.001
Physical activity score	2.922	1.306	.026
Muscle area	0.003	0.001	<.001
Testosterone, ng/ml	1.821	0.823	.028

Notes: Values are expressed as unstandardized regression coefficients ± standard error (*SE*).

*Values were also adjusted for WHR, mean arterial blood pressure, drug intake, myoglobin, calcium, albumin, muscle density, and muscle mass.

BMI = body mass index; HOMA = homeostasis model assessment; WHR = waist–hip ratio.

Discussion

Using data from a representative sample of the general population, we demonstrated that an elevated degree of IR is associated with poor muscle strength. In sex-stratified analyses adjusted for confounders, the relationship between IR and handgrip strength was evident and statistically significant in women, whereas it was negligible and not significant in men.

There is growing evidence that age-related changes of hormonal regulation play a role in pathophysiological mechanisms implicated in the pathogenesis of age-related muscle functioning decline (9,10). Insulin is known to play a pivotal role in muscle functioning by increasing glucose uptake and promoting intracellular glucose metabolism (24). The contraction of type I fibers is more dependent on glucose entry and metabolism than is the contraction of type IIa (fast twitch, oxidative, glycolytic) or IIb (fast twitch, glycolytic) fibers (25). Type I fibers are more responsive to insulin, larger in women, and more represented in the muscle of older persons (26). In accordance with these data, Krivickas and colleagues (27) suggested that, in elderly women, impaired muscle function results from an age-related decline of maximal unloaded shortening velocity of type I fibers. This is consistent with our findings and provides a feasible explanation as to why IR is independently associated with muscle strength in women, but not in men.

Two mechanisms may explain how IR negatively affects muscle strength weakening. First, age-related IR is associated with impaired muscle glucose handling which impairs intracellular energy production and results in weaker muscle contraction. Second, a vicious circle connects insulin action and an age-related decline in physical activity (28), which progressively aggravates the degree of IR. Lazarus and colleagues (29) have also hypothesized that IR may be a result, rather than the cause, of impaired muscle strength in elderly men. Such hypothesis is based on the evidence that handgrip muscle strength was an independent determinant of fasting insulin levels in men. For reasons that remain unclear, we failed to confirm their findings.

In addition, some reports (4,13) have underlined that the aging process is significantly associated with both reduced muscle strength and IR. Many studies have suggested that weaker muscle strength is in large part attributable to an age-related reduction of muscle mass (2,28,29–31). In both sexes, muscle mass reaches its maximum between the second and third decade of life. However, peak muscle mass is higher in men than in women (2). Because handgrip muscle strength is considered to be an essential component in the frailty syndrome and frailty has been observed to be more common among women, the female sex could confer an intrinsic risk, considering that women have lower lean mass and strength than do age-matched men (32). It has also been observed that women may have a greater vulnerability to frailty on sarcopenia than men may have (32). We specifically tested the association between IR and midlife handgrip strength, because handgrip strength has been recognized as an important marker of functional capacity in old age (21). Moreover, in women with type 2 diabetes mellitus a more prevalent decline in muscle strength was found compared to men (33). Considering that IR is involved in the pathogenesis of type 2 diabetes mellitus, a worsening degree of IR could have a more negative effect on muscle strength in older women.

During the aging process, changes both in the contractile efficiency of muscle fibers and in tissue quality, such as pericellular fat infiltration, may also contribute to altered muscle function (34,35). Moreover, IR could be further worsened by the occurrence of pericellular fat accumulation both directly and through the increased production of pro-inflammatory cytokines (36). An increased proteolytic state, commonly observed in older persons, reflects a significant depletion in protein activity and has been reported to be associated with risk factors related to muscle strength and function, such as impaired mobility and balance, suggesting a link with sarcopenia (32). It is well known that insulin is capable of preventing protein breakdown by increasing amino acid availability needed for protein synthesis in muscle tissue (13). Therefore, age-related IR may define protein catabolism and muscle weakness. Furthermore, a decline in aged skeletal muscle force might also be due to a reduction of L-type calcium channels (37). Insulin has a stimulatory effect on intracellular calcium uptake (37), thus IR may negatively affect muscle contraction through this mechanism.

Recent findings have shown that low plasma IGF-1 levels have been associated with an age-related decline in muscle mass (38) and strength (39,40). In our study, we found a positive correlation between handgrip muscle strength and IGF-1, but such a relationship was no longer statistically significant after adjusting for multiple confounders.

It should be underlined that a potential limitation of our study could be in the use of the HOMA. Unquestionably, HOMA is less precise than the glucose clamp, but HOMA has a strong correlation with the euglycemic glucose clamp method in populations with a large age range (16).

Conclusion

Many studies have suggested that age-associated muscle strength impairment is multifactorial (1–5, 26). Our findings suggest that one of these critical factors results from metabolic changes that occur during the aging process. More studies will need to verify the role of IR on specific muscle tissue and functioning in aged individuals. Indeed, our data highlight a possible role of an IR state on determining skeletal muscle weakening in older women.

Acknowledgments

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