Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study

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Summary

Introduction: Sarcopenia, the loss of muscle mass and strength with age, is significantly associated with type 2 diabetes in older people.

Aim: To determine whether there is a relationship between grip strength and features of the metabolic syndrome.

Design: Cross-sectional study.

Methods: Data were collected on grip strength, fasting glucose, triglycerides and HDL cholesterol, blood pressure, waist circumference and 2 h glucose after an oral glucose tolerance test, in a population-based sample of 2677 men and women aged 59–73 years.

Results: In men and women combined, a standard deviation (SD) decrease in grip strength was significantly associated with higher: fasting triglycerides (0.05 SD unit increase, 95%CI 0.02–0.09, $p = 0.006$); blood pressure (OR 1.13, 95%CI 1.04–1.24, $p = 0.004$); waist circumference (0.08 SD unit increase, 95%CI 0.06–0.10, $p < 0.001$); 2 h glucose (0.07 SD unit increase, 95%CI 0.03–0.11, $p = 0.001$) and HOMA resistance (0.05 SD unit increase, 95%CI 0.01–0.09, $p = 0.008$), after adjustment for gender, weight, age, walking speed, social class, smoking habit and alcohol intake. Lower grip strength was also significantly associated with increased odds of having the metabolic syndrome according to both the ATPIII (OR 1.18, 95%CI 1.07–1.30, $p < 0.001$) and IDF definitions (OR 1.11, 95%CI 1.01–1.22, $p = 0.03$).

Discussion: Our findings suggest that impaired grip strength is associated with the individual features, as well as with the overall summary definitions, of the metabolic syndrome. The potential for grip strength to be used in the clinical setting needs to be explored.

Introduction

Recent work has shown that sarcopenia, the loss of muscle mass and strength with age, is significantly associated with type 2 diabetes in older people,[1,2] in addition to the well-documented relationships with falls, fractures, disability and mortality.[3–6] The findings also suggested a graded association between increased glucose level and weaker muscle strength in those with impaired glucose tolerance and normal levels of blood glucose. This is important because it suggests that there may be a link between the mechanical and metabolic functions of ageing muscle. The mechanism is unclear, but sarcopenia and insulin-resistant states share common cellular and molecular changes. For example, both are associated with the accumulation of myofibre lipids,[7,8] which may affect the insulin-signalling pathway.[9] In addition, an impaired synthesis rate of key structural muscle proteins such as the myosin heavy chain,[10] for example, in response to anabolic post-prandial stimuli,[11] is seen in both ageing and insulin resistance.

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The link between impaired mechanical and metabolic function may extend to other important insulin-resistant glucose-intolerant states, such as central obesity and the metabolic syndrome. Metabolic syndrome is defined as a clustering of inter-related metabolic risk factors for atherosclerotic cardiovascular disease and type 2 diabetes, and it has an estimated worldwide prevalence of 16% in adults aged >20 years.[12] The objective of this study was to determine whether there is a relationship between sarcopenia, as characterized by grip strength,[13] and the constellation of risk factors of metabolic origin that constitutes the metabolic syndrome.

Methods

In 1998, 3822 men and 3284 women born in Hertfordshire, UK, between 1931 and 1939 were traced with the aid of the National Health Service central registry in Southport, and confirmed as currently registered with a family doctor in Hertfordshire. Permission to contact 3126 (82%) men and 2973 (91%) women was obtained from their General Practitioners; 1684 (54%) men and 1541 (52%) women agreed to take part in a home interview, and provided information on medical and social history, including self-reported customary walking speed (unable to walk, very slow, stroll at an easy pace, normal speed, fairly brisk, fast) as a marker of physical activity,[14] smoking habit, alcohol consumption and current use of prescribed medications.

Of those interviewed at home, 1579 (94%) of the men and 1418 (92%) of the women subsequently attended a clinic. Those who were not previously known to be diabetic (1471 men and 1344 women) attended after an overnight fast. Fasting plasma samples were taken for triglyceride, HDLc, total cholesterol, calculated LDLc, glucose and insulin concentrations. Plasma lipids and glucose were measured by standard methods on an Advia 1650 autoanalyser (Bayer Diagnostics). Intact insulin was measured by an in-house immunofluorimetric two-site assay ('DELFIA' system) based on published methods.[15] An index of insulin resistance was derived using the HOMA formula.[16] An oral glucose tolerance test was performed using the equivalent of 75 g anhydrous glucose, with blood samples for plasma glucose and insulin obtained at 30 and 120 min. Diabetes mellitus and impaired glucose tolerance were classified on 1454 men and 1317 women using WHO criteria, i.e. 2 h glucose concentration of ⩾11.1 mmol/l and 7.0–11.0 mmol/l,

respectively (17 men and 27 women were unclassified due to missing data).[17]

Height was measured to the nearest 0.1 cm using a Harpenden pocket stadiometer, and weight to the nearest 0.1 kg on a SECA floor scale. Body mass index (BMI) was calculated as weight divided by height^2 (kg/m^2). Waist circumference was measured to the nearest 0.1 cm. Skin-fold thickness (SFT) was measured with Harpenden skin-fold callipers in triplicate at the triceps, biceps, sub-scapular and supra-iliac sites on the non-dominant side.[18] Average measures were used to derive body fat percentage.[19] Fat mass was derived by multiplying body weight by body fat percentage, and non-fat mass by subtracting fat mass from body weight. Systolic and diastolic blood pressures were measured three times in the right arm, using an automated Dinamap recorder, with the participant in a seated position after having rested for 5 min. The mean of the three readings was used, and high blood pressure was defined as average systolic pressure ⩾160 mmHg and/or diastolic pressure ⩾90 mmHg, or current use of prescribed anti-hypertensives. Presence or absence of the metabolic syndrome was identified for each individual on the basis of the International Diabetes Foundation (IDF) and Adult Treatment Panel III (ATPIII) definitions of the metabolic syndrome. These definitions require differing cut-offs and combinations of increased body weight, increased triglyceride and decreased HDL-cholesterol levels, raised blood pressure and increased glucose levels.[12] Grip strength was measured three times on each side using a Jamar handgrip dynamometer.[20] The best of the six grip measurements was used to characterize maximum muscle strength. Data were available for grip strength and all of the data items required to code HOMA resistance and the IDF and ATPIII definitions of the metabolic syndrome in 1438 men and 1239 women; these 2677 men and women were thus the sample for this study. The study had ethical approval from the North and East Hertfordshire Local Research Ethics Committee and all subjects gave written informed consent.

Statistical methods

Normality of variables was assessed and weight, BMI, fat mass, fasting glucose, triglycerides, HDL cholesterol, 2 h glucose, and HOMA resistance were log$_e$ transformed for statistical analyses. Variables were summarized for men and women separately, using means and SD or frequency and percentage distributions. Means and SD for log$_e$-transformed variables were back transformed to geometric means and SD on the original scale of measurement.

All subsequent analyses were done for men and women combined, with adjustment for gender.

Relationships between anthropometry (weight, height, BMI and fat mass) and components of the metabolic syndrome, insulin resistance and grip strength were analysed using partial correlation coefficients and analysis of variance (ANOVA). These analyses enabled an assessment of the potential confounding influence of anthropometric status on the relationships between grip strength and components of the metabolic syndrome and insulin resistance.

Sex-specific SD scores were calculated for grip strength and fasting glucose, triglycerides, HDL cholesterol, waist circumference, 2 h glucose and HOMA resistance. The relationships between an SD decrease in grip strength and each of these SD scores were explored using multiple linear regression. These regression models yielded estimated changes (and 95%CIs) in SD units for each component of the metabolic syndrome or insulin resistance per SD decrease in grip strength. The relationships between an SD decrease in grip strength and the binary variables representing high blood pressure and the ATPIII and IDF definitions of the metabolic syndrome, were analysed using multiple logistic regression. These logistic regression models yielded odds ratios (and 95%CIs) for high blood pressure, or each definition of the metabolic syndrome, per SD decrease in grip strength. We tested for homogeneity of the association between grip strength and each component of the metabolic syndrome or insulin resistance in men and women, by including an interaction term for gender and grip strength SD score in each linear or logistic regression model.

All statistical analyses used Stata, release 8 (StataCorp).

Results

The characteristics of the study group are displayed in Table 1. Average grip strength was 44.3 kg for men and 26.7 kg for women. Prevalence of the metabolic syndrome was 31.1% for men and 33.6% for women, according to the ATPIII definition, or 50.3% for men and 49.6% for women, according to the IDF definition.

The associations between anthropometric status (weight, height, BMI and fat mass) and components of the metabolic syndrome, insulin resistance and grip strength are shown in Table 2. Weight was positively associated with grip strength and components of the metabolic syndrome and insulin resistance; it therefore had the potential to

Table 1 Summary characteristics of study participants

Characteristic	Men (n = 1438)	Women (n = 1239)
Age (years)	65.7 (2.9)	66.6 (2.7)
Grip strength (kg)	44.3 (7.4)	26.7 (5.7)
Non-manual social class[a]	567 (39.4%)	523 (42.2%)
Moderate/high alcohol consumption[b]	631 (43.9%)	204 (16.5%)
Current smoker	223 (15.5%)	116 (9.4%)
Walking speed		
Slow	58 (4.0%)	75 (6.1%)
Average	905 (63.0%)	802 (64.7%)
Fast	474 (33.0%)	362 (29.2%)
Weight (kg)[c]	81.1 (1.2)	69.7 (1.2)
Height (cm)	174.2 (6.5)	160.8 (5.9)
Body mass index (kg/m²)[c]	26.8 (1.1)	27.0 (1.2)
Body fat percentage	28.6 (5.3)	39.7 (4.8)
Fat mass (kg)[c]	22.8 (1.4)	27.5 (1.3)
Non-fat mass (kg)	58.1 (6.7)	42.3 (5.9)
Fasting glucose (mmol/l)[c]	6.0 (1.2)	5.8 (1.1)
Fasting triglycerides (mmol/l)[c]	1.45 (1.62)	1.46 (1.56)
Fasting HDL cholesterol (mmol/l)[c]	1.32 (1.27)	1.66 (1.28)
High blood pressure[d]	540 (37.6%)	488 (39.4%)
Waist circumference (cm)	100.2 (10.4)	91.6 (12.3)
2 h glucose (mmol/l)[c]	6.8 (1.4)	7.4 (1.4)
HOMA resistance[c]	2.79 (2.07)	2.56 (1.92)
ATPIII metabolic syndrome	447 (31.1%)	416 (33.6%)
IDF metabolic syndrome	723 (50.3%)	614 (49.6%)

Data are means/geometric means (SD) or numbers (%) as appropriate. [a]Classes IIIM, IV and V of the 1990 OPCS Standard Occupational Classification scheme for occupation and social class. [b]11 units or more per week for men, and 8 units or more per week for women. [c]Geometric mean (SD). [d]Defined as high measured blood pressure (systolic pressure ⩾160 mmHg or diastolic ⩾100 mmHg) or use of antihypertensive therapy.

negatively confound (i.e. to mask) any relationship between lower grip strength and the metabolic syndrome and insulin resistance. Fat mass showed a similar pattern of associations, and of the two closely related anthropometric measures, weight was used in the final multiple regression analysis, as it was more strongly related to grip strength. Height was strongly and positively associated with grip strength, but not consistently with components of the metabolic syndrome or insulin resistance. Conversely, BMI was strongly associated with components of the metabolic syndrome or insulin resistance, but not with grip strength. Therefore,

Table 2 Relationships between grip strength, components of the metabolic syndrome and anthropometric characteristics of study participants

Anthropometric characteristic	Weight (kg)	Height (cm)	BMI (kg/m^2)	Fat mass (kg)
Grip strength (kg)[a]	0.19	0.35	0.03	0.13
p	<0.001	<0.001	0.12	<0.001
Fasting glucose (mmol/l)[a]	0.24	−0.00	0.27	0.25
p	<0.001	0.84	<0.001	<0.001
Fasting triglycerides (mmol/l)[a]	0.30	−0.01	0.33	0.33
p	<0.001	0.53	<0.001	<0.001
Fasting HDL cholesterol (mmol/l)[a]	−0.32	−0.03	−0.34	−0.34
p	<0.001	0.14	<0.001	<0.001
High blood pressure (yes vs. no)[b]	5.8 (4.4–7.1)*	−0.6 (−1.1 to −0.1)	6.5 (5.3–7.7)*	11.6 (9.0–14.2)*
p	<0.001	0.02	<0.001	<0.001
Waist circumference (cm)[a]	0.87	0.12	0.89	0.85
p	<0.001	<0.001	<0.001	<0.001
2 h glucose (mmol/l)[a]	0.22	−0.10	0.29	0.27
p	<0.001	<0.001	<0.001	<0.001
HOMA resistance[a]	0.42	0.01	0.45	0.46
p	<0.001	0.73	<0.001	<0.001
ATPIII metabolic syndrome[b] (yes vs. no)	17.4 (16.0–18.8)*	0.4 (−0.1 to 0.9)	16.9 (15.7–18.2)*	34.0 (31.1–36.9)*
p	<0.001	0.15	<0.001	<0.001
IDF metabolic syndrome[b] (yes vs. no)	16.0 (14.7–17.3)*	0.1 (−0.3 to 0.6)	15.8 (14.6–17.0)*	32.3 (29.6–35.1)*
p	<0.001	0.54	<0.001	<0.001

Data are [a]partial correlations adjusted for gender, or [b]mean differences (95%CI) adjusted for gender. *Weight, BMI and fat mass were log$_e$ transformed for analyses. Percentage differences are therefore presented for these variables according to high blood pressure, ATPIII, and IDF metabolic syndrome. BMI, body mass index.

neither height nor BMI were likely to act as confounders of the relationship between grip strength and the metabolic syndrome and insulin resistance, and neither was included in the final multiple regression analysis.

The associations between grip strength and components of the metabolic syndrome and insulin resistance are presented in Table 3. The table presents results from two sets of linear and logistic regression models: firstly, models adjusted for gender only (Model 1) and secondly, models adjusted for the potential confounding influences of gender, weight, age, walking speed as a marker of physical activity, social class, smoking habit and alcohol intake (Model 2). We tested for homogeneity of the association between grip strength and each component of the metabolic syndrome or insulin resistance in men and women, by including an interaction term for gender and grip strength in the first set of models (Model 1). In general, the associations were homogenous in men and women and it was therefore appropriate to have pooled men and women (*p* values for homogeneity: *p* = 0.02 for fasting glucose; *p* = 0.36 for triglycerides; *p* = 0.36 for HDL; *p* = 0.35 for high blood pressure; *p* = 0.04 for waist circumference;

p = 0.96 for 2 h glucose; *p* = 0.88 for HOMA resistance; *p* = 0.75 for ATPIII metabolic syndrome and *p* = 0.71 for IDF metabolic syndrome).

Only high blood pressure, waist circumference and 2 h glucose were related to grip strength in gender-adjusted analyses (Model 1). However, also adjusting for weight (which was expected to act as a negative confounder as described above), age, walking speed, social class, smoking habit and alcohol intake (Model 2) revealed associations between lower grip strength and a wide range of components of the metabolic syndrome and insulin resistance (Figure 1). Specifically, a SD decrease in grip strength was significantly associated with higher: fasting triglycerides (0.05 SD unit increase, 95%CI 0.02–0.09, *p* = 0.006); blood pressure (OR 1.13, 95%CI 1.04–1.24, *p* = 0.004); waist circumference (0.08 SD unit increase, 95%CI 0.06–0.10, *p* < 0.001); 2 h glucose (0.07 SD unit increase, 95%CI 0.03–0.11, *p* = 0.001); HOMA resistance (0.05 SD unit increase, 95%CI 0.01–0.09, *p* = 0.008) and with increased odds of having the metabolic syndrome according to the ATPIII (OR 1.18, 95%CI 1.07–1.30, *p* < 0.001) and IDF definitions (OR 1.11, 95%CI 1.01–1.22, *p* = 0.03).

Table 3 Relationships between grip strength and components of the metabolic syndrome and insulin resistance

Component	Model 1	Model 2
Fasting glucose (SDS)	−0.01 (−0.05 to 0.03)	0.02 (−0.02 to 0.06)
p	0.63	0.38
Fasting triglycerides (SDS)	0.01 (−0.02 to 0.05)	0.05 (0.02 to 0.09)
p	0.49	0.006
Fasting HDL cholesterol (SDS)	0.02 (−0.02 to 0.06)	−0.02 (−0.06 to 0.01)
p	0.37	0.20
High blood pressure (yes vs. no)*	1.15 (1.07 to 1.25)	1.13 (1.04 to 1.24)
p	<0.001	0.004
Waist circumference (SDS)	−0.05 (−0.09 to −0.01)	0.08 (0.06 to 0.10)
p	0.01	<0.001
2 h glucose (SDS)	0.07 (0.03 to 0.11)	0.07 (0.03 to 0.11)
p	0.001	0.001
HOMA resistance (SDS)	−0.01 (−0.05 to 0.03)	0.05 (0.01 to 0.09)
p	0.58	0.008
ATPIII metabolic syndrome (yes vs. no)*	1.00 (0.92 to 1.09)	1.18 (1.07 to 1.30)
p	0.97	<0.001
IDF metabolic syndrome (yes vs. no)*	0.96 (0.89 to 1.04)	1.11 (1.01 to 1.22)
p	0.32	0.03

SDS, standard deviation score; Data are change in metabolic syndrome or insulin resistance component, in SD units (95%CI) per SD decrease in grip strength, or *OR (95%CI) per kg decrease in grip strength. Model 1, adjusted for gender. Model 2, adjusted for gender, weight, age, walking speed, social class, smoking habit and alcohol intake.
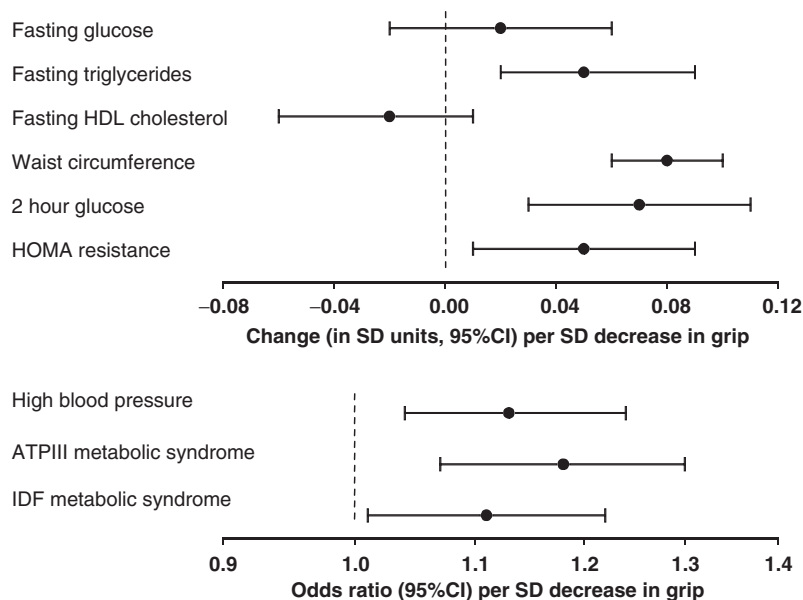
Figure 1. Relationships between grip strength and components of the metabolic syndrome and insulin resistance.

Discussion

We have demonstrated that lower grip strength as a marker of sarcopenia is associated with individual features of the metabolic syndrome including higher fasting triglycerides, blood pressure and waist circumference, as well as with the overall ATPIII and IDP summary definitions. Furthermore, lower grip strength was associated with insulin resistance in terms of higher 2 h glucose levels and HOMA resistance. These findings were independent of weight, level of physical

activity and age, within the narrow age range studied.

Few studies to date have examined loss of muscle mass and strength with insulin resistance, although many have described the loss of muscle mass and strength with age. At the cellular level, this is explained by a reduction in both the number and size of myocytes. This has potential for adverse metabolic consequences in terms of reduced glucose uptake and hyperglycaemia, because the transporter protein GLUT4 expression at the plasma membrane is related to fibre volume in human skeletal muscle fibres.[21] It has been proposed that hyperglycaemia has a direct adverse effect on muscle contractile function and force generation.[22,23] For example, it has been proposed that a hyperglycaemia-driven increase in flux through the polyol pathway, with increased production of sugar alcohols, results in slowing of muscle fibre contraction and relaxation.[24]

Furthermore prolonged hyperglycaemia can result in non-enzymic glycosylation of intracellular and extracellular proteins. Glycation of myosin, the molecular motor protein in skeletal muscle that converts chemical energy into mechanical work, has been associated with altered structural and functional properties of the protein.[25] Our study is cross-sectional, therefore it is not possible to ascertain the direction of the association between muscle strength and metabolic function, but it is possible that influences in both directions are important. Longitudinal and interventional studies are required to investigate this further.

Age-related processes such as impaired mitochondrial function may also be important. Mitochondrial dysfunction has recently been related to the development of insulin resistance,[26] type 2 diabetes and obesity.[27] A key master regulator of metabolism is PGC-1, which is a co-activator of the insulin sensitizing nuclear factor PPARg. PGC-1 also regulates mitochondrial biogenesis by directly associating with the orphan nuclear receptor oestrogen-related receptor-alpha (ERR-alpha). PGC-1alpha and ERR-alpha are both present at high levels in skeletal muscle.[28] PGC 1a is not only key to mitochondrial biogenesis and function, but also enhances slow-twitch oxidative muscle fibres in rodents by cooperating with transcription factors Mef2 and FKHR to enhance calcineurin signalling and terminal muscle differentiation.[29,30] Thus insulin-resistant states are closely linked with key regulators of mitochondrial function and muscle structure.

We have considered potential caveats to the interpretation of our findings. Losses to follow-up occurred, and response bias may have been introduced. However we were able to characterize those who did not take part in the study in a number of ways, and with the exception of smoking, participants and non-participants were similar. Also comparisons were internal, therefore unless the relationship between glucose concentration and adult grip strength differed between those who did and did not come to clinic, no bias should have been introduced. The relationships were more consistent between grip strength and metabolic syndrome defined by the ATPIII than the IDF criteria. The reasons are unclear, but may reflect the narrower inclusion criteria for the ATPIII definition, as evidenced by the lower prevalence for metabolic syndrome defined this way.

In conclusion, grip strength was significantly associated with major features of the metabolic syndrome as well as insulin resistance in this population-based study of older men and women. The underlying mechanisms require investigation, and our results need to be verified in younger populations and different ethnic groups. Our study provides evidence that impaired grip strength is associated with an adverse metabolic profile, in addition to loss of physical function, and the potential for grip strength to be used in the clinical setting needs to be explored. These data also suggest that interventions should be tested that are designed to improve muscle strength *per se*. These interventions may have wider advantages than previously appreciated in attenuating the impact of the metabolic syndrome.

Acknowledgements

References

1. Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? *Diabetes Care* 2005; **28**:2541–2.

2. Cetinus E, Buyukbese MA, Uzel M, Ekerbicer H, Karaoguz A. Hand grip strength in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2005; **70**:278–86.

3. Wickham C, Cooper C, Margetts BM, Barker DJ. Muscle strength, activity, housing and the risk of falls in elderly people. *Age Ageing* 1989; **18**:47–51.

4. Cooper C, Barker DJ, Wickham C. Physical activity, muscle strength, and calcium intake in fracture of the proximal femur in Britain. *Br Med J* 1988; **297**:1443–6.

5. Sayer AA, Syddall HE, Martin HJ, Dennison EM, Roberts HC, Cooper C. Is grip strength associated with health-related

quality of life? Findings from the Hertfordshire Cohort Study. *Age Ageing* 2006; **35:**409–15.

6. Gale CR, Martyn CN, Cooper C, Sayer AA. Grip strength, body composition, and mortality. *Int J Epidemiol.* 2007; **36:**228–35.

7. Janssen I, Ross R. Linking age-related changes in skeletal muscle mass and composition with metabolism and disease. *J Nutr Health Aging* 2005; **9:**408–19.

8. Furler SM, Poynten AM, Kriketos AD, Lowy AJ, Ellis BA, Maclean EL, *et al.* Independent influences of central fat and skeletal muscle lipids on insulin sensitivity. *Obes. Res* 2001; **9:**535–43.

9. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000; **106:**171–6.

10. Nair KS. Aging muscle. *Am J Clin Nutr* 2005; **81:**953–63.

11. Rasmussen BB, Fujita S, Wolfe RR, *et al.* Insulin resistance of muscle protein metabolism in aging. *FASEB J* 2006; **20:**768–9.

12. Grundy SM, Cleeman JI, Daniels SR, *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112:**2735–52.

13. Lauretani F, Russo CR, Bandinelli S, *et al.* Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl.Physiol* 2003; **95:**1851–60.

14. Dallosso HM, Morgan K, Bassey EJ, Ebrahim SB, Fentem PH, Arie TH. Levels of customary physical activity among the old and the very old living at home. *J Epidemiol.Community Health* 1988; **42:**121–7.

15. Sobey WJ, Beer SF, Carrington CA, *et al.* Sensitive and specific two-site immunoradiometric assays for human insulin, proinsulin, 65–66 split and 32–33 split proinsulins. *Biochem. J* 1989; **260:**535–41.

16. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; **27:**1487–95.

17. World Health Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part I: Diagnosis and classification of diabetes mellitus.* Geneva, World Health Organization, 1999.

18. Fidanza F. Anthropometric methodology. In: Fidanza F, ed. *Nutritional status assessment.* London, Chapman Hall, 1991:1–62.

19. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr* 1974; **32:**77–97.

20. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985; **66:**69–74.

21. Gaster M, Vach W, Beck-Nielsen H, Schroder HD. GLUT4 expression at the plasma membrane is related to fibre volume in human skeletal muscle fibres. *APMIS* 2002; **110:**611–19.

22. Helander I, Westerblad H, Katz A. Effects of glucose on contractile function, [Ca2+]i, and glycogen in isolated mouse skeletal muscle. *Am J Physiol Cell Physiol* 2002; **282:**C1306–12.

23. Lesniewski LA, Miller TA, Armstrong RB. Mechanisms of force loss in diabetic mouse skeletal muscle. *Muscle Nerve* 2003; **28:**493–500.

24. Cotter MA, Cameron NE. Metabolic, neural and vascular influences on muscle function in experimental models of diabetes mellitus and related pathologica states. *Basic Appl Myol* 1994; **4:**293–307.

25. Ramamurthy B, Jones AD, Larsson L. Glutathione reverses early effects of glycation on myosin function. *Am J Physiol Cell Physiol* 2003; **285:**C419–24.

26. Petersen KF, Befroy D, Dufour S, *et al.* Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* 2003; **300:**1140–2.

27. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes* 2002; **51:**2944–50.

28. Ichida M, Nemoto S, Finkel T. Identification of a specific molecular repressor of the peroxisome proliferator-activated receptor gamma Coactivator-1 alpha (PGC-1alpha). *J Biol.Chem.* 2002; **277:**50991–5.

29. Chang JH, Lin KH, Shih CH, Chang YJ, Chi HC, Chen SL. Myogenic basic helix-loop-helix proteins regulate the expression of peroxisomal proliferator activated receptor-gamma coactivator-1alpha. *Endocrinology* 2006; **147:**3093–106.

30. Lin J, Wu H, Tarr PT, *et al.* Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature* 2002; **418:**797–801.