

Association between insulin resistance, lean mass and muscle torque/force in proximal versus distal body parts in healthy young men

T. Gysel¹, P. Calders¹, D. Cambier¹, T. Roman de Mettelinge¹, J-M. Kaufman^{2,3}, Y. Taes², H-G. Zmierzak³, S. Goemaere³

¹Department of Rehabilitation Sciences and Physiotherapy, Ghent University, De Pintelaan 185, 1B3, Ghent, Belgium;

²Department of Endocrinology, Ghent University Hospital, De Pintelaan 185, 9K12 Ghent, Belgium;

³Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, De Pintelaan 185, 9K12 Ghent, Belgium

Abstract

Objectives: The purpose of this study was to investigate whether there is already an association of insulin resistance (IR) with muscle mass and –force/torque in an adult population and whether this relationship is the same in distal and proximal body parts. **Methods:** 358 Healthy young men were divided into a more insulin sensitive (MIS) (n=89) and a less insulin sensitive (LIS) group (n=89), respectively using lower and upper quartiles of HOMA-IR index (Homeostasis Model Assessment of IR). Muscle force/torque and lean mass, were compared between the two groups. **Results:** LIS subjects had higher absolute thigh lean mass, but not higher thigh muscle torque, resulting in a lower torque per kg muscle. In upper arm, lean mass was higher in LIS subjects, but also absolute muscle torque resulted higher. For handgrip force, the LIS and MIS group had similar results, despite a trend towards higher forearm lean mass in LIS subjects. Lean mass % of total lean mass is lower in LIS subjects in more distal body parts. **Conclusions:** Already in a young healthy population, IR seems to be associated with lower force/torque per muscle mass and lower lean mass % of total lean mass predominantly in more distal body parts.

Keywords: Insulin Resistance, Muscle, Torque, Force, Proximal, Distal

Introduction

Type 2 diabetes mellitus (T2DM) is a major health problem, and is commonly associated with cardiovascular disease, neuropathy, retinopathy and nephropathy. Skeletal muscle disease or ‘myopathy’, is a much less studied complication of T2DM.

Diabetes has been associated with an increased prevalence of sarcopenia¹ and with an accelerated reduction of skeletal muscle mass percentage of total body weight as well as muscle weakness^{2,3}, both especially in the lower extremity⁴. In T2DM

patients, insulin resistance is negatively associated with knee extension force divided by body weight⁵. According to Sun and colleagues⁶, it is the impaired insulin action (or insulin resistance) in the skeletal muscle that underpins the diverse metabolic, structural and functional changes in the skeletal muscle of T2DM patients.

Insulin resistance (IR) in the skeletal muscle is due to an accumulation of intracellular lipid metabolites. They indirectly inhibit insulin-stimulated glucose transport into the cell (GLUT 4 - glucose transporter 4- activity)⁷. Thus, the impaired response of muscle to insulin, is a consequence of the metabolic impact of increasing obesity and fat deposition in humans⁸. Insulin resistance (IR) is a pathophysiological stage that precedes T2DM⁹. In this stage, the pancreas compensates this lower insulin-effectiveness by increasing the insulin secretion in order to maintain normal blood glucose levels. Once the beta cell function fails to maintain glucose control, impaired glucose tolerance and diabetes mellitus are the consequences¹⁰.

Recently, increasing research effort has been focusing on the relation between insulin resistance and muscle function/physi-

The authors have no conflict of interest.

Corresponding author: Tineke Gysel, Ghent University, Dept. of Rehabilitation Sciences and Physiotherapy, De Pintelaan 185, 1B3, 9000 Ghent, Belgium
E-mail: Tineke.Gysel@ugent.be

Edited by: J. Rittweger
Accepted 4 February 2014

cal function in people without diabetes. However, data on this matter are still scarce.

Previous studies in non-diabetics tended to focus on insulin resistance in elderly. In this older, non-diabetic group, insulin resistance is associated with lower quadriceps torque per kilogram lean mass¹¹, and with lower gait speed but not with lower absolute peak leg force¹².

Recent studies suggest that there is a dramatic increase in T2DM among individuals in their thirties, whereas in the past, T2DM usually manifested in the late sixties of susceptible individuals¹³. Since IR is apparent approximately 10 years earlier than T2DM¹⁴, it may be presumed that, also IR might have an earlier onset nowadays, what also might be associated with an earlier decrease of muscle mass and force/torque. We hypothesized that relative muscle mass, estimated by lean mass percentage (of total body weight or total lean mass) and relative muscle force/torque would decrease with a decrease in insulin sensitivity, estimated by HOMA index (Homeostasis Model Assessment of Insulin Resistance), even in a young healthy population.

To the best of our knowledge, only two authors focused on a (young) adult population. Unni et al.¹⁵ have shown that reduced insulin sensitivity in healthy adult men (18-34 years) is associated with reduced relative lean mass and reduced standardized handgrip force (expressed as maximal voluntary contraction divided by forearm muscle area). Srikanthan & Karlamangla¹⁶ confirmed an inverse relationship between insulin resistance and relative muscle mass (the ratio of estimated skeletal muscle mass to total body weight, expressed as a percentage) in an adult population (31-58 years) of people with and without diabetes, and this association persisted when people with diabetes were excluded from the analytic sample.

Although some of the above cited studies have only studied the effect of IR on muscles in lower limbs, they often generalize the resulting effects of IR to the upper and lower limbs. In some studies the determination of muscle force or torque was restricted to the upper extremities. Unni and colleagues¹⁵ for instance, only assessed handgrip force. According to Olsen et al.¹⁷ glucose clearance may not be evenly distributed throughout the muscles of the whole body. In people with diabetes, glucose clearance in leg muscles is lower than in arm muscles, because of a better preserved insulin sensitivity in arm muscles¹⁷. According to Andersen et al.⁴, muscle torque loss in diabetes seems larger in distal muscles compared to proximal muscles. This may be related to the presence and severity of peripheral neuropathy⁴. Peripheral neuropathy can already be present in people with impaired glucose tolerance not having diabetes^{18,19}. We hypothesized that, in a population without diabetes, insulin resistance would have a larger influence on distal muscle characteristics (like muscle mass, muscle torque and muscle force) compared to proximal muscles.

To test our hypotheses, we compared thigh-, lower leg-, upper arm- and forearm lean mass (as a surrogate for skeletal muscle mass), as well as muscle performance (torque of elbow- and knee flexor/extensor and handgrip force) of a more insulin sensitive (MIS) group with a less insulin sensitive

group (LIS) of healthy young men. As far as we know, this is the first study that measures both upper and lower body muscle torque and compares distal and proximal muscle volumes in a young healthy population.

Materials and methods

Subjects

The population for this study was selected (using upper and lower quartiles of HOMA index) from a group of 358 young unrelated healthy adult men who were, in turn, randomly selected, choosing one brother out of a sibling-pair study²⁰ which included 276 pairs, 17 triplets, two quartets of dizygotic brothers, and 63 single participants. These men, aged 24 to 45 years, were recruited from population lists of semirural communities around Ghent (Belgium). Exclusion criteria were illnesses or medication use that may affect body composition, bone metabolism or sex steroid levels. All men were in good health and completed questionnaires about previous illness and smoking. Subjects were not excluded based on weight, risk factors for diabetes or daily exercise level. Subjects with diabetes (HbA1c measured in a fasting blood sample $\geq 6,5\%$ or 48 mmol/mol²¹) were excluded from the present study.

The study was approved by the Ethical Committee of the Ghent University Hospital and was performed in accordance with the Declaration of Helsinki. All participants gave their written informed consent.

Measurements of muscle –mass

To determine lean mass and fat mass of the dominant upper and lower extremity, all participants underwent total-body dual-energy X-ray absorptiometry (DEXA) using a Hologic QDR 4500 DXA Discovery A device, Hologic Inc., Bedford, MA, USA). Appendicular muscle mass (kg) was determined assuming that lean mass (= non-fat and non-bone tissue) would be skeletal muscle²². Thighs were defined as all tissue between a diagonal line drawn through and perpendicular to the axis of the femoral neck (angled with the pelvic brim) and a horizontal line drawn through the interarticular space of the knee. Lower legs were defined as all tissue beneath this horizontal line. Upper arms were defined as the tissue extending from the center of the arm socket to the interarticular space of the elbow and forearms were defined as all tissue extending from this interarticular space to the phalange tips. This procedure is based on the procedure of Kim et al. (2002) that has been validated against measurements with Magnetic Resonance Imaging²². Thigh-, lower leg-, upper arm- and forearm muscle mass are given in absolute mass and were also calculated as percentage of body weight.

Measurement of muscle torque

The torque of knee- and elbow- flexors and extensors (large muscle groups) was assessed using an isokinetic dynamometer (Biodex Corporation, New York, NY, USA) at the dominant limbs. The muscle contractions were performed at a preset constant angular velocity of 180°/sec. For each condition three trial-efforts and five maximal efforts were allowed to produce

	More insulin sensitive (n=89)	Less insulin sensitive (n=89)	P-value
Age (years)	33.2±5.4	35.6±5.3	0.003*
Height (m)	1.80±6.18	1.79±6.57	0.521
Body weight (kg)	76.0±8.18	91.0±13.7	<0.001*
Body Mass Index (kg/m ²)	23.4±3.3	28.2±3.9	<0.001*
Fat mass (kg)	12.6±4.5	21.7±7.1	<0.001*
Lean mass % of Total body weight	83.7±0.5	77.0±0.5	<0.001*
Lean mass (kg)	63.6±5.9	68.9±7.5	<0.001*
Physical activity (score/15)	8.65±1.41	7.98±1.39	0.002*
Pack years	4.36±7.65	5.80±9.06	0.256
Smoking(%)			
- Yes	24.7	25.8	
- No	75.3	74.2	0.500

*significant difference between groups ($p<0.05$).

Table a. Characteristics of the subjects. Age, anthropometric data, body composition, physical activity and smoking habits in the two subject groups. (Values are means ± Standard Deviations, only the present smoking status is reported in %).

five overlying curves. The subjects were verbally encouraged to exert maximal efforts and a 60-second rest period was provided between each condition. The peak torque was recorded in Newton meters and used for the analysis. Isokinetic data were presented as absolute values (Nm) and relative values were calculated by taking the ratio of torque to the corresponding (upper arm- or thigh-) lean mass measured by DEXA.

Measurement of muscle force

A calibrated, Jamar dynamometer (Smith and Nephew, Irvington, NY 10533, USA) was used to assess hand grip force at the dominant hand (representing a smaller and more distal muscle group in the upper extremity). Three measurements of each grip were obtained at 15s intervals (preceded by two trial-efforts) and mean values were used in the analysis. The %CV (percent coefficient of variation) for the measurement was 16.3%. Next to the measured absolute values (in kg), relative values (the ratio of hand grip force (kg) to the corresponding forearm lean mass measured by DEXA) were calculated.

Measures of insulin resistance

Fasting plasma glucose and insulin concentrations were measured in a morning blood sample (before 10 am). The HOMA-IR index (Homeostasis Model Assessment of Insulin Resistance) was calculated as [fasting serum insulin (mU/l) * fasting plasma glucose (mmol/l)/22.5], with higher values indicating a higher degree of insulin resistance²³. By using lower and upper quartiles²⁴ of IR, the more insulin sensitive group had HOMA-indices of ≤0.96 and the less insulin sensitive group had HOMA-indices of ≥2.09. The cut-off value, used in literature, to identify individuals as being “insulin resistant”, varies widely (from the 75th percentile²⁵⁻²⁷ to the 90th percentile^{28,29}), that’s why we use the term “less insulin sensitive subjects” instead of “insulin resistant subjects”. Glucose (hexokinase method) and insulin concentrations were determined

on a Modular P and E respectively using Roche Diagnostics consumables (Roche Diagnostics, Mannheim, Germany).

Covariates

Standing height and weight were obtained from each participant, and body mass index (BMI) was calculated. Age of participants was determined to the nearest year. The ‘Baecke questionnaire’ was used to determine levels of physical activity. Cumulative exposure to cigarette smoking was summarized by multiplying the average number of packs smoked per day (cigarettes smoked per day divided by 20) by the number of years smoked (pack years of smoking), regardless of whether smoking status was former or current.

Statistical data analysis

Descriptive statistics are reported as means ± SD (only the present smoking status is reported in %). To compare the subject characteristics, independent t-tests for means were used for comparing continuous variables, the chi-square test was used to compare categorical variables. Since age and physical activity can influence muscle mass and force/torque, (and because we are interested in the extra influence of IR on mass/force/torque, on top of the influence of age and physical activity), they were controlled for in subsequent analyses. Lean mass (as a surrogate for muscle mass) is not only displayed in absolute numbers, but also relative to body weight. Muscle mass in its turn determines muscle force and torque, therefore force and torque parameters were expressed both in absolute numbers and relative to the corresponding muscle mass. Statistical analysis between the groups in the upper and lower quartile for insulin resistance were assessed using univariate analysis of covariance (ANCOVA), correcting for age and level of physical activity (they were entered as covariates). All of the analyses were performed using SPSS software version 19.0.0 for Windows (Statistical Package for the Social Sci-

	More insulin sensitive (n=89)	Less insulin sensitive (n=89)	P-value	Relative Δ (%)
Absolute lean mass (kg)				
Upper arm	2.337±0.342	2.649±0.430	<0.001*	11.8%
Forearm	1.475±0.188	1.531±0.199	0.074	3.6%
Thigh	7.047±0.814	7.728±1.049	<0.001*	8.8%
Lower leg	3.359±0.377	3.439±0.448	0.102	2.4%
Relative lean mass (% of total body weight)				
Upper arm	3.08±0.340	2.93±0.358	0.023*	-4.9%
Forearm	1.95±0.219	1.71±0.239	<0.001*	-12.3%
Thigh	9.29±0.687	8.54±0.686	<0.001*	-8.1%
Lower leg	4.44±0.432	3.82±0.428	<0.001*	-14%
Relative lean mass (% of total lean mass)				
Upper arm	3.67±0.343	3.81±0.358	0.004*	3.7%
Forearm	2.31±0.205	2.21±0.217	0.001*	-4.3%
Thigh	11.06±0.544	11.15±0.635	0.048*	0.8%
Lower leg	5.28±0.369	4.98±0.362	<0.001*	-5.7%

*significant difference between groups ($p<0.05$), p -values are from age- & physical activity adjusted ANCOVA, comparing MIS and LIS subjects.

Table b. Comparison of absolute and relative lean mass (using DEXA) in dominant upper and lower limbs between MIS and LIS subjects. (Values are means ± Standard Deviations).

ences Inc., Chicago, IL, USA) and statistical significance was assumed at $P<0.05$.

Results

Among the 358 healthy adult men, the 89 subjects in the lower quartile for insulin resistance had HOMA indices of ≤ 0.96 and formed the more insulin sensitive (MIS) group, the 89 subjects in the upper quartile ($\text{HOMA} \geq 2.09$) formed the less insulin sensitive (LIS) group. Descriptive characteristics of the groups are presented in Table a. The LIS group was older, had greater body mass, fat mass, BMI, lower lean mass % of total body weight and reported less physical activity ($p<0.05$, each) than their more insulin sensitive (MIS) counterparts. There was no difference in smoking habits between the two groups (not in pack years, not in present smoking status).

The LIS subjects had significantly higher upper arm and thigh (more proximal body parts) lean mass (estimated by DEXA) than their MIS counterparts (relative difference of respectively 11.8% and 8.8%, both $p<0.001$) (Table b). In forearm and lower leg (more distal body parts) the LIS subjects also tended to have more absolute lean mass (respectively 3.6% and 2.4%), however, this difference was not statistically significant ($p=0.074$ and $p=0.102$, respectively).

When expressing lean mass in different body parts relative to total body weight, LIS subjects had lower appendicular lean mass percentage of total body weight when compared to the MIS individuals, with a relative difference of -14% in lower leg ($p<0.001$), followed by a relative difference of -12.3% in forearm ($p<0.001$), -8.1% in thigh ($p<0.001$) and -4.9% in

upper arm ($p=0.023$) (Table b).

When expressing lean mass in the different body parts relative to total lean mass, LIS subjects had lower values in the most distal body parts, with a relative difference of -5.7% ($p<0.001$) in lower leg and -4.3% ($p=0.001$) in forearm. In the more proximal body parts, LIS subjects show higher values, with a relative difference of 0.8% in thigh and 3.7% in upper arm (Table b).

Table c presents the comparison of absolute handgrip force (representing forearm muscles) and absolute knee and elbow flexor/extensor torque between the 89 LIS and 89 MIS subjects. These data show that the LIS subjects had a significantly higher elbow extension torque (8%, $p<0.05$) and borderline significantly higher elbow flexion torque (5%, $p=0.083$) than the MIS group. LIS subjects did not show higher values for the isokinetic knee flexion/extension torque. For absolute handgrip force, both groups showed almost identical mean values.

Table d presents the comparison of muscle torque or -force, normalized to the corresponding lean mass. Isometric handgrip force, normalized to forearm lean mass, has been found to be significantly lower in LIS individuals compared to the MIS group (-5.5%, $p<0.005$). Considering the relative isokinetic data, knee flexion and extension torque, normalized to thigh lean mass also seems lower in the LIS group (with a difference of -10.3%, $p<0.05$ and -7.3%, $p<0.05$, respectively). In upper arm, the relative elbow flexion torque (but not the relative elbow extension torque) seems lower in the LIS group (a difference of -7.6%, $p<0.05$).

All these results are independent of the fact that the LIS group is older and reported less physical activity.

	More insulin sensitive (n=89)	Less insulin sensitive (n=89)	P-value	Relative Δ (%)
Absolute Peak Torque (Nm)				
Upper arm				
- Elbow flexion	40.3±9.4	42.2±9.2	0.083	5.0%
- Elbow extension	32.2±6.7	35.0±8.5	0.008*	8.0%
Absolute Peak Torque (Nm) Thigh				
- Knee flexion	72.3±17.3	71.1±20.2	0.750	-1.7%
- Knee extension	137.9±26.5	141.2±36.7	0.363	2.3%
Absolute handgrip force (kg) (forearm)				
	52.9±9.29	51.7±7.66	0.266	-2.3%

*significant difference between groups ($p < 0.05$), p-values are from age- & physical activity adjusted ANCOVA, comparing MIS and LIS subjects.

Table c. Comparison of absolute muscle torque and -force in dominant upper and lower extremity between MIS and LIS subjects. (Values are means \pm Standard Deviations).

	More insulin sensitive (n=89)	Less insulin sensitive (n=89)	P-value	Relative Δ (%)
Peak Torque / upper arm lean mass (Nm/kg)				
- Flexion	17.25±3.32	15.94±2.85	0.022*	-7.6%
- Extension	13.83±2.32	13.27±2.62	0.229	-4.0%
Peak Torque / Thigh lean mass (Nm/kg)				
- Flexion	10.22±1.90	9.17±2.35	0.012*	-10.3%
- Extension	19.64±3.37	18.20±4.18	0.017*	-7.3%
Handgrip force / forearm lean mass (kg/kg)				
	35.93±4.56	33.97±4.41	0.003*	-5.5%

*significant difference between groups ($p < 0.05$), p-values are from age- & physical activity adjusted ANCOVA, comparing MIS and LIS subjects.

Table d. Comparison of relative muscle torque and -force in dominant upper and lower extremity between MIS and LIS subjects. (Values are means \pm Standard Deviations).

Discussion

One of the main findings of the present study was that LIS adults did not only have more body mass and more fat mass, but they also have been found to have larger absolute upper arm and thigh muscle mass than the MIS adults. Obese persons usually have more absolute muscle mass³⁰ (as well as subjects with lower insulin sensitivity³¹) and more absolute torque or force than non-obese persons^{32,33}. As an explanation, many researchers have suggested that the extra weight chronically carried by obese individuals might serve as a favorable training stimulus to increase muscle mass³⁴. Unlike muscle mass in upper arm and thigh, muscle mass in forearm and lower leg (more distal body parts) were not statistically higher in the LIS group, there was only a borderline significance (respectively $p=0.074$ and $p=0.102$), possibly indicating a more pronounced negative influence of insulin resistance in the more distal body

parts (in turn, lowering muscle mass). When body weight was taken into account, a higher fat and lower muscle mass percentage of total body weight was found in the LIS group (both in arms and legs). This is in line with previous findings of Unni et al.¹⁵ and Srikanthan & Karlamangla¹⁶ also focusing on an adult population. As hypothesized, insulin resistance in the present young healthy population, is associated with lower muscle mass percentage respective to total body weight (as a consequence of the higher fat mass percentage) and higher absolute muscle mass in proximal body parts. The largest differences (between the 2 groups) in lean mass percentage of total body weight, were seen in lower leg (with a relative difference of -14%), followed by forearm (-12.3%), thigh (-8.1%) and finally upper arm (-4.9%). When total lean mass was taken into account, a lower percentage of total lean mass was found in the most distal body parts of the LIS group (-5.7% in lower leg and -4.3% in forearm), indicating a different muscle mass

distribution (in contrast to the previous parameter: muscle mass % of total body weight, which can be a result of a different fat distribution in large part). In the more proximal body parts, LIS subjects show higher muscle mass percentages of total lean mass (0.8% in thigh and 3.7% in upper arm). This fits with our hypothesis that insulin resistance is associated with lower relative muscle mass in the most distal body parts.

We don't have any data on neuropathy in this healthy cohort, but finding similar results in relative muscle mass of people with a higher chance developing diabetes, this distribution could possibly indicate an early onset of distal neuropathic processes in these healthy individuals with lower insulin sensitivity. The development of neuropathy in diabetes mellitus takes time and there are arguments that support the direct action of insulin resistance on the pathogenesis of neuropathy. Hyperinsulinemia (a compensatory response to IR) has been reported to cause neuropathic changes³⁵, and neurons can also become 'insulin resistant'³⁶. According to Sumner et al. (2003), peripheral neuropathy can already be present in people without diabetes but with an impaired glucose tolerance (IGT). Ziegler et al. also found a slightly increased prevalence of polyneuropathy in individuals with IGT and impaired fasting glucose (IFG). Distal symmetric polyneuropathy is the most common variety of neuropathy. The nerve fibers are affected in a length-dependent pattern; feet and lower leg are affected first, followed by hands, and later on, more proximal body parts such as thighs are influenced³⁷.

Isokinetic data demonstrated that, in general, LIS subjects had significantly higher absolute elbow flexion/extension torque than their MIS counterparts, in accordance with the larger absolute amounts of upper-arm lean mass. But surprisingly, LIS subjects, in general, did not show significantly higher absolute knee flexion/extension torque in lower limbs, despite their larger absolute thigh lean mass. This finding supports previous research in non-diabetic elderly^{11,12}. Kuo et al. noted that HOMA-IR is not associated with absolute peak knee extensor force¹². Barzilay et al., found a significant positive association of absolute quadriceps lean mass with HOMA-IR, and did not find a significant association between absolute quadriceps torque and HOMA-IR¹¹. This lower efficacy, found in thigh, but not necessarily in elbow muscles, was confirmed in our study by a lower relative thigh muscle torque (knee flexion and extension torque, normalized to thigh lean mass) in LIS adults compared to their MIS counterparts.

Muscle torque or force is determined by the available absolute muscle mass, the muscle density (which is a measure of fat infiltration in the muscle organ envelope), the blood flow to the muscle, the metabolic capacity of the muscle fibers (meaning: fiber type, the number of mitochondria and mitochondrial efficiency in the muscle fibers), and the degree of activation (nerve control). Muscle quantity is higher in the LIS group, but thigh torque is not higher. This lower efficacy in thigh muscles could therefore be due to higher fat infiltration in the muscle, lower blood flow to the muscle fibers, lower metabolic capacity of the fibers and/or a loss in degree of muscle activation (a potential nerve function decline). Several authors have shown that

insulin resistance in a healthy population is associated with lower muscle density as measured with CT, indicating higher fat infiltration in thigh muscles^{38,39}. Goodpaster et al.⁴⁰ showed that lower quadriceps density can indeed account for differences in muscle torque not attributed to muscle quantity. Subjects in an insulin resistant state seem to have a higher degree of sympathetic activation than age-matched insulin sensitive subjects⁴¹. This sympathetic overactivity would partly be caused by hyperinsulinemia⁴² in this group. It can produce vasoconstriction and can diminish the regional blood flow and tissue glucose delivery^{42,43}. The impaired hemodynamic effect of insulin to facilitate access to the muscle cells for nutrients may manifest (in chronic situations) as a decreased capillary density of muscle⁴⁴, enlarging the diffusion distance in IR individuals⁴⁵. Activation of adrenergic peripheral β -receptors also changes proportion between slow and fast twitch muscle fibers⁴⁶. The inability to modify fuel oxidation in response to changes in nutrient availability has been implicated in the accumulation of intramyocellular lipid and insulin resistance⁴⁷. This reduced ability to switch from fat to carbohydrate oxidation is called "metabolic inflexibility". IR causes metabolic disturbance characterized by reduced cellular glucose uptake and fatty acid oxidation, leading to an augmented lipid deposition and oxidative stress, in turn associated with a reduced mitochondrial density⁶ and function⁴⁸ in skeletal muscle tissue. We don't have any data on thigh nerve function in this healthy cohort, but Oltman et al.⁴⁹ found a sciatic neural dysfunction in non-diabetic rats with an impaired glucose tolerance. They had a lower motor nerve conduction velocity and lower endoneurial blood flow in sciatic nerve compared with age-matched lean control rats. Thigh nerve dysfunction in insulin resistant subjects, still has to be demonstrated in humans. Adding an EMG to assess amplitude and nerve conduction velocity of different nerves may have an added value in future research. The lower thigh muscle efficacy could thus possibly be the result of the combination of lower thigh muscle density, blood flow, metabolic capacity and/or thigh nerve function decline.

Since not only upper arm lean mass is higher, but also upper arm muscle torque is generally higher and lower relative torque values are only found in the LIS group for elbow flexion, but not for elbow extension, we can conclude that the lower efficacy is definitely less pronounced in upper arm muscles, when compared to thigh muscles. A potential explanation for lower relative torque values in elbow flexion, but not extension could be the following. IR mainly targets type 1 muscle fibers^{50,51}. In general, elbow extensors (triceps brachii) have a higher percentage of type 2 muscle fibers than the elbow flexors (biceps brachii)^{52,53}, what makes those extensor muscles 'less susceptible' for insulin resistance.

In our study, isometric data of a more distal part of the upper limb showed that both groups had almost identical mean values for absolute hand grip force (while there was a trend for larger forearm muscle mass in LIS subjects), possibly suggesting a lower muscle efficacy in forearm. This is confirmed in our study by the significantly lower handgrip force per kg lean forearm mass in LIS individuals. In 2009, Unni et al.¹⁵ found

a positive significant association between insulin sensitivity and handgrip force divided by forearm muscle area, analogous to our results. We can conclude that the lower efficacy is more pronounced in forearm muscles, when compared to upper arm muscles. And just like in thigh muscles, the lower forearm muscle efficacy could possibly be the result of a combined lower forearm muscle density, blood flow, metabolic capacity and/or a nerve function decline in the distal upper limb.

Our study has several limitations. First, we did not measure muscle torque or force in the lower leg, while this might have supported our conclusions on the differential influence of insulin resistance in proximal versus distal body parts. Second, we acknowledge that this cross-sectional study examines only associations between IR and muscle mass/force/torque. These associations neither can prove causality nor define the manner in which they are related. The association of IR and relative muscle mass/force/torque could simply be epiphenomena of changes in muscle physiology⁵⁴, or it may be a vicious cycle. For example, it is possible that a lowered relative muscle mass/force/torque may lead to lowered physical activity, a positive energy balance, greater deposition of intramuscular lipid, more IR and in turn further lowering of muscle force/torque. Hence, the relationship between muscle force/torque and insulin sensitivity is difficult to explain in terms of cause and effect and should be prospectively explored.

In conclusion, despite these limitations, this study puts forward that, even in a young non-diabetic population, insulin resistance is associated with lower muscle mass relative to total mass and lower muscle force/torque relative to muscle mass (just like in non-diabetic elderly¹¹), and this can predominantly be seen in distal body parts (just like in diabetes⁴). Early detection and reduction of IR and its risk factors may also contribute to preserving muscle function next to preventing the evolution towards type 2 diabetes mellitus.

Acknowledgements

The authors are grateful to K. Toye and B. Van Eetvelde for their excellent technical assistance. This study is supported by grants from the Fund for Scientific Research – Flanders (FWO-Vlaanderen grant #G.0662.07 and G.0867.11). YT is holder of a postdoctoral fellowship of the Research Foundation – Flanders (FWO).

References

- Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). *Diabetes Care* 2010;33:1497-1499.
- Andreassen CS, Jakobsen J, Ringgaard S, Ejsskjær N, Andersen H. Accelerated atrophy of lower leg and foot muscles - a follow-up study of long-term diabetic polyneuropathy using magnetic resonance imaging (MRI). *Diabetologia* 2009;52:1182-1191.
- Park S W, Goodpaster BH, Strotmeyer ES, Kuller LH, Broudeau R, Kammerer C, de Rekeneire N, Harris TB, Schwartz AV, Tylavsky FA, Cho YW, Newman AB. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes - The Health, Aging, and Body Composition Study. *Diabetes Care* 2007;30:1507-1512.
- Andersen H, Nielsen S, Mogensen CE, Jakobsen J. Muscle strength in type 2 diabetes. *Diabetes* 2004;53:1543-1548.
- Nomura T, Ikeda Y, Nakao S, Ito K, Ishida K, Suehiro T, Hashimoto K. Muscle strength is a marker of insulin resistance in patients with type 2 diabetes: A pilot study. *Endocr J* 2007;54:791-796.
- Sun ZL, Liu LL, Liu NF, Liu YF. Muscular response and adaptation to diabetes mellitus. *Front Biosci-Landmark* 2008;13:4765-4794.
- Petersen KF, Shulman GI. Etiology of insulin resistance. *Am J Med* 2006;119:10s-16s.
- Shavlakadze T, Grounds M. Of bears, frogs, meat, mice and men: complexity of factors affecting skeletal muscle mass and fat. *Bioessays* 2006;28:994-1009.
- Lann D, LeRoith D. Insulin resistance as the underlying cause for the metabolic syndrome. *Med Clin N Am* 2007;91:1063-77, viii.
- DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. *Diabetes Care* 1992;15:318-368.
- Barzilay JI, Cotsonis GA, Walston J, Schwartz AV, Satterfield S, Miljkovic I, Harris TB, Health ABCS. Insulin resistance is associated with decreased quadriceps muscle strength in nondiabetic adults aged ≥ 70 years. *Diabetes Care* 2009;32:736-738.
- Kuo CK, Lin LY, Yu YH, Wu KH, Kuo HK. Inverse association between insulin resistance and gait speed in nondiabetic older men: results from the U.S. National Health and Nutrition Examination Survey (NHANES) 1999-2002. *BMC geriatrics* 2009;9:49.
- Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M, Consensus Workshop G. Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. *Diabetes Care* 2004;27:1798-1811.
- Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow Glucose Removal Rate and Hyperinsulinemia Precede the Development of Type-II Diabetes in the Offspring of Diabetic Parents. *Ann Intern Med* 1990; 113:909-915.
- Unni US, Ramakrishnan G, Raj T, Kishore RP, Thomas T, Vaz M, Kurpad AV. Muscle mass and functional correlates of insulin sensitivity in lean young Indian men. *European journal of clinical nutrition* 2009;63:1206-1212.
- Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. *J Clin Endocr Metab* 2011; 96:2898-2903.
- Olsen DB, Sacchetti M, Dela F, Ploug T, Saltin B. Glucose clearance is higher in arm than leg muscle in type 2

- diabetes. *The Journal of physiology* 2005;565:555-562.
18. Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology* 2003;60:108-111.
19. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A, Group KS. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. *Diabetes care* 2008;31:464-469.
20. Crabbe P, Bogaert V, De Bacquer D, Goemaere S, Zmierzczak H, Kaufman JM. Part of the interindividual variation in serum testosterone levels in healthy men reflects differences in androgen sensitivity and feedback set point: contribution of the androgen receptor polyglutamine tract polymorphism. *The Journal of clinical endocrinology and metabolism* 2007;92:3604-3610.
21. American Diabetes A. Standards of medical care in diabetes-2013. *Diabetes Care* 2013;36(Suppl 1):S11-66.
22. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. *The American journal of clinical nutrition* 2002;76:378-383.
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-419.
24. Choi KM, Lee J, Kim YH, Kim KB, Kim DL, Kim SG, Shin DH, Kim NH, Park IB, Choi DS, Baik SH, Koreans-Southwest Seoul S. Relation between insulin resistance and hematological parameters in elderly Koreans-Southwest Seoul (SWS) Study. *Diabetes Res Clin Pract* 2003;60:205-212.
25. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* 2004;27:1249-1249.
26. Bugianesi E, Pagotto U, Manini R, Vanni E, Gastaldelli A, de Iasio R, Gentilcore E, Natale S, Cassader M, Rizzetto M, Pasquali R, Marchesini G. Plasma adiponectin in non-alcoholic fatty liver is related to hepatic insulin resistance and hepatic fat content, not to liver disease severity. *J Clin Endocr Metab* 2005;90:3498-3504.
27. Svegliati-Baroni G, Bugianesi E, Bousserhal T, Marini F, Ridolfi F, Tasseti F, Ancarani F, Petrelli E, Peruzzi E, Lo Cascio M, Rizzetto M, Marchesini G, Benedetti A. Post-load insulin resistance is an independent predictor of hepatic fibrosis in virus C chronic hepatitis and in non-alcoholic fatty liver disease. *Gut* 2007;56:1296-1301.
28. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, Sowers MR. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering - Prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* 2008;168:1617-1624.
29. Manu P, Tsang J, Napolitano BA, Lesser ML, Correll CU. Predictors of insulin resistance in the obese with metabolic syndrome. *Eur J Intern Med* 2010;21:409-413.
30. Ruan XY, Gallagher D, Harris T, Albu J, Heymsfield S, Kuznia P, Heshka S. Estimating whole body intermuscular adipose tissue from single cross-sectional magnetic resonance images. *J Appl Physiol* 2007;102:748-754.
31. Albu JB, Kovera AJ, Allen L, Wainwright M, Berk E, Raja-Khan N, Janumala I, Burkey B, Heshka S, Gallagher D. Independent association of insulin resistance with larger amounts of intermuscular adipose tissue and a greater acute insulin response to glucose in African American than in white nondiabetic women. *American Journal of Clinical Nutrition* 2005;82:1210-1217.
32. Visser M, Langlois J, Guralnik JM, Cauley JA, Kronmal RA, Robbins J, Williamson JD, Harris TB. High body fatness, but not low fat-free mass, predicts disability in older men and women: the Cardiovascular Health Study. *The American journal of clinical nutrition* 1998;68:584-590.
33. Payette H, Hanusaik N, Boutier V, Morais JA, Gray-Donald K. Muscle strength and functional mobility in relation to lean body mass in free-living frail elderly women. *European journal of clinical nutrition* 1998;52:45-53.
34. Duche P, Ducher G, Lazzer S, Dore E, Tailhardat M, Bedu M. Peak power in obese and nonobese adolescents: effects of gender and braking force. *Med Sci Sports Exerc* 2002;34:2072-2078.
35. Sugimoto K, Baba M, Suda T, Yasujima M, Yagihashi S. Peripheral neuropathy and microangiopathy in rats with insulinoma: association with chronic hyperinsulinemia. *Diabetes-Metabolism Research and Reviews* 2003;19:392-400.
36. Kim B, Feldman EL. Insulin resistance in the nervous system. *Trends Endocrinol Metab* 2012;23:133-141.
37. Misra UK, Kalita J, Nair PP. Diagnostic approach to peripheral neuropathy. *Annals of Indian Academy of Neurology* 2008;11:89-97.
38. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 1997;46:1579-1585.
39. Kim D, Nam S, Ahn C, Kim K, Yoon S, Kim J, Cha B, Lim S, Kim K, Lee H, Huh K. Correlation between midthigh low-density muscle and insulin resistance in obese nondiabetic patients in Korea. *Diabetes care* 2003;26:1825-1830.
40. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, Stamm E, Newman AB. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. *J Appl Physiol* (1985) 2001;90:2157-2165.
41. Grassi G, Seravalle G, Trevano FQ, Dell'Oro R, Scopelliti F, Facchini A, Mancia G. Potentiating effects of the metabolic syndrome on the sympathetic abnormalities characterizing human obesity. *J Hypertens* 2005;23:S266-S266.
42. Egan BM. Insulin resistance and the sympathetic nervous system. *Curr Hypertens Rep* 2003;5:247-254.

43. Sinski M, Lewandowski J, Abramczyk P, Narkiewicz K, Gaciong Z. Why study sympathetic nervous system? *Journal of physiology and pharmacology: an official journal of the Polish Physiological Society* 2006;57(Suppl 11):79-92.
44. Clark MG, Barrett EJ, Wallis MG, Vincent MA, Rattigan S. The microvasculature in insulin resistance and type 2 diabetes. *Seminars in vascular medicine* 2002;2:21-31.
45. Lillioja S, Mott DM, Zawadzki JK, Young AA, Abbott WG, Knowler WC, Bennett PH, Moll P, Bogardus C. *In vivo* insulin action is familial characteristic in nondiabetic Pima Indians. *Diabetes* 1987;36:1329-1335.
46. Julius S. Corcoran Lecture. Sympathetic hyperactivity and coronary risk in hypertension. *Hypertension* 1993; 21:886-893.
47. Galgani JE, Heilbronn LK, Azuma K, Kelley DE, Albu JB, Pi-Sunyer X, Smith SR, Ravussin E, Grp LAAR. Metabolic flexibility in response to glucose is not impaired in people with type 2 diabetes after controlling for glucose disposal rate. *Diabetes* 2008;57:841-845.
48. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *The New England journal of medicine* 2004;350:664-671.
49. Oltman CL, Coppey LJ, Gellett JS, Davidson EP, Lund DD, Yorek MA. Progression of vascular and neural dysfunction in sciatic nerves of Zucker diabetic fatty and Zucker rats. *Am J Physiol-Endoc M* 2005;289:E113-E122.
50. Oberbach A, Bossenz Y, Lehmann S, Niebauer J, Adams V, Paschke R, Schon MR, Bluher M, Punkt K. Altered fiber distribution and fiber-specific glycolytic and oxidative enzyme activity in skeletal muscle of patients with type 2 diabetes. *Diabetes care* 2006;29:895-900.
51. Lillioja S, Young AA, Culter CL, Ivy JL, Abbott WG, Zawadzki JK, Yki-Jarvinen H, Christin L, Secomb TW, Bogardus C. Skeletal muscle capillary density and fiber type are possible determinants of *in vivo* insulin resistance in man. *The Journal of clinical investigation* 1987;80:415-424.
52. Johnson CP, Lynam N, Burns J. An autopsy study of the variability of vertebral artery loops in relation to the investigation of fatal vertebral artery injury. *J Pathol* 1996;179:A49-A49.
53. Elder GCB, Bradbury K, Roberts R. Variability of Fiber Type Distributions within Human Muscles. *J Appl Physiol* 1982;53:1473-1480.
54. Lazarus R, Sparrow D, Weiss ST. Handgrip strength and insulin levels: Cross-sectional and prospective associations in the normative aging study. *Metabolism-Clinical and Experimental* 1997;46:1266-1269.