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

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**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 sarcopenia[1] 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 extremity[4]. In T2DM patients, insulin resistance is negatively associated with knee extension force divided by body weight[5]. According to Sun and colleagues[6], 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 humans[8]. Insulin resistance (IR) is a pathophysiological stage that precedes T2DM[9]. 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 consequences[10].

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

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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 mass[11], and with lower gait speed but not with lower absolute peak leg force[12].

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 individuals[13]. Since IR is apparent approximately 10 years earlier than T2DM[14], 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 & Karlamangla[16] 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 colleagues[15] 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 muscles[17]. 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 neuropathy[4]. 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 study[20] 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 ≥6,5% or 48 mmol/mol[21]) 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 muscle[22]. 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 Imaging[22]. 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, Irwington, 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 resistance[23]. By using lower and upper quartiles[24] 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 75$^{th}$ percentile[25-27] to the 90$^{th}$ 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 (HOMA ≥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 ± 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 ± 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 mass[30] (as well as subjects with lower insulin sensitivity[31]) 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 mass[34]. 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 & Karlamangla[16] 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 changes[35], 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 influenced[37].

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 force[12]. 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-IR[11]. 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 subjects[41]. This sympathetic overactivity would partly be caused by hyperinsulinemia[42] 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 manifests (in chronic situations) as a decreased capillary density of muscle[44], enlarging the diffusion distance in IR individuals[45]. Activation of adrenergic peripheral ß-receptors also changes proportion between slow and fast twitch muscle fibers[46]. The inability to modify fuel oxidation in response to changes in nutrient availability has been implicated in the accumulation of intramyocellular lipid and insulin resistance[47]. 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 density[6] and function[48] 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 physiology[54], 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 elderly[11]), and this can predominantly be seen in distal body parts (just like in diabetes[4]). 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.

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