Tissue Insulin Sensitivity in Aging: A Large-Scale PET Study of Skeletal Muscle, Adipose Tissue, Myocardium and Liver

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Abstract

Context

Aging and insulin resistance are both characterized by unfavorable changes in body composition, insulin receptor expression and activity and metabolic flexibility. However, it remains unclear how aging independently affects tissue-specific insulin sensitivity in humans.

Methods

We examined the association between age and insulin-stimulated glucose uptake, measured with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) during hyperinsulinemic, euglycemic clamp in a cross-sectional cohort of 503 individuals who participated in clinical research studies in Turku PET Centre (Turku, Finland) between 1997 and 2023.

Results

Aging was associated with reduced whole-body insulin sensitivity (*M* value, β = -0.177, $P < .0001$). This was primarily driven by impaired insulin-mediated suppression of endogenous glucose production ($\beta = 0.094$, $P = .001$), and decreased glucose uptake in subcutaneous adipose tissue (β = -0.104, $P < .0001$), but not in skeletal muscle ($P = .31$). In the liver and myocardium, higher age associated with increased glucose uptake ($\beta = 0.116$, $P = .0002$ and $\beta = 1.159$, $P = .041$, respectively). Aging had a more significant association with whole-body and visceral adipose tissue glucose uptake in men, while no sex-specific differences were observed in other tissues.

Conclusions

Aging affects glucose metabolism primarily in adipose tissue and the liver, while skeletal muscle glucose uptake appears to be more dependent on other contributors to insulin resistance, such as the co-existence of type 2 diabetes.

Introduction

Aging affects many metabolic processes, including a well-documented decrease in whole-body insulin sensitivity with age (1). Several mechanisms contribute to this decline, such as changes in adipose tissue distribution, lipotoxicity, impaired adipogenesis, chronic inflammation and cellular senescence (2). In addition to changes in lipid metabolism, aging is associated with reduced muscle mass and strength (sarcopenia) (3–5). Conversely, type 2 diabetes and insulin resistance are themselves known to accelerate aging and sarcopenia (2), also independently of body weight (6).

At the cellular level, insulin resistance is characterized by reduced expression of insulin receptors and, more importantly, impaired signaling through the insulin receptor substrate (IRS)–phosphatidylinositol-3-kinase (PI3K)–protein kinase B (AKT) pathway (7). This signaling cascade becomes less effective with age (8), similarly to mitochondrial function and the oxidative capacity, reducing metabolic flexibility (9). Another factor contributing to insulin resistance is the accumulation of intracellular lipids and ceramides (9,10). These lipids disrupt glucose uptake by impairing GLUT4 translocation to the cell membrane, which reduces cellular glucose transport and contributes to insulin resistance. Altered fatty acid metabolism and increased lipid infiltration, both of which are linked to aging, further promote ceramide accumulation. (9)

In addition to its metabolic effects, insulin resistance disrupts cellular growth and autophagy by interfering with key signaling pathways, including the mammalian target of rapamycin (mTOR), sirtuins, and AMP-activated protein kinase (AMPK), and also contributes to epigenetic modifications (11). These alterations impair stress responses and cellular repair mechanisms, thereby accelerating age-related changes. To counteract tissue insulin resistance, aging is also associated with a rise in circulating insulin levels, which in turn might induce cellular senescence (12).

Despite these known associations, there is limited literature on how aging affects insulin sensitivity in different tissues of the human body. Whole-body insulin sensitivity can be assessed using the hyperinsulinemic, euglycemic clamp technique, which is considered the gold standard for such measurements (13). This method involves elevating plasma insulin concentrations to postprandial levels via continuous insulin infusion, while maintaining euglycemia (plasma glucose ~5 mmol/L) through a variable glucose infusion. The amount of glucose needed to maintain euglycemia reflects the body's insulin sensitivity. When combined with positron emission tomography (PET) imaging using the glucose analogue [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), this approach allows for the evaluation of insulin-stimulated glucose uptake in specific tissues in vivo.

In this study, we examined how aging is associated with insulin sensitivity in skeletal muscle, liver, myocardium, and subcutaneous and visceral adipose tissue.

Methods

Study population

The study population consists of 503 individuals who participated in [^{18}F]FDG-PET/CT studies during a hyperinsulinemic, euglycemic clamp at Turku PET Center, Turku, Finland between 1997 and 2023, and who had given their consent for later use of the data collected. A summary of all the studies can be found in the supplementary material (Supplementary Tables 1 and 2). This data-collecting study is part of the CMgene study registered in ClinicalTrials.gov (NCT03310502).

PET/CT scans

The participants were instructed to fast for 10–12 hours before the PET/CT-scans and not to take any medication on the day of the scanning. On the morning of the scans, two cannulas were inserted in

veins of opposite forearms, one for the [^{18}F]FDG injection and infusion of glucose and insulin, and the other one for collection of arterialized, venous blood samples. A detailed description of the analysis of the blood work can be found in the supplements.

After collecting the fasting blood samples, a hyperinsulinemic euglycemic clamp was started. During the clamp, fast-acting human insulin (Actrapid, NovoNordisk) was administered at a steady rate of 40 mU/m^2 body surface area/min. Euglycemia (plasma glucose levels 5.0 ± 0.5 mmol/L) was sustained by moderating the infusion rate of 20 % glucose solution based on plasma glucose levels, which were measured from arterialized venous samples collected every 5 to 10 minutes. The clamp was continued until the end of the PET scan. To ensure adequate insulin levels throughout the clamp, we measured plasma insulin levels at fasting and every 30 min. We also measured serum free fatty acids (FFAs) at fasting and every 60 min, to investigate insulin's effect on lipolysis. The suppression of lipolysis was measured in percents to fasting. Whole-body glucose disposal (*M* value; (13)) is presented as an average of three to four 20-min periods during steady euglycemia.

After 60 minutes, when a steady euglycemia was reached, study participants were transferred to a PET/CT scanner and instructed to lay in supine position. The scanners used were CTI-Siemens ECAT 931 during the years 1997-2004 (N=183), GE Advance during the years 2004-2010 (N=69), GE Discovery VCT during the years 2011-2015 (N=56), GE D690 during the years 2012-2022 (N=192) and GE Discovery MI during the years 2022-2023 (N=3). First an initial scout CT was performed, in order to select scanning locations. After this the subjects were injected with 169 ± 41 MBq of [^{18}F]FDG and a PET scan was started from injection. Separate, dynamic frames covered the myocardium and the liver, abdominal adipose tissue, and mid-thigh skeletal muscles. The amount of tracer lost in urine was measured from an urine sample at the end of the scan.

Liver fat content and body fat percentage

Liver fat percentage was determined with 1.5 T MR imaging with ^{1}H MR spectroscopy and in-phase and out-of-phase imaging of the liver. Three fat indexes were calculated from the signal intensity (SI) measured on the images as described earlier. (14)

Body fat percentage was either estimated or measured. Estimations were done with the impedance method (Body Impedance Analyser; Akern, RJL Systems, Florence, Italy) or from 7 skin fold sites (chest, midaxillary, triceps, subscapular, suprailiac, abdominal, and thigh), as measured with a caliper. Measures were done with air displacement plethysmography (Cosmed USA, Concord, CA) after at least 4 h of fasting, or using a bioelectrical impedance scale (Omron, model HBF-400-E, Omron Healthcare, Lake Forest, IL, USA).

Data analysis

Prior to analysis, the PET data were corrected for dead time, decay and photon attenuation. The analyses on peripheral tissue glucose uptake were performed using the in-house developed Carimas software (15). Volumes of interest were drawn free-hand on the quadriceps femoris muscle on both thighs, right lobe of the liver, subcutaneous adipose tissue at the waist and in several locations within the abdominal cavity for visceral adipose tissue. Input curve was determined from plasma samples or by combining image- and plasma-derived input. Tissue glucose uptake was calculated by graphical analysis by plotting the accumulation of [^{18}F]FDG in tissues to the amount of radiotracer available in circulation (16,17), and by multiplying the resulting fractional uptake (K_i) of [^{18}F]FDG (16) or its approximation fractional uptake rate (FUR) (17), with plasma glucose concentration during the scan, and dividing it by tissue density and a constant accounting for the differences in transportation of glucose and [^{18}F]FDG (lumped constant; 1,2 for skeletal muscle, 1,0 for liver and myocardium and 1,14 for adipose tissue). (18–24)

158

159 The mean rate of endogenous glucose production (EGP) during the PET scan was calculated as
160 described by Iozzo et al. (2006) (25) by subtracting the glucose infusion rate from the rate of glucose
161 disappearance (R_d). R_d was obtained from [^{18}F]FDG clearance adjusted with [^{18}F]FDG lost to urine
162 (25).

163

164 *Statistical methods*

165 The study population was divided into < 50 years and >= 50 years of age for descriptive purposes,
166 according to the mean age of the total study population. Differences in population characteristics
167 between the participants who were < 50 years and >= 50 years were analyzed with Student´s *t*-test
168 (normally distributed variables) for continuous variables and with ChiSquare test for categorical
169 variables. The variables with skewed distributions were corrected using logarithmic transformation
170 ($\log_e$). The associations between age and variables of interest (fasting glucose; fasting insulin;
171 HOMA-IR; *M* value; R_d; EGP; suppression of lipolysis; and glucose uptake in skeletal muscle, liver,
172 subcutaneous adipose tissue, visceral adipose tissue and myocardium; liver fat percentage; and whole
173 body fat percentage) were analyzed with a linear model, adjusted for type 2 diabetes and sex. All
174 other variables except liver and whole-body fat percentage were also adjusted for body mass index
175 (BMI). We also analyzed the possible sex-specific differences by testing for an interaction for age*sex
176 for all variables of interest in a model which included BMI and previously diagnosed type 2 diabetes
177 as covariates. If the interaction term was statistically significant ($P < .05$), stratified analyses were
178 performed for men and women. All statistical analyses were performed with JMP Pro 17 (SAS
179 institute, Cary, NC, USA). Statistical significance was set at $P<0.05$ (two-tailed).

180

Results

Population characteristics

Descriptive data of the study population is shown in Table 1. The total number of participants in the included studies was 503. The prevalence of type 2 diabetes and obesity was higher in the group of participants over 50 years of age. As a result, fasting plasma glucose, fasting plasma insulin and HbA1c levels were also higher in this group. There were no significant differences between age groups in liver fat content, total cholesterol, and high- and low-density lipoprotein cholesterol levels. Serum FFAs were higher in the age group over 50 years during fasting, but not under hyperinsulinemic conditions.

Association Between Age and Fasting Indices of Insulin Resistance

Of the indices of insulin resistance measured under fasting conditions, higher fasting plasma glucose level and HOMA-IR were associated with higher age. In contrast, no significant associations were observed between age and fasting plasma insulin levels (Table 2).

Body Fat Distribution and Aging

Total body fat percentage increased with age, while no association was found between age and liver fat content (Table 2).

Whole-body insulin sensitivity and aging

Higher age was linked to lower whole-body insulin sensitivity (*M* value) and a lower rate of glucose disappearance (R_d) during PET imaging (Figure 1A; Table 2). A rise in the insulin-induced suppression of lipolysis − measured as the percentage decrease in serum FFAs from fasting to 60 minutes of hyperinsulinemia – was also associated with higher age. (Table 2).

206

207 *Aging-related changes in tissue insulin sensitivity*

208 Age-related differences in insulin-stimulated glucose uptake varied by tissue. Subcutaneous, but not
209 visceral, adipose tissue glucose uptake was lower in aging individuals (Figure 1B, Table 2). In skeletal
210 muscle, no significant association with age was observed (Figure 1C). In contrast, hepatic and
211 myocardial glucose uptake increased with age (Figure 1D and 1E). In addition, advancing age was
212 associated with impaired insulin-mediated suppression of EGP (Figure 1F).

213

214 *The influence of sex on age-related changes in studied variables*

215 Sex was observed to influence whole-body insulin sensitivity (*M* value) (age*sex interaction P =
216 .001), rate of glucose disappearance (R_d) during PET imaging (P = .007) as well as whole-body fat
217 percentage (P = .02). The analyses stratified by sex showed that for all of these variables the age-
218 related changes were significant only in males, with M value (β = -0.241, P < .0001 *vs* P = .11 in
219 females) and R_d (β = -0.199, P = .04 *vs* P = .31 in females) decreasing, and whole-body fat percentage
220 increasing with age (β = 0.252, P < .0001 *vs* P = .14 in females).

221 In the whole study population, aging did not associate with changes in visceral adipose tissue insulin-
222 stimulated glucose uptake, while sex had a significant association with the result (P=.009). Again,
223 the effect was only seen in male participants, with visceral adipose tissue glucose uptake decreasing
224 with age (β = -0.118, P = .01). Sex was not seen to influence the glucose uptake of the liver (P = .13),
225 heart (P = .87), skeletal muscle (P = .31) or subcutaneous adipose tissue (P = .66).

226

227 **Discussion**

228 In this large dataset we showed that aging is associated with decreasing whole-body insulin
229 sensitivity, mostly driven by impaired suppression of EGP by insulin and declined insulin-stimulated
230 glucose uptake in abdominal subcutaneous adipose tissue. Also, higher age was modestly associated

with increased hepatic and myocardial glucose uptake under hyperinsulinemic conditions, as well as a higher insulin mediated suppression on lipolysis. There were also sex-specific changes, showing that aging was significantly associated with impaired whole-body and visceral adipose tissue insulin sensitivity only in males.

Although we found higher levels of fasting plasma glucose and insulin, and higher prevalence of type 2 diabetes in participants over 50 years of age, the analyses adjusted for BMI, sex and type 2 diabetes showed an association only between higher age and fasting plasma glucose levels as well as HOMA-IR. These results confirm previous observations of higher fasting glucose levels and impaired glucose tolerance in aging individuals (26), but in our study the difference was significant already when using a smaller age gap. In the study by Basu et al. (26), both higher fasting glucose levels and decreased glucose tolerance were thought to be derived from decreasing insulin secretion and activity (26). As body fat distribution is known to correlate with glucose tolerance (27), after correcting for BMI, we found no association between age and fasting insulin levels similarly to Basu et al. (26). A positive correlation between aging and HOMA-IR has also been seen earlier (28).

Regarding whole-body insulin resistance, we found an association between increasing age and lower *M* value and lower rate of glucose disappearance during the imaging. Similar associations between age and whole-body insulin resistance have been documented earlier (29–32). We also demonstrated a correlation between age and impaired suppression of EGP by insulin, which represents a higher glucose production predominantly in the liver during the hyperinsulinemic, euglycemic clamp, indicating hepatic insulin resistance (33). Impaired suppression of EGP by insulin with increasing age has been documented earlier in mice (34) and rats (35), but not in humans.

Our data revealed no association between age and insulin-stimulated glucose uptake in skeletal muscle. This finding is consistent with previous *in vivo* studies in rats (36,37), although some *in vitro* studies using human (38) and rat (39) myocytes have suggested that aging impairs glucose uptake in skeletal muscle. This is an important observation given that skeletal muscle is the principal site of insulin-stimulated glucose uptake (4). In addition to a decline in muscle mass (40), aging is also associated with increased intramuscular adipose tissue (41) and accumulation of intramyocellular triglycerides (42), as well as impairments in insulin signaling in muscles (43). These factors collectively contribute to insulin resistance and sarcopenia (9). Fortunately, studies have also shown that skeletal muscle has a reserve to increase glucose uptake in response to exercise also in the elderly (44–48). Unfortunately, we did not collect data on the physical activity levels of the participants; therefore, this issue cannot be examined using the present dataset.

In contrast, in our dataset higher age was associated with lower insulin-stimulated glucose uptake in abdominal subcutaneous adipose tissue in both sexes and a lower visceral adipose tissue glucose uptake in males. Earlier results have been conflicting, with aging being associated with increased adipose tissue glucose uptake measured *in vivo* in rats (49), and *in vitro* studies producing again opposite results (50). It has been speculated that the lowered insulin sensitivity associated with age could be caused by an abundance of free fatty acids (FFA) and a higher body fat percentage, as well as a more central fat distribution of the body (51,52). It has also been shown that increasing age correlates to development of a more hyperplastic form of adipose tissue (53).

However, insulin's most important function in the adipose tissue, the suppression of lipolysis, was seen to rise in the aging individuals. This is contrast to a previous study, where postprandial lipolysis was less effectively suppressed in elderly individuals (54). However, in the previous study insulin secretion was also significantly lower in the elderly individuals, whereas in the current study plasma

insulin levels were comparable across all age groups. Earlier studies have mainly demonstrated age-induced reduction of catecholamine-induced lipolysis and lipolysis impairment both in mice (55,56) and humans (57,58). Insulin mediated suppression of lipolysis has been seen to decrease with age in earlier studies performed with rat cells in cell cultures (59).

We also demonstrated an association between higher hepatic glucose uptake and aging. In earlier studies age has been linked to a reduced hepatic glucose uptake in rats and mice (49), as well as in garden lizards (60). Earlier studies have also demonstrated that hepatic insulin extraction rises with age (26,61), although there are also studies with opposite findings (62). Higher hepatic glucose uptake might depict a change in hepatic insulin effectivity or metabolism (26). A higher hepatic insulin extraction combined with a lowered whole-body insulin clearance leads to a restricted amount of insulin in extrahepatic tissues (26). It has also been seen that restricting the amount of insulin in the liver causes a compensatory rise in muscle and adipose tissue glucose uptake (49). The liver´s role in modulating how insulin secretion leads to peripheral insulin transportation has also been shown to be directly associated with age (40). In contrast to our findings, it has been shown that the liver fat percentage rises with age (42), although this has been speculated to be explained with higher whole-body fat percentage and a higher visceral adipose tissue amount (40).

Our study demonstrated an increase in myocardial glucose uptake with advancing age. In resting state, healthy myocardium generally prefers fatty acids as energy substrates, while higher glucose uptake has been seen to correlate to many heart diseases such as heart failure, ischemia and cardiomyopathy (63,64). The increased need for glucose during insulin stimulation is likely associated with the impaired mitochondrial function and oxidative capacity in the aging myocardium, while the oxidative stress might also stimulate glucose uptake to fulfil pentose phosphate pathway needs (65).

We also show that increasing age was associated with a higher whole-body fat percentage exclusively in men, together with reduced whole-body and visceral adipose tissue insulin-stimulated glucose uptake. Previous clamp-based studies have demonstrated that chronological aging *per se* is often less strongly associated with insulin resistance than age-related changes in body composition, particularly increased adiposity and reduced lean mass in males (27). Moreover, sexual dimorphism in fat distribution and tissue-specific insulin action has been well documented, with men exhibiting greater visceral adiposity and lower insulin-stimulated glucose uptake to visceral adipose tissue compared with women (66). Experimental work also suggests that male adipose tissue may display impaired insulin signaling and less effective suppression of lipolysis, potentially predisposing men to greater age-related deterioration in systemic metabolic function. Our findings extend these findings by demonstrating that, even after accounting for BMI and diabetes status, aging in men is accompanied by reduced visceral adipose tissue glucose uptake, supporting the concept of sex-specific alterations in adipose tissue insulin responsiveness. Only 2 individuals were reported to be on testosterone therapy and 5 individuals on estrogen replacement therapy, so the effect of these could not be estimated.

Our study also had limitations regarding the layout of the study, since our study is a cross-sectional study and not a longitudinal follow-up study. Another limitation is that the study is composed of several individual studies. Partly due to this, the different scans have been conducted during a long period of time which might cause a bias via different inclusion criteria in the studies. Strengths of the study are that we used the golden standard for measuring insulin resistance, the hyperinsulinemic euglycemic clamp technique, and that we have all the studied tissues scanned from each person during the same PET scan with similar protocols across different sub-studies.

To conclude, we demonstrate here that age correlates with a lower insulin sensitivity on the whole-body level, driven by impaired subcutaneous adipose tissue glucose uptake and higher endogenous glucose production during hyperinsulinemia. In contrast myocardial glucose uptake and hepatic glucose uptake or extraction increased with age in the same study condition. Also, there were sex-specific changes in the effects of aging on whole-body and visceral adipose tissue insulin sensitivity. However, longitudinal studies would be needed to confirm our findings in the future.

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537 **Table 1.** Participant characteristics

	Whole population	Age <50 years	Age ≥50 years	*P* value
N	503	211	292	
Age (years)	50.0 (SD 16.3)	34 (SD 9.8)	62 (SD 7.5)	
Sex, N (female)	207 (41 %)	70 (33 %)	137 (47 %)	.002
Type 2 diabetes (N(%))	143 (28 %)	20 (4 %)	123 (25 %)	<.0001
BMI (kg/m^2)	29.0 (SD 6.0)	28.1 (SD 7.1)	29.6 (SD 5.1)	.01
Fasting glucose (mmol/L)	5.7 (IQR 5.3, 6.4)	5.3 (IQR 5.1, 5.7)	6.1 (IQR 5.6, 7)	<.0001
Fasting insulin (pmol/L)	55.6 (IQR 34.7, 78.7)	48.6 (IQR 34.7, 76.4)	55.6 (IQR 41.7, 83.3)	.04
HbA1c (mmol/mol)	37.7 (IQR 33.3, 42.1)	34.4 (IQR 31.0, 37.7)	40 (IQR 36.6, 47.5)	<.0001
Total cholesterol (mmol/L)	4.7 (SD 2.3)	4.8 (SD 3.3)	4.7 (SD 0.9)	.92
HDL cholesterol (mmol/L)	1.4 (SD 0.4)	1.3 (SD 0.4)	1.4 (SD 0.4)	.03
LDL cholesterol (mmol/L)	2.7 (SD 0.8)	2.7 (SD 0.8)	2.8 (SD 0.8)	.16
Fasting FFA (mmol/L)	0.57 (SD 0.24)	0.52 (SD 0.22)	0.61 (SD 0.24)	<.0001
60 min FFA (mmol/L)	0.11 (SD 0.07)	0.10 (SD 0.08)	0.11 (SD 0.07)	.87
Liver fat percentage (%)	4.32 (IQR 1.7, 9.6)	3.5 (IQR 1.5, 8.8)	4.6 (IQR 1.9, 10.2)	.43

Whole-body fat percentage (%)	32.4 (SD 12.0)	28.3 (SD 12.5)	36.5 (SD 10.1)	<.0001

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539 The data are represented as mean (standard deviation) for normally distributes variables and as median (interquartile
540 range) for variables with a skewed distribution. P-values represent differences between individuals under and over
541 50 years, assessed with Student's t-test for continuous variables and Chi-Squared test for categorical variables. BMI
542 body mass index, HDL high-density lipoprotein, LDL low-density lipoprotein, FFA serum free fatty acids

543

544 **Table 2.** Associations between age and measures of insulin sensitivity

Age	N	β	95% CI	Standardized β	*P* value
Fasting glucose (mmol/L)	502	0.003	0.0018, 0.0035	0.224	<.0001
Fasting insulin (pmol/L)	493	0.0019	-0.0013, 0.005	0.049	.24
HOMA-IR	493	0.0045	0.0010, 0.0079	0.105	.01
M value (µmol/kg body weight/min)	500	-0.177	-0.247, -0.107	-0.184	<.0001
R_d (µmol/kg body weight/min)	231	-0.150	-0.253, -0.046	-0.153	.005
EGP (µmol/kg body weight/min)	272	0.094	0.038, 0.149	0.203	.001
Suppression of lipolysis (%)	465	0.131	0.003, 0.259	0.091	.05
Skeletal muscle GU (µmol/tissue kg/min)	470	0.012	-0.114, 0.139	0.009	.85
Liver GU (µmol/tissue kg/min)	409	0.116	0.055, 0.177	0.184	.0002
Subcutaneous AT GU (µmol/tissue kg/min)	340	-0.104	-0.142, -0.065	-0.241	<.0001

Visceral AT GU (µmol/tissue kg/min)	333	-0.019	-0.094, 0.057	-0.026	.63
Myocardial GU (µmol/tissue kg/min)	370	1.159	0.047, 2.272	0.117	.04
Liver fat percentage (%)	281	-0.007	-0.019, 0.0059	-0.075	.29
Whole-body fat percentage (%)	363	0.142	0.079, 0.204	0.198	<.0001

Beta, 95% CI, standardized beta and p-value are derived from linear regression analysis and represent the independent association between age and each dependent variable of interest, adjusted for sex, BMI and Type 2 diabetes where applicable. Logarithmic transformation was used for fasting glucose, fasting insulin, HOMA-IR and liver fat percentage to achieve a normal distribution. R_d rate of glucose disappearance, EGP endogenous glucose production, AT adipose tissue, GU glucose uptake.

Figure 1. During euglycemic hyperinsulinemia, aging was associated with decreased rate of glucose disappearance (R_d, A), decreased subcutaneous adipose tissue glucose uptake (B), no alteration in skeletal muscle glucose uptake (C), increased glucose uptake into the liver (D) and myocardium (E), and impaired suppression of endogenous glucose production during hyperinsulinemia (F). Black dots represent individuals without and circles with type 2 diabetes. The graphs contain non-standardized, original values, while the reported standardized β- and P-values are from data adjusted for BMI, diagnosis of type 2 diabetes and sex, where applicable.