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Increased plasma fatty acid clearance, not fatty acid concentration, is associated with muscle insulin resistance in people with obesity

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Abstract

Background: Although it is well-accepted that increased plasma free fatty acid (FFA) concentration causes lipid overload and muscle insulin resistance in people with obesity, plasma FFA concentration poorly predicts insulin-resistant glucose metabolism. It has been proposed that hyperinsulinemia in people with obesity sufficiently inhibits adipose tissue triglyceride lipolysis to prevent FFA-induced insulin resistance. However, we hypothesized enhanced FFA clearance in people with obesity, compared with lean people, prevents a marked increase in plasma FFA even when FFA appearance is high.

Methods: We assessed FFA kinetics during basal conditions and during a hyperinsulinemic-euglycemic clamp procedure in 14 lean people and 46 people with obesity by using [^{13}C]palmitate tracer infusion. Insulin-stimulated muscle glucose uptake rate was evaluated by dynamic PET-imaging of skeletal muscles after [^{18}F]fluorodeoxyglucose injection.

Results: Plasma FFA clearance was accelerated in participants with obesity and correlated negatively with muscle insulin sensitivity without a difference between lean and obese participants. Furthermore, insulin infusion increased FFA clearance and the increase was greater in obese than lean participants.

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AUTHOR CONTRIBUTIONS

BM designed the study. CC, HCEK, SVV, BWP, DNR, and BM contributed to data acquisition, data analysis, and data interpretation. CC and BM wrote the first draft of the paper. All authors contributed to the revision of the paper. BM is the guarantor of this work, had full access to all the data in the study, and assumes full responsibility for the integrity of the data and the accuracy of the data analysis.

DECLARATION OF INTEREST

The authors report no conflicts of interest relevant to this article.

CLINICAL TRIALS REGISTRATION NUMBERS

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Conclusions: Our findings suggest plasma FFA extraction efficiency, not just plasma FFA concentration, is an important determinant of the cellular fatty acid load and the stimulatory effect of insulin on FFA clearance counteracts some of its antilipolytic effect.

Keywords

Obesity; insulin resistance; adipose tissue; fatty acids

1. INTRODUCTION

It is a widely accepted view that increased fatty acid release from adipose tissue in people with obesity causes an increase in plasma free fatty acid (FFA) concentration, which in turn causes insulin resistance in the liver and skeletal muscles (i.e., impaired insulin action on hepatic glucose production and muscle glucose uptake) [1, 2]. And yet, plasma FFA concentration is a poor predictor of insulin-resistant glucose metabolism and plasma FFA are often not elevated in people with obesity and insulin resistance [3–6]. It has been proposed that hyperinsulinemia in people with obesity compensates for reduced adipose tissue insulin sensitivity and sufficiently inhibits adipose tissue triglyceride lipolysis to prevent FFA-induced insulin resistance [3, 7]. However, plasma FFA concentration is determined by both the FFA appearance rate in plasma and the plasma FFA clearance rate. Accordingly, it is possible that a high plasma FFA clearance rate in people with insulin resistance prevents a marked increase in plasma FFA concentration even when FFA release from adipose tissue is high. Results from studies conducted in rats support this idea [8]. Moreover, they demonstrate that insulin increases muscle FFA clearance [8, 9], suggesting the insulin-mediated decrease in plasma FFA concentration is not only due to decreased adipose tissue triglyceride lipolysis — as is commonly thought — but also increased plasma FFA clearance.

Here, we studied the effects of adiposity and insulin on plasma FFA clearance and its relationship with insulin sensitivity in lean people and people with obesity. We hypothesized that plasma FFA clearance would be greater in participants with obesity than lean participants and would be negatively correlated with muscle insulin sensitivity. Furthermore, we hypothesized that an acute increase in plasma insulin would increase plasma FFA clearance. FFA clearance was determined during basal conditions and during a hyperinsulinemic-euglycemic clamp procedure (HECP) by using a stable isotope-labeled palmitate tracer infusion. Muscle insulin sensitivity was assessed as insulin-stimulated glucose uptake rate, which we determined by using [^{18}F]-labeled fluorodeoxyglucose (FDG) infusion in conjunction with positron-emission tomography (PET).

2. EXPERIMENTAL DESIGN AND METHODS

2.1. Study participants

The data included in this analysis were obtained from 14 lean people and 46 people with obesity who participated in two ongoing studies (NCT02994459, NCT03408613) that used the same experimental protocol. All participants provided written informed consent before initiating the study protocols, which were approved by the Institutional Review Board at

Washington University in St. Louis, MO. Participants completed a medical examination, after they fasted overnight, that included a medical history and physical examination, standard blood tests, and an oral glucose tolerance test. Potential participants were excluded if they: i) had a disease or were taking medications or dietary supplements that could affect the study outcome measures; ii) consumed excessive amounts of alcohol; iii) had ≥3% body weight changes within the past six months; or iv) participated in structured exercise for more than 90 min/week. Body composition was determined by using dual-energy x-ray absorptiometry (Lunar iDXA, GE Healthcare).

2.2. Metabolic testing, sample processing, and calculations

All participants completed a basal metabolic study and a HECP (50 mU insulin/m^2 body surface area/min) after they fasted overnight [10]. To determine FFA kinetics, [U-^{13}C]palmitate was infused intravenously (6.0 nmol/kg fat-free mass/min during basal conditions; 4.5 nmol/kg fat-free mass/min during the HECP) [11]. Approximately 150 min after starting the HECP, [^{18}F]fluorodeoxyglucose (185 MBq) was administered intravenously and muscle glucose uptake was determined by dynamic PET [10]. Blood samples to determine plasma palmitate enrichment, and fatty acid, glucose, and insulin concentrations were obtained before starting the tracer infusions and during the last 30 min of the basal period and the HECP. Plasma glucose concentration was determined by using a glucose analyzer (YSI 2300 STAT, YSI Inc, Yellow Springs, OH). Plasma insulin concentration was determined by using an immunoassay (Elecsys®, Roche Diagnostics). The plasma palmitate tracer-to-tracee ratio and plasma FFA concentrations were determined by using gas-chromatography mass spectrometry, and palmitate flux (appearance rate in and disappearance rate from plasma) was calculated as previously described [7, 11, 12], assuming a steady state, because both plasma palmitate concentration (not shown) and the plasma palmitate enrichment were steady during the sampling periods (Supplemental Figure 1). Plasma palmitate clearance rate, which represents the volume of plasma that is cleared of palmitate per unit of time, was calculated by dividing the palmitate disappearance rate by the plasma palmitate concentration. Palmitate mean residence time, which represents the amount of time each palmitate molecule spends in the circulation, was calculated as the inverse of the palmitate fractional disappearance rate, which is the fraction of the total plasma pool that disappears per unit of time.

2.3. Statistical analysis

Student's *t*-test for independent samples was used to evaluate differences in participants' age, body composition, basic metabolic profile, and insulin sensitivity between the lean and obese groups. Repeated measures analysis of variance was used to evaluate differences in palmitate kinetics during basal conditions and during the HECP between the lean and obese groups. Skewed data sets were log-transformed to achieve normality before analysis. Values are reported as mean ± SEM or median (quartiles). Correlations between variables were evaluated by using the Pearson product moment coefficient. To evaluate potential differences in outcomes between men and women, we also included sex as a covariate in these analyses. However, no differences between men and women were observed. A P-value ≤0.05 was considered statistically significant. Statistical analyses were performed by using STATA, version 16.0 (StataCorp LLC).

3. RESULTS

3.1 Participant general metabolic characteristics

Participants with obesity had more body fat, higher fasting plasma insulin concentration, impaired glucose tolerance, and reduced whole-body and muscle insulin sensitivity (assessed as the glucose infusion rate and muscle glucose uptake rate during the HECP, respectively) than lean participants (Table 1). Fasting plasma glucose concentration and plasma glucose and insulin concentrations during the HECP were not significantly different between the lean and obese groups (Table 1). Therefore, the assessment of whole-body and muscle insulin sensitivity was not confounded by potential differences in plasma insulin between the lean and obese groups. In fact, the unadjusted whole-body and muscle glucose uptake rates (expressed in μmol/min and μmol/kg muscle/min, respectively) correlated strongly ($r \geq 0.95$; $P < 0.001$) with whole-body (data not shown) and muscle (Supplemental Figure 2) glucose uptakes rate adjusted for the plasma insulin concentration (expressed in [μmo/min]/(mU/l)] and [μmol/kg muscle/min]/(mU/l)], respectively).

3.2. Plasma palmitate and total FFA concentrations

During basal conditions, plasma palmitate and total FFA concentrations were about 15% greater in the obese than in the lean group (Table 1 and Figure 1A). Plasma palmitate concentration correlated strongly with total FFA concentration ($r=0.95$, $P<0.001$), confirming that palmitate is a good surrogate for total FFA kinetics [11]. Plasma palmitate and total FFA concentrations during the HECP were several-times lower ($P<0.001$) compared with basal conditions in both the lean and obese groups and plasma palmitate and total FFA concentrations during the HECP were not different between the lean and obese groups (Table 1 and Figure 1A).

3.3. Palmitate kinetics

Basal palmitate appearance rate in plasma was about twice as great in the obese compared with the lean group, and as expected [7], was several-fold lower ($P<0.001$) during the HECP compared with basal conditions in both the lean and obese groups (Figure 1B). The difference in palmitate appearance rate between the lean and obese groups (Figure 1B) was much greater than the difference in plasma palmitate concentration (Figure 1A). Furthermore, the relative decrease from basal values in plasma palmitate concentration was greater than the relative decrease in palmitate appearance rate (Figure 1C). These data demonstrate that the difference in appearance rate between the lean and obese groups alone cannot explain the difference in concentration and the decrease in appearance during the HECP compared with basal conditions alone cannot explain the decrease in concentration during the HECP. In fact, basal plasma palmitate clearance rate was about 50% higher and palmitate mean residence time in the circulation was about 20% shorter in the obese compared with the lean group (Figures 1D, 1E). In addition, plasma palmitate clearance rate was about 30% greater ($P<0.001$) and palmitate mean residence time was about 30% shorter ($P<0.001$) during the HECP than during basal conditions (Figures 1D, 1E) and the increase in clearance from basal conditions was greater in the obese than the lean group (group × condition interaction, $P<0.001$). Because we found insulin increases plasma palmitate clearance and basal plasma insulin concentration was significantly higher in the obese

compared with the lean group, we also evaluated the effect of obesity on plasma palmitate clearance with statistical adjustment for plasma insulin and found palmitate clearance was significantly higher in the obese than the lean group (P=0.003) even after adjusting for plasma insulin concentration. Furthermore, the greater increase in palmitate clearance from basal values during the HECP in the obese compared with the lean group occurred despite a similar or even smaller increase in plasma insulin.

3.4 Relationships between plasma palmitate concentration and palmitate kinetics

There was a significant negative correlation between basal plasma palmitate concentration and basal plasma palmitate clearance rate in both the lean and obese groups (Figure 2A), demonstrating that the efficiency of palmitate removal from plasma decreases as palmitate concentration increases. Furthermore, at any plasma palmitate concentration, plasma palmitate clearance rate and both total palmitate disappearance rate (μmol/min) and palmitate disappearance rate in relation to fat-free mass were higher (~50% and 30%, respectively) in the obese than the lean group (Figures 2A–C).

3.5. Relationships between plasma palmitate clearance rate and insulin sensitivity

There was no significant correlation between plasma palmitate concentration or total FFA concentration and muscle insulin sensitivity (Figure 3A, Supplemental Figure 3A) and whole-body insulin sensitivity (glucose infusion rate during the HECP; Supplemental Figure 3B). However, there were strong negative correlations between plasma palmitate clearance rate and whole-body (not shown) and muscle insulin sensitivity (Figure 3B), and also between plasma palmitate disappearance rate and whole-body (not shown) and muscle insulin sensitivity (Figure 3C). Moreover, these relationships were not different (P>0.15) between the lean and obese groups (Figures 3B, 3C).

4. DISCUSSION

Plasma FFA are an important fuel source for skeletal muscles and other lean tissues, but FFA delivery in excess of energy needs can cause ectopic lipid accumulation and impair insulin-mediated muscle glucose uptake [1, 2]. Although it is conventional wisdom that excessive adipose tissue FFA release causes an increase in plasma FFA concentration and, in turn lipid overload and muscle insulin resistance in people with obesity [1, 2, 13], we hypothesized alterations in tissue FFA clearance might also be involved. Indeed, we found plasma FFA clearance was enhanced in participants with obesity, compared with lean ones. Furthermore, muscle insulin sensitivity correlated negatively with plasma FFA clearance and the relationship was not different between the lean and obese groups. On the other hand, plasma FFA concentration did not significantly correlate with insulin sensitivity. In addition, we found insulin infusion increases plasma FFA clearance and the insulin-mediated increase is greater in people with obesity compared with lean people. These findings have important implications, because they suggest: i) factors that regulate cellular fatty acid transport, not only plasma FFA concentration, determine the cellular fatty acid load, and ii) the plasma FFA-lowering effect of insulin is not only due to inhibition of adipose tissue triglyceride lipolysis but also due to increased plasma FFA clearance. Accordingly, although insulin decreases FFA supply from adipose tissue to lean tissues, it also promotes the translocation

of FFA from plasma into cells where they can presumably interfere with insulin signaling [2].

The exact mechanisms responsible for increased basal plasma FFA clearance associated with insulin resistance are unclear. Results from studies conducted in animals and with giant sarcolemmal vesicles prepared from skeletal muscle biopsies from people demonstrate insulin resistance is associated with increased FFA clearance by skeletal muscles, but not liver or adipose tissue [8, 14]. Furthermore, FFA uptake into adipose tissue contributes only a small fraction (<10%) of total whole-body FFA disposal [12]. Accordingly, muscle was the most likely site of increased FFA clearance in people with obesity and insulin resistance in our study. FFA uptake in myocytes occurs primarily by facilitated diffusion [15, 16]. Both obesity and insulin resistance are associated with increased expression of CD36 and other fatty acid transporter proteins [8, 14, 17–19], which helps explain the increase in muscle fatty acid clearance. However, the exact mechanisms involved in causing this increase are unclear.

Insulin infusion significantly increased plasma FFA clearance above basal values in our study. Furthermore, the ability of insulin to increase plasma FFA clearance was not impaired in people with obesity and was even greater in the obese than the lean group, despite insulin resistance to glucose uptake in the obese. Therefore, the hyperinsulinemia in people with obesity likely contributed to their higher basal FFA clearance. However, it was not solely responsible for it, because basal FFA clearance was greater in the obese than the lean group even after adjusting for the difference in basal plasma insulin concentration. Accordingly, additional mechanisms are responsible for the enhanced plasma FFA clearance in people with obesity and insulin resistance. The dissociation between insulin sensitivity of glucose uptake and FFA clearance in people with obesity suggests different signaling mechanisms are involved in mediating insulin-stimulated glucose and fatty acid uptake in muscle. Results from studies conducted in vitro demonstrate insulin stimulates FFA uptake in muscles and adipose tissue [8, 9, 20], presumably because it inhibits the degradation of fatty acid transporters, stimulates their translocation to the plasma membrane, and activates their enzymatic activity [21–24]. The primary mechanism by which insulin stimulates glucose uptake in muscle involves the translocation of glucose transporter 4 to the plasma membrane [2].

Insulin is also a potent inhibitor of hormone sensitive lipase in adipose tissue and even small increases in plasma insulin concentration above basal values almost completely inhibit release of FFA from adipose tissue in both lean people and people with obesity [7, 12, 25]. Therefore, it is commonly accepted that inhibition of adipose tissue triglyceride lipolysis is the key mechanism responsible for the plasma FFA-lowering effect of insulin [3, 7, 13]. The data from our study mostly support this notion, because we found the FFA appearance rate in plasma is more responsive to insulin than plasma FFA clearance rate. Nonetheless, plasma FFA clearance increased substantially during the HECP and the greater increase in plasma FFA clearance in the obese compared with the lean group was responsible for the greater decrease in plasma FFA concentration in the obese compared with the lean group. Accordingly, insulin is an important regulator of plasma FFA concentration, not only

because it inhibits adipose tissue triglyceride lipolysis but also because it increases plasma FFA clearance.

We did not evaluate the metabolic fate of fatty acids that are extracted from plasma, which could have important implications. The results from a previous study suggest obesity is associated with increased non-oxidative, but not oxidative, fatty acid disposal [26]. This observation suggests fatty acids that are extracted “in excess” in people with obesity compared with lean people are preferentially used to synthesize lipids that might be involved in causing insulin resistance [1, 2]. This in turn would support the relationship between plasma FFA clearance and insulin resistance we observed. Another limitation of our study includes the single dose of insulin we used, which was within the range of peak postprandial plasma insulin concentrations [10]. Therefore, we cannot determine the responsiveness of plasma FFA clearance to smaller changes in insulin as they occur during the transition from postabsorptive to postprandial conditions.

5. CONCLUSIONS

The data presented here demonstrate: i) plasma FFA clearance rate is an important determinant of plasma FFA concentration, ii) insulin stimulates FFA clearance, iii) the effect of insulin on FFA clearance is augmented in people with obesity, and iv) FFA clearance is inversely associated with muscle insulin sensitivity. Together, these findings suggest increased FFA extraction efficiency by lean tissues, not only fatty acid delivery from adipose tissue, determines the cellular fatty acid load in people with insulin resistance. Hyperinsulinemia in people with obesity curbs the release of FFA from adipose tissue but also promotes their plasma clearance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Plasma free fatty acid (FFA) clearance is higher in obese than lean people
- Insulin increases FFA clearance and the increase is greater in obese than lean people
- High FFA clearance in the obese keeps plasma FFA concentration low relative to FFA flux
- Plasma FFA clearance correlates negatively with muscle insulin sensitivity
- There is no relationship between plasma FFA concentration and muscle insulin sensitivity

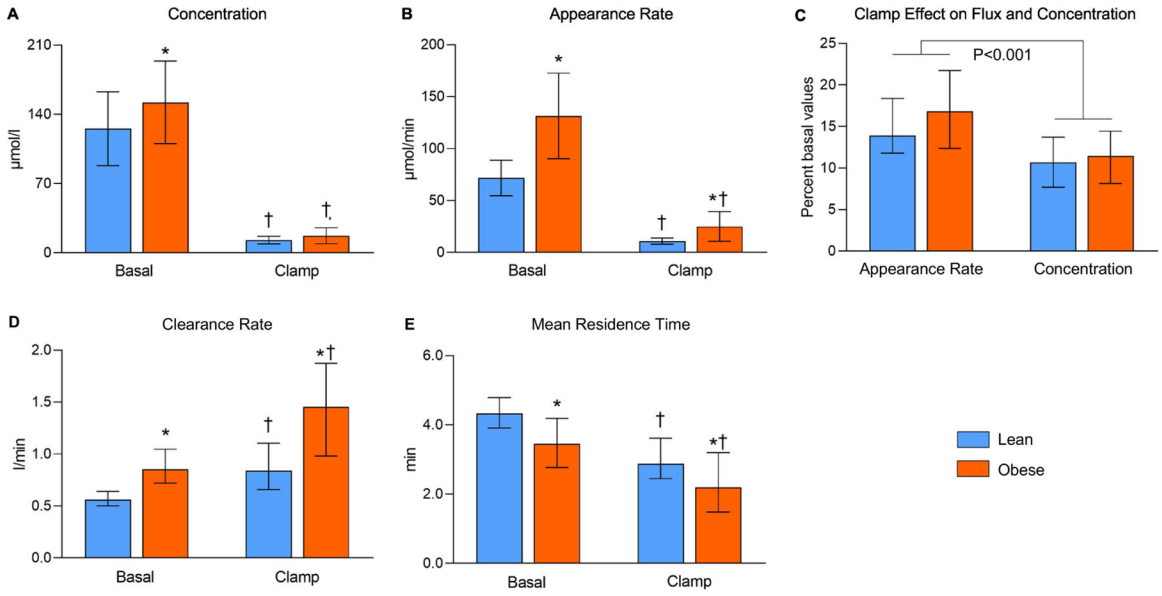

Figure 1.

Palmitate concentration in plasma (A), appearance rate in plasma (B), plasma clearance rate (D), and mean residence time in the circulation (E) during basal conditions and during the hyperinsulinemic-euglycemic clamp procedure, and clamp-induced changes in palmitate appearance rate and plasma concentration (C). Values are median and interquartile range. For the outcomes in panels A, B, D, and E, there was a significant group (lean vs obese) × condition (basal vs clamp) interaction, $P < 0.001$. * Significantly different from the corresponding value in the lean group, $P < 0.05$. † Significantly different from the corresponding basal value, $P < 0.05$.

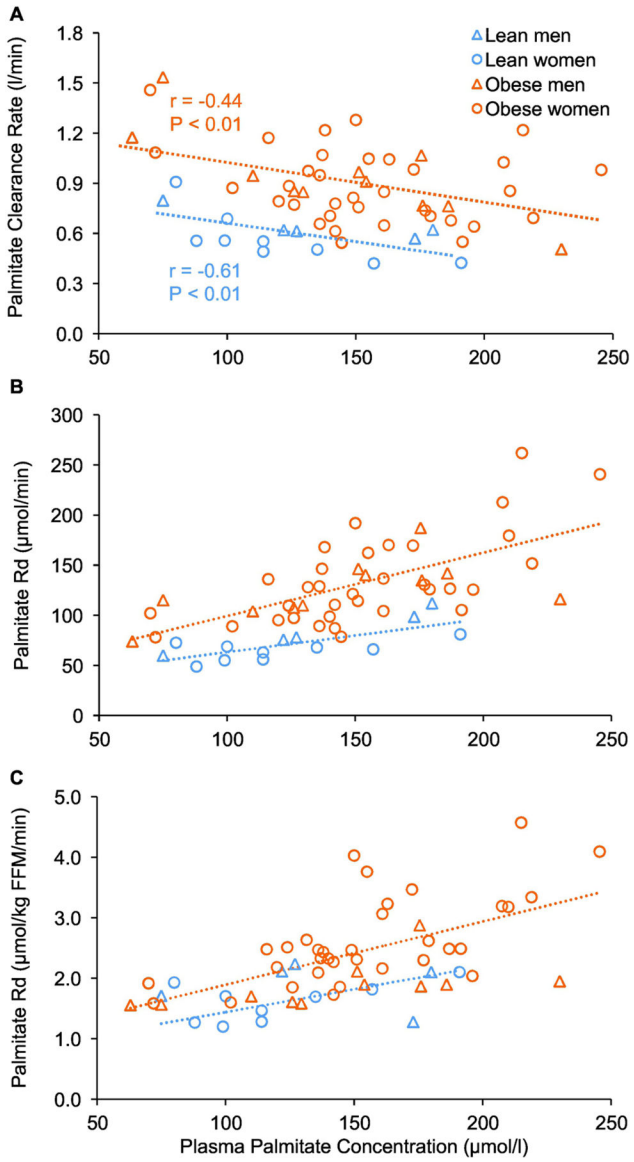

Figure 2.

Relationships between basal plasma palmitate concentration and plasma palmitate clearance rate (A), total palmitate disappearance rate (B), and palmitate disappearance rate in relation to fat-free mass (C). Abbreviations: FFM, fat-free mass.

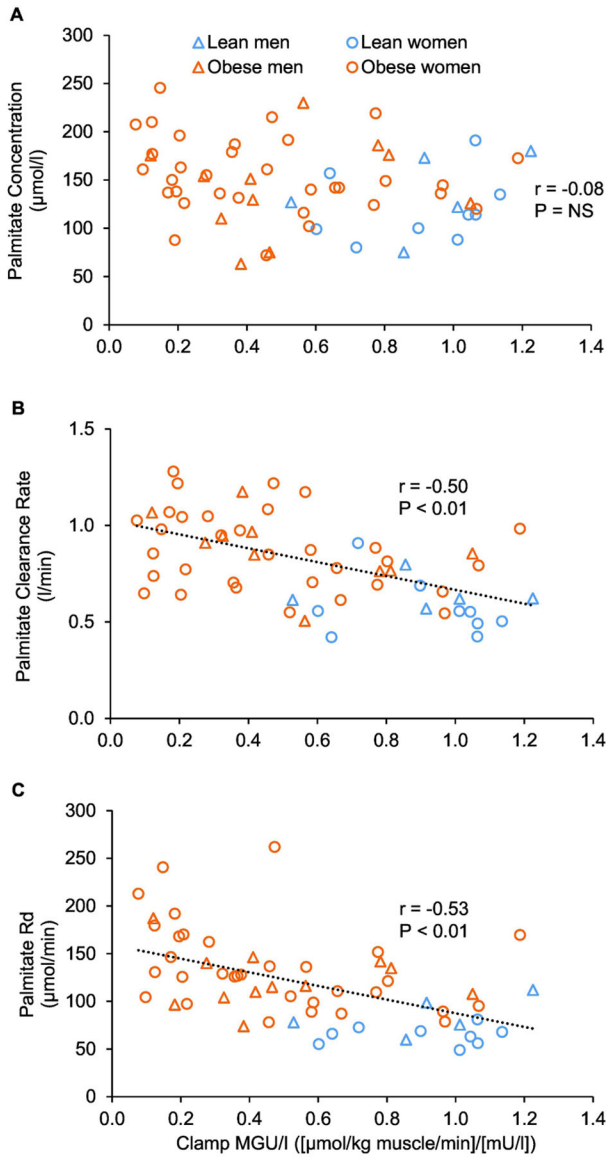

Figure 3.

Relationships between muscle insulin sensitivity, assessed as muscle glucose uptake rate in relation to plasma insulin concentration during the hyperinsulinemic-euglycemic clamp procedure, and basal plasma palmitate concentration (A), plasma palmitate clearance rate (B), and palmitate disappearance rate from plasma (C). Abbreviations: MGU/I, muscle glucose uptake rate in relation to plasma insulin concentration; Rd, disappearance rate.

Table 1.

Participants' age, body composition, plasma metabolic profile, and insulin sensitivity

	Lean	Obese	P value
N (M, F)	14 (5, 9)	46 (12, 34)	
Age (years)	39.7 ± 3.3	45.2 ± 1.6	0.113
Height (cm)	168.4 ± 1.8	168.2 ± 1.2	0.950
Total body mass (kg)	64.1 ± 1.5	107.2 ± 2.5	<0.001
Body surface area (m^2)	1.73 ± 0.03	2.15 ± 0.03	<0.001
Body mass index (kg/m^2)	22.6 ± 0.5	37.8 ± 0.7	<0.001
Fat-free mass (kg)	44.5 ± 1.9	55.6 ± 1.6	0.001
Fat mass (kg)	19.0 ± 1.4	49.6 ± 1.5	<0.001
Body fat (%)	30.1 ± 2.2	47.1 ± 0.9	<0.001
Fasting plasma glucose (mg/dl)	91.1 ± 1.5	95.2 ± 1.5	0.144
2-h OGTT plasma glucose (mg/dl)	117.1 ± 6.8	142.8 ± 4.5	0.006
Plasma glucose during the HECP (mg/dl)	110.9 ± 2.7	108.3 ± 1.1	0.301
Fasting plasma insulin (mU/l)	5.8 ± 0.5	16.9 ± 1.4	<0.001
Plasma insulin during the HECP (mU/l)	108.2 ± 4.4	115.3 ± 3	0.247
Fasting plasma FFA (μmol/l)	501.6 ± 38.7	596.8 ± 24.0	0.053
Plasma FFA during the HECP (μmol/l)	43.9 ± 3.6	53.0 ± 4.2	0.102
GIR during the HECP (μmol/min)	3,724 ± 287	2,493 ± 169	<0.001
GIR/I during the HECP (μmol/min)/(mU/l)	35.1 ± 3.0	22.3 ± 1.5	<0.001
GIR_{BM} during the HECP (μmol/kg BM/min)	58.4 ± 4.0	23.9 ± 1.7	<0.001
GIR_{FFM} during the HECP (μmol/kg FFM/min)	84.3 ± 6.4	46.3 ± 3.2	<0.001
MGU during the HECP (μmol/kg muscle/min)	97.7 ± 6.7	52.8 ± 4.9	<0.001
MGU/I during the HECP (μmol/kg muscle/min)/(mU/l)	0.91 ± 0.06	0.47 ± 0.04	<0.001

Values are mean ± SEM. Abbreviations: BM, body mass; GIR, glucose infusion rate; GIR/I, glucose infusion rate in relation to plasma insulin concentration; FFM, fat-free mass; HECP, hyperinsulinemic-euglycemic clamp; MGU, muscle glucose uptake rate; MGU/I, muscle glucose uptake rate in relation to plasma insulin concentration; OGTT, oral glucose tolerance test.