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Effects of an overnight intravenous lipid infusion on intramyocellular lipid content and insulin sensitivity in African–American versus Caucasian adolescents

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ABSTRACT

Objective. To explain the predisposition for insulin resistance among African American (AA) adolescents, this study aimed to: 1) examine changes in intramyocellular lipid content (IMCL), and insulin sensitivity with intralipid (IL) infusion; and 2) determine whether the increase in IMCL is comparable between AA and Caucasian adolescents.

Materials and Methods. Thirteen AA and 15 Caucasian normal-weight adolescents (BMI <85th) underwent a 3-h hyperinsulinemic–euglycemic clamp, on two occasions in random order, after an overnight 12-h infusion of: 1) 20% IL and 2) normal saline (NS). IMCL was quantified by ^{1}H magnetic resonance spectroscopy in tibialis anterior muscle before and after IL infusion.

Results. During IL infusion, plasma TG, glycerol, FFA and fat oxidation increased significantly, with no race differences. Hepatic insulin sensitivity decreased with IL infusion with no difference between the groups. IL infusion was associated with a significant increase in IMCL, which was comparable between AA (Δ 105%; NS: 1.9±0.8 vs. IL: 3.9±1.6 mmol/kg wet weight) and Caucasian (Δ 86%; NS: 2.8±2.1 vs. IL: 5.2±2.4 mmol/kg wet weight), with similar reductions ($P<0.01$) in insulin sensitivity between the groups (Δ −44%: NS: 9.1±3.3 vs. IL: 5.1±1.8 mg/kg/min per μU/ml in AA) and (Δ −39%: NS: 12.9±6.0 vs. IL: 7.9±3.8 mg/kg/min per μU/ml in Caucasian) adolescents.

Conclusions. In healthy adolescents, an acute elevation in plasma FFA with IL infusion is accompanied by significant increases in IMCL and reductions in insulin sensitivity with no race differential. Our findings suggest that AA normal-weight adolescents are not more susceptible than Caucasians to FFA-induced IMCL accumulation and insulin resistance.

Abbreviations: AA, African American; C, Caucasian; IL, Intralipid; NS, Normal saline; IMCL, Intramyocellular lipid; TG, Triglyceride; FFA, Free fatty acids.

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1. Introduction

Skeletal muscle is the primary site of the FFA-mediated decrease in insulin-stimulated glucose uptake [1]. Lipid accumulation within muscle cells (intramyocellular lipid, IMCL) is associated with insulin resistance in obesity and T2DM [2–4]. Racial differences in insulin sensitivity have been noted in adults [5,6] and children [7,8], such that African–Americans have lower insulin sensitivity than their Caucasian peers despite similar BMI or total fat. IMCL is an ectopic fat depot that may in part explain the racial differences in insulin sensitivity. Studies in adults regarding racial differences in skeletal muscle lipid have been inconclusive, with some reporting that IMCL is lower in healthy African–American (AA) than Caucasian women [9] and others reporting no racial differences in women or both genders combined [5,10]. All of these studies included individuals with varying BMI from normal to obese, and reported that IMCL correlated with insulin sensitivity in whites, but not in blacks [5,9,10]. In obese AA and Caucasian adolescents, no differences in IMCL and insulin sensitivity were reported [11]. Likewise, we did not observe differences in mid-thigh skeletal muscle lipid content in obese black vs. white adolescents, and similar to adults, while all markers of skeletal muscle lipid content correlated with *in vivo* insulin sensitivity in whites, only intermuscular fat correlated in blacks [12]. Currently, it is unknown if the lack of racial differences in IMCL in obese adolescents holds true for healthy normal-weight adolescents, and whether differences in IMCL could potentially explain the previously reported lower insulin sensitivity in black vs. white normal-weight youth [7,8].

Plasma free fatty acid (FFA) levels are elevated in obese individuals [13,14] and play a major role in the pathogenesis of insulin resistance [15]. In healthy adults, acute elevation of plasma FFA by high-fat feeding [16] or IL infusion [17] is associated with a significant increase in IMCL content, accompanied by a concomitant decrease in insulin sensitivity. Whether or not there could be a black/white differential response in IMCL accumulation with IL infusion is unknown. Therefore, the present pilot investigation tested if: 1) analogous to the findings in obese adolescents, IMCL in normal-weight adolescents is similar between AA and Caucasians, and if 2) overnight IL infusion will result in increased IMCL and decreased insulin sensitivity in both AA and Caucasian adolescents.

2. Methods

2.1. Subjects

Thirteen AA and 15 Caucasian normal-weight (BMI <85th) adolescents were recruited via advertisements in the greater Pittsburgh area, flyers posted in the city public transportation and posters placed on University campus. This study was conducted from November, 2008 through February, 2011 at the Children's Hospital of Pittsburgh (CHP) of University of Pittsburgh Medical Center. The investigation was approved by the University of Pittsburgh Institutional Review Board. Parental informed consent and child assent were obtained from all participants before participation. Inclusion criteria required that the subjects be 11–17 years of age in Tanner II–V, healthy (no chronic medical conditions), non-smokers and weight stable prior to participation. Participants were excluded if they have been dieting or have experienced significant weight change in the preceding months. None were taking medications (including contraceptive pills) known to affect body composition or glucose metabolism. Pubertal development was assessed according to Tanner criteria (breast development in females, genital development in males, and pubic hair in both) by a certified nurse practitioner and was confirmed by measurement of plasma testosterone in males, estradiol in females and dehydroepiandrosterone sulfate in both. Racial background was verified by self-identification in three generations on both sides of the parents as shown previously [7,12]. All participants underwent a complete physical examination and routine hematological and biochemical tests at the Pediatric Clinical and Translational Research Center (PCTRC) at Children's Hospital of Pittsburgh. Participants were instructed to avoid strenuous exercise and were prescribed a weight-maintaining diet containing 55% carbohydrate, 30% fat, and 15% protein for one week before and during the hospital stay, and studies were performed during the follicular phase of the menstrual cycle in those females who had menses as previously described [18].

2.2. Total and abdominal fat

Total fat and fat free mass was assessed by DEXA at the PCTRC. Abdominal fat was measured at L4–L5 with a 3.0 T MR scanner (Siemens Medical Systems, Erlangen, Germany) as previously described [12].

2.3. Hyperinsulinemic–euglycemic clamp with and without 20% intralipid

Subjects underwent a 3-h hyperinsulinemic (40 $\mu U/m^2/min$)–euglycemic clamp on two occasions, 1–3 weeks apart, with overnight 12.5-h infusion of 20% intralipid (IL) without heparin or normal saline (NS) in random order. Randomization was done by a raffle of intralipid vs. normal saline experimental condition assignment.

For each condition, one intravenous catheter was inserted in a forearm vein for administration of test infusions and a second in a vein of the contralateral heated hand for sampling of arterialized venous blood [18]. Either a triglyceride emulsion of 20% IL (20% soybean oil, 1.2% egg yolk phospholipids, and 2.25 % glycerol; Kabi Pharmacia, Clayton, NC) or 0.9% saline was infused at 0.02 $ml \cdot kg^{-1} \cdot min^{-1}$ starting at midnight and continuing through the 3-h hyperinsulinemic clamp [total 12.5 h of infusion (9.5 h pre clamp+3 h during the hyperinsulinemic–euglycemic clamp)] (Fig. 1). After blood samples were obtained at 0730 h (–120 min from the start of the hyperinsulinemic–euglycemic clamp), a primed (2.2 μmol/kg) constant infusion of [6,6-$^2H_2$]glucose (0.22 μmol/kg/min) was started from 0730 to 1230 h. Blood was sampled at –120 min and every 10 min from –30 to 0 min (basal period 0900–0930h) for determination of plasma glucose, insulin, C-peptide, FFA and isotopic enrichment. Plasma triglycerides were determined at –30 and 0 min of the basal infusion period.

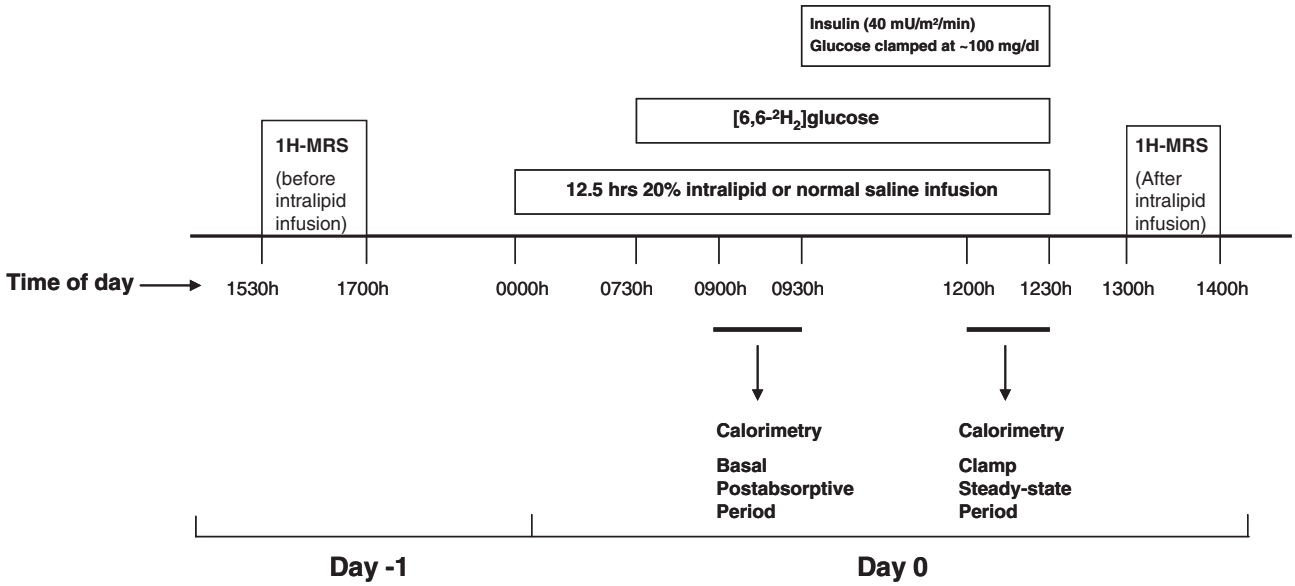

Fig. 1 – Schematic illustration of the study protocol.

After the basal period a hyperinsulinemic–euglycemic clamp was performed between 0930 and-1230 h. Intravenous crystalline insulin (Humulin; Lilly, Indianapolis, IN) was infused at a constant rate of 40 mU/m^2/min for 3 h. Plasma glucose was clamped at 100 mg/dl with a variable rate infusion of 20% dextrose, enriched with [6,6-$^2H_2$]glucose [19] based on arterialized plasma glucose determinations every 5 min. Blood was sampled every 10 min over the last 30 min of the clamp (150–180 min) for determination of insulin, FFA, and isotope enrichment. Triglycerides were determined at 150 and 180 min of the clamp.

For each condition, indirect calorimetry was performed using a ventilated hood system (Parvo Medics, Salt Lake City, UT) for a 30-min period before starting (–30 to 0 min, basal period) and at the end of the clamp (150–180 min). Urine was collected overnight from 2300 h until 0700 h for urinary nitrogen measurement to calculate baseline substrate oxidation, and from 0700 h until 1300 h for calculating substrate oxidation during the clamp as shown previously [19].

2.4. *IMCL content by proton magnetic resonance spectroscopy (^1H MRS)*

IMCL was measured in the tibialis anterior muscle of the right leg with a 3.0 T MR system (Siemens, Tim Trio, Erlangen, Germany) using a CP extremity coil (Siemens, Erlangen, Germany) at the University of Pittsburgh Magnetic Resonance Research Center. IMCL measurement was performed between 1530 h and 1700 h the day before the IL infusion and between 1300 h and 1400 h immediately after the completion of the IL clamp (Fig. 1). Repositioning of the subject and placement of the coil and voxels were carefully monitored on the localizer images to ensure that the repeat scan was performed in the same location. Spectra were acquired using a PRESS sequence with a repetition time (TR) of 2.0 s, number of averaged spectra 128, and an echo time (TE) of 30 ms. A voxel (12 × 11 × 18 mm^3) was placed in the tibialis anterior muscle, carefully avoiding vascular structures and adipose tissue deposits within the voxels. The MR spectra were acquired with water suppression for the determination of IMCL and one single-shot without water suppression for the quantitation. The spectra were fitted using the AMARES algorithm in the Java-based magnetic resonance user interface (jMRUI) software package [20]. Absolute concentrations of IMCLs were obtained from the area under the curve of the methylene signals of lipids at 1.28 ppm, using tissue water content as an internal reference according to literature [21].

2.5. *Biochemical measurements*

Plasma glucose was measured by the glucose oxidase method with a glucose analyzer (YSI, Inc., Yellow Springs, OH), and plasma insulin and C-peptide concentrations were determined by radioimmunoassay [7]. Enzymatic colorimetric methods were used to determine FFA (Wako nonesterified fatty acid [NEFA] C test kit; Wako, Osaka, Japan) and triglyceride concentrations. Urinary nitrogen was measured by the Kjeldahl method [18]. Deuterium enrichment of plasma glucose was determined on a Hewlett Packard model 5985A gas chromatography mass spectrometer [7,19,22]. Standard curves of known enrichments were performed with each assay. The inter- and intra-assay coefficients of variation were: 6.9% and 5.3% for C-peptide RIA, 10.3% and 3.8% for insulin RIA and 7.1% and 1.7% for FFA, respectively.

2.6. *Calculations*

Basal rate of appearance (R_a) of endogenous glucose in the plasma or hepatic glucose production (HGP) was calculated during the last 30 min of the postabsorptive period (–30 to 0 min) using steady-state tracer dilution equations [19]. An index of fasting hepatic insulin sensitivity was calculated as the inverse of the product of HGP and fasting insulin concentration [1000/(HGP x fasting insulin)] as before [23,24]. Peripheral insulin sensitivity was calculated over the last 30 min of the 3 h clamp

(150–180 min) by dividing insulin-stimulated glucose disposal rate by the steady-state clamp insulin levels during the same period (mg/kg/min per μU/ml × 100) [7].

Basal and insulin-stimulated substrate oxidation rates were calculated from indirect calorimetric data during each period [25]. Basal and insulin-stimulated nonoxidative glucose R_d was estimated by subtracting the rate of glucose oxidation from the total R_d during the last 30 min of the basal period (–30 to 0 min) and clamp (150–180 min).

2.7. *Statistical analyses*

Statistical procedures were performed using SPSS (Version 15; SPSS, Inc., Chicago, IL). Independent t tests were used to compare racial differences in subject characteristics (Table 1). A 2×2 repeated measures ANOVA was used to evaluate main effects (condition, race) and group interactions (condition × race) for metabolic data, insulin sensitivity and IMCL (Table 2, Fig. 2). Relationship between IMCL and insulin sensitivity was examined using Pearson correlation coefficients. Retrospective power and sample size analyses [26] were calculated using our preliminary pilot data of observed racial differences in IMCL, and the theoretical impact of ethnic IMCL differences on racial differences in insulin sensitivity was modeled using linear regression. All data are presented as means±SD.

3. Results

Subject characteristics are shown in Table 1. Age, Tanner stage, BMI and body fat (%) were similar between AA and Caucasian, but visceral fat and triglyceride (TG) were lower ($P<0.05$) in AA than in Caucasian.

3.1. *Metabolic variables during the baseline postabsorptive period*

Metabolic variables during the final 30 min of the baseline postabsorptive period are shown in Table 2. Insulin, C-peptide, glycerol, triglyceride and FFA levels increased with IL infusion (main effect of condition for all, $P<0.01$), with no differences between AA and Caucasian adolescents. In addition, fat oxidation significantly increased (main effect of condition, $P<0.01$) and oxidative glucose disposal decreased (main effect of condition, $P=0.01$) with IL infusion in both AA and Caucasian adolescents, with no significant differences between groups. Hepatic insulin sensitivity decreased with IL infusion (main effect of condition, $P<0.01$) in AA and Caucasian adolescents by a similar magnitude.

Table 1 – Subject characteristics.

	African–American	Caucasian	*P*
N	13	15	
Gender (M/F)	6/7	7/8	NS
Tanner stage (II–III/IV–V)	2/11	6/9	NS
Age (years)	14.1±1.7	14.5±1.8	NS
Weight (kg)	56.8±10.2	55.2±10.1	NS
BMI (kg/m^2)	20.7±2.2	20.3±1.8	NS
Fat free mass (kg)	41.8±10.3	37.7±8.4	NS
Fat mass (kg)	12.4±4.5	14.8±4.3	NS
Body fat (%)	22.5±8.4	27.3±6.4	NS
Visceral fat (cm^2)	25.1±5.3	38.0±19.7	0.03
Subcutaneous fat (cm^2)	99.0±52.0	118.8±51.8	NS
Total cholesterol (mg/dl)	143.4±28.7	151.1±20.2	NS
Triglycerides (mg/dl)	52.9±12.8	67.9±22.5	0.04
HDL (mg/dl)	48.2±10.4	54.3±10.9	NS
LDL (mg/dl)	84.6±27.2	83.2±20.3	NS
VLDL (mg/dl)	10.6±2.6	13.6±4.5	0.04

Data are mean±SD. NS, not significant ($P>0.05$).

3.2. *Metabolic variables during hyperinsulinemic–euglycemic clamp*

Metabolic variables during the final 30 min of the 3-h hyperinsulinemic–euglycemic clamp are shown in Table 2. Steady-state plasma glucose level was similar between NS and IL infusion, and between AA and Caucasian adolescents. Steady-state plasma insulin concentration, triglycerides, FFA and fat oxidation were higher during IL vs. NS infusion (main effect of condition for all, $P<0.01$), with no differences between AA and Caucasian adolescents. Insulin sensitivity (main effect of race, $P=0.03$) and non-oxidative glucose disposal (main effect of race, $P=0.05$) were lower in AA than in Caucasian adolescents, and decreased significantly with IL infusion (main effect of condition, $P<0.01$ in both groups) in AA (Δ 44%, NS: 9.1±3.3 vs. IL: 5.1±1.8 mg/kg/min per μU/ml) and Caucasian (Δ 39%, NS: 12.9±6.0 vs. IL: 7.9±3.8 mg/kg/min per μU/ml) adolescents.

3.3. *IMCL content*

At baseline, IMCL content did not differ between AA (1.9±0.8 mmol/kg wet weight) and Caucasian (2.8±2.1 mmol/kg wet weight) adolescents ($P=0.2$). After IL infusion, IMCL increased significantly ($P<0.01$) in both AA (NS: 1.9±0.8 vs. IL: 3.9±1.6 mmol/kg wet weight) and Caucasian (NS: 2.8±2.1 vs. IL: 5.2±2.4 mmol/kg wet weight) adolescents, with no difference between the two groups ($P=0.45$; Fig. 2). There was an inverse relationship between initial IMCL content and the increase in IMCL (% of baseline IMCL) ($r=-0.47$, $P=0.01$) after IL infusion, such that subjects with low IMCL content at baseline had higher increases in IMCL after IL infusion.

In a multiple regression analysis with insulin sensitivity as the dependent variable and race, IMCL, VAT and gender as the independent variables, race and visceral fat combined explained 51% of the variance in IS at baseline ($P<0.01$) and 49% after IL infusion ($P<0.01$). IMCL and gender did not enter the model significantly ($P>0.1$). Adding Tanner stage to the independent variables in the model did not change the outcome.

4. Discussion

The results from the present investigation reveal that: a) parallel with observations in obese adolescents, IMCL in normal-weight AA adolescents is not different from that in their Caucasian peers; and b) overnight IL infusion results in increased IMCL and decreased *in vivo* insulin sensitivity

Table 2 – Metabolic variables in the normal saline versus intralipid infusion conditions.

	African–American		Caucasian		Effect, P		
	Normal saline	Intralipid	Normal saline	Intralipid	Condition	Race	Interaction
Baseline postabsorptive period							
Glucose (mg/dl)	97.4±6.1	97.3±6.6	94.0±4.2	97.3±4.5	0.01	NS	0.01
Insulin (μU/ml)	17.2±6.2	28.8±15.5	15.4±5.0	24.1±9.5	<0.01	NS	NS
C-peptide (ng/ml)	1.8±0.6	2.4±0.6	1.8±0.5	2.5±0.7	<0.01	NS	NS
Hepatic insulin sensitivity (mg/kg/min per μU/ml)$^{-1}$	15.5±5.5	10.7±4.5	18.5±5.6	13.1±4.9	<0.01	NS	NS
FFA (mmol/l)	0.3±0.1	1.9±1.2	0.3±0.1	1.3±0.8	<0.01	NS	NS
Triglycerides (mg/dl)	49.6±12.2	1048.9±896.1	67.0±20.0	660.7±397.0	<0.01	NS	NS
Fat oxidation (mg/kg/min)	1.3±0.5	1.8±0.5	1.5±0.6	1.8±0.6	<0.01	NS	NS
Glucose oxidation (mg/kg/min)	1.5±0.7	0.9±0.7	1.3±1.1	1.1±0.8	0.01	NS	NS
Final 30 min of the 3-h hyperinsulinemic–euglycemic clamp							
Glucose (mg/dl)	100.7±1.9	101.2±1.8	101.3±1.7	101.8±2.3	NS	NS	NS
Insulin (μU/ml)	121.8±31.7	142.1±56.2	105.3±26.2	114.9±30.1	<0.01	NS	NS
Peripheral insulin sensitivity (mg/kg/min per μU/ml)	9.1±3.3	5.1±1.8	12.9±6.0	7.9±3.8	<0.01	0.03	NS
FFA (mmol/l)	0.2±0.1	1.8±1.2	0.1±0.1	1.3±0.9	<0.01	NS	NS
Triglycerides (mg/dl)	42.2±12.5	962.9±794.7	50.9±17.0	632.4±506.1	<0.01	NS	NS
Fat oxidation (mg/kg/min)	0.6±0.5	1.6±0.6	0.8±0.5	1.5±0.6	<0.01	NS	NS
Glucose oxidation (mg/kg/min)	3.4±1.0	2.1±0.9	3.3±0.9	2.2±1.1	<0.01	NS	NS
Non-oxidative glucose disposal (mg/kg/min)	7.0±2.7	4.2±1.4	8.8±3.1	5.5±2.8	<0.01	0.05	NS

NS, not significant ($P>0.05$).

with no differences between African American and Caucasian adolescents. These findings suggest that AA and Caucasian normal-weight adolescents are similarly susceptible to FFA-induced insulin resistance and IMCL accumulation.

Similar to our shorter-term (6 h) IL infusion study without examining IMCL [19], overnight 12 h infusion of IL in the current study resulted in significantly increased fasting insulin and C-peptide levels and decreased hepatic and peripheral insulin sensitivity, with no differences between AA and Caucasian normal-weight adolescents. It is possible that a longer duration of IL infusion and FFA elevations, over several days, may be required to unravel race-related differences in FFA-induced insulin resistance and IMCL accumulation. Alternatively, it is possible that irrespective of the duration and severity of FFA elevation, IMCL deposition may not differ between blacks and whites especially against the backdrop of similar baseline IMCL. The comparable IMCL between AA and Caucasian normal-weight adolescents is consistent with our previous findings in obese adolescents using computed tomography of the mid-thigh skeletal muscle [12], and another pediatric study using MRS [11] and some of the adult studies [5,10].

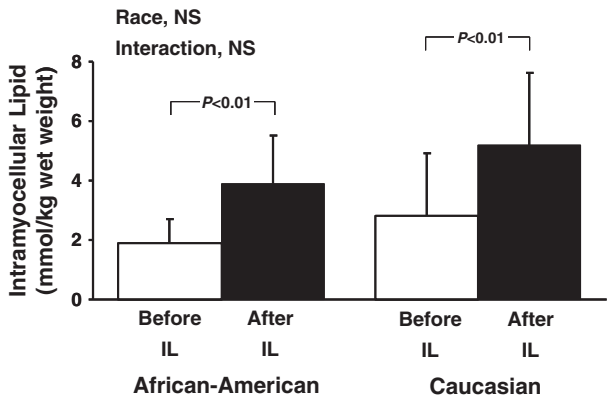

Fig. 2 – Intramyocellular lipid (IMCL) content in African–American and Caucasian adolescents before (white bars) and after (black bars) 20% intralipid (IL) infusion overnight. Data are mean±SD.

The present study is the first to examine IL and FFA-induced increases in IMCL content in youth. Our findings in healthy adolescents of significant increases in IMCL content in the tibialis anterior muscle with IL infusion, and significant decline in insulin sensitivity are consistent with observations in adults [17]. A 40% reduction in glucose uptake following a 4-h IL infusion in healthy men and women was associated with a corresponding increase in IMCL content in the soleus muscle in a dose-dependent manner. Similarly, after ingestion of a high-fat diet (55%–60% of energy intake) for 3 days, IMCL in the tibialis anterior muscle significantly increased (~50%) and insulin-stimulated glucose uptake decreased (~17%) in healthy normal-weight men [16]. By contrast, acutely normalizing the chronically elevated plasma FFA levels by Acipimox, a long-acting antilipolytic drug, resulted in a two-fold increase in insulin sensitivity and 30% decreases in glucose- and insulin-area under the curve during an oral glucose tolerance test in obese subjects with and without type 2 diabetes [27]. Taken together, these observations provide evidence that increased plasma FFA level is an important contributor to the development of skeletal muscle insulin resistance in healthy individuals and obese patients with and without T2DM.

The concurrent increase in IMCL and the decrease in insulin sensitivity after an IL challenge shown in the current study are in line with previous cross-sectional investigations reporting a significant relationship between IMCL and insulin-

stimulated glucose uptake in offsprings of T2DM [2,3]. However, a direct cause–effect relationship between IMCL and insulin resistance and the underlying mechanism by which increased IMCL causes insulin resistance is not firmly established. Boden et al. [15,17] suggest that the long delay (3-4 h) between the rise in plasma FFAs and the onset of FFA-induced insulin resistance makes direct effect of FFAs on insulin sensitivity unlikely. However, the increase in IMCL level occurred several hours after the elevation of plasma FFA levels and coincided with the development of insulin resistance, suggesting that plasma FFAs first need to enter the muscle cells and be re-esterified to IMLC before they cause insulin resistance [15,17]. In support of this, the same group [28] subsequently demonstrated significantly increased levels of skeletal muscle lipid metabolites, such as diacylglycerol, and protein kinase C-BII and -δ, after a 6-h IL infusion in skeletal muscle of healthy normal-weight men, suggesting that muscle lipid metabolites play a significant role in the pathogenesis of fatty acid-induced insulin resistance.

The strengths and limitations of this study warrant mention. In our continued pursuit to probe the underlying cause(s) for the disparity in insulin sensitivity between AA and Caucasian youth, the current study demonstrates that ectopic IMCL levels are similar between AA and Caucasian youth and unlikely to explain the lower insulin sensitivity in blacks [7,8]. Furthermore, building on our prior findings of lack of a race differential in the deterioration in insulin sensitivity in response to short-term IL infusion [19], the present experiments, using ^{1}H MRS, show that longer-term IL infusion does not unravel a heightened susceptibility to FFA-induced IMCL accumulation in blacks. To our knowledge, such studies of IL challenge and changes in IMCL and *in vivo* insulin sensitivity in youth, particularly with respect to race differences, have not been reported in the literature. However, due to our small sample, we could not examine gender differences in the effect of an IL challenge on IMCL and insulin sensitivity, but previously we did not observe gender differences in insulin sensitivity with IL infusion [19]. Nevertheless, the lack of association between IMCL and insulin sensitivity was surprising, but is unlikely to be an effect of low power. The results from the present pilot study indicate that one would require 129 adolescents per racial group to attain statistically significant racial differences in IMCL. However, the clinical relevance of this magnitude of IMCL difference between AA and Caucasian youth appears to be quite small. Even if the IMCL difference in this study was significant, the magnitude of the difference in IMCL between AA and Caucasians would only account for 5% of the racial difference in insulin sensitivity; only a small fraction of the 42% lower insulin sensitivity in AA compared to Caucasians. Further work remains to examine whether similar findings of IMCL accumulation with IL would be observed in youth at different developmental stages such as pre-pubertal children, especially that important developmental differences exist in the response to IL challenge in white youth as reported by us [29]. Additional work should also take into account differences in aerobic physical fitness as potential modulators of the aforementioned relationships. Finally, due to the supraphysiological levels of FFA induced by a 12-h IL infusion, the clinical implications of our observations remain to be determined. Clearly there is a need to investigate the effects of dietary fat intake on insulin action and IMCL accumulation in youth and to determine whether racial differences exist in these measures. The translational value of demonstrating racially-driven contrast or lack thereof in response to dietary fat-induced changes in insulin sensitivity or muscle composition would be the potential to design race appropriate recommendations to lessen the risk of insulin resistance.

In conclusion, our findings demonstrate that AA and Caucasian normal-weight adolescents have similar IMCL content and are equally susceptible to FFA-induced IMCL accumulation and insulin resistance following an overnight infusion of IL. The lower insulin sensitivity in AA normal-weight adolescents, despite their lower visceral fat, compared with their Caucasian peers is unlikely due to differences in intramyocellular ectopic lipid.

Author contributions

The authors' contributions were as follows. SoJung Lee, Ph.D., wrote the manuscript, conducted analyses of abdominal MRI and IMCL, analyzed the data and participated in data interpretation together with Silva Arslanian, M.D.; Dr. Chris Boesch together with Dr. Lee established MRS protocol at the MRRC at the University of Pittsburgh, assisted MRS data analyses and interpretations, and participated in critical revision of the manuscript; Jennifer Kuk, Ph.D., aided in statistical analyses and participated in critical revision of the manuscript: Silva Arslanian, M.D., is responsible for study concept and design, acquisition of data, analysis and interpretation of data, obtained funding, provided administrative, technical and material support, and study supervision, drafting of the manuscript, critical revision of the manuscript for important intellectual content and primary responsibility for the final content. Silva Arslanian is the guarantor of this work, had full access to all the data and takes full responsibility for the integrity of data and the accuracy of data analysis. All authors have no conflicts of interest to declare.

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Conflicts of interest

All authors have no conflicts of interest to declare.

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