Effect of a Multicomponent Intervention on Hepatic Steatosis Is Partially Mediated by the Reduction of Intermuscular Abdominal Adipose Tissue in Children With Overweight or Obesity: The EFIGRO Project

Cristina Cadenas-Sanchez,[1,2,3] Fernando Idoate,[4] Rafael Cabeza,[5] Arantxa Villanueva,[2,5,6] Beatriz Rodríguez-Vigil,[7] María Medrano,[3] Maddi Osés,[1,2] Francisco B. Ortega,[3,8] Jonatan R. Ruiz,[3,9] and Idoia Labayen[1,2]

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OBJECTIVE

In adults, there is evidence that improvement of metabolic-associated fatty liver disease (MAFLD) depends on the reduction of myosteatosis. In children, in whom the prevalence of MAFLD is alarming, this muscle-liver crosstalk has not been tested. Therefore, we aimed to explore whether the effects of a multicomponent intervention on hepatic fat is mediated by changes in intermuscular abdominal adipose tissue (IMAAT) in children with overweight/obesity.

RESEARCH DESIGN AND METHODS

A total of 116 children with overweight/obesity were allocated to a 22-week family-based lifestyle and psychoeducational intervention (control group, *n* = 57) or the same intervention plus supervised exercise (exercise group, *n* = 59). Hepatic fat percentage and IMAAT were acquired by MRI at baseline and at the end of the intervention.

RESULTS

Changes in IMAAT explained 20.7% of the improvements in hepatic steatosis ($P < 0.05$). Only children who meaningfully reduced their IMAAT (i.e., responders) had improved hepatic steatosis at the end of the intervention (within-group analysis: responders −20% [$P = 0.005$] vs. nonresponders −1.5% [$P = 0.803$]). Between-group analysis showed greater reductions in favor of IMAAT responders compared with nonresponders (18.3% vs. 0.6%, $P = 0.018$), regardless of overall abdominal fat loss.

CONCLUSIONS

The reduction of IMAAT plays a relevant role in the improvement of hepatic steatosis after a multicomponent intervention in children with overweight/obesity. Indeed, only children who achieved a meaningful reduction in IMAAT at the end of the intervention had a reduced percentage of hepatic fat independent of abdominal fat loss. Our findings suggest that abdominal muscle fat infiltration could be a therapeutic target for the treatment of MAFLD in childhood.

[1]Institute for Innovation & Sustainable Food Chain Development (ISFOOD), Department of Health Sciences, Public University of Navarre, Pamplona, Navarre, Spain
[2]Healthcare Research Institute of Navarre (IdiSNA), Pamplona, Spain
[3]Promoting Fitness and Health Through Physical Activity (PROFITH) Research Group, Sport and Health University Research Institute (iMUDS), Faculty of Sport Sciences, Department of Physical and Sports Education, University of Granada, Granada, Spain
[4]Radiology Department, Mutua Navarra, Department of Health Sciences, Public University of Navarre, Pamplona, Spain
[5]Department of Electrical, Electronic and Communications Engineering, Public University of Navarre, Pamplona, Spain
[6]Smart Cities Institute, Public University of Navarre, Pamplona, Spain
[7]Department of Magnetic Resonance Imaging, Osatek, University Hospital of Alava (HUA), Vitoria-Gasteiz, Spain
[8]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland
[9]Instituto de Investigación Biosanitaria (ibs.Granada), Granada, Spain

Corresponding authors: Cristina Cadenas-Sanchez, cadenas@ugr.es, and Idoia Labayen, idoia.labayen@unavarra.es

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Nonalcoholic fatty liver disease (recently renamed as metabolic-associated fatty liver disease [MAFLD]) is currently a leading cause of cirrhosis and hepatocellular carcinoma worldwide (1). Indeed, MAFLD has become the most common chronic liver disorder, affecting 25% of the world adult population (1).

In parallel with the childhood obesity epidemic, pediatric MAFLD is affecting nearly 8% of the general population and ~35% of children with overweight or obesity (2). Children with MAFLD have higher rates of overall and cancer-, liver-, and cardiometabolic-specific mortality compared with their peers without MAFLD (3). Thus, pediatric MAFLD is a major public health challenge because of its elevated prevalence, associated morbidity, and expected increase in the short and midterm (4).

There is evidence of a muscle-liver crosstalk. Thus, sarcopenia is a risk factor for the development and progression of MAFLD in adults (5). A study in adult patients with morbid obesity shed light on the potential contribution of fat infiltration in psoas skeletal muscle mass (i.e., myosteatosis) on the physiopathology of MAFLD (6). In children, information about the link between myosteatosis and MAFLD is scarce. We have observed that intermuscular abdominal adipose tissue (IMAAT) was associated with the presence and degree of hepatic steatosis in preadolescent children with overweight/obesity, supporting the potential contribution of IMAAT in the physiopathology of MAFLD (7). Interestingly, Nachit et al. (6) reported that patients with significantly reduced fat infiltration in the psoas after either a dietary intervention or bariatric surgery achieved nonalcoholic steatohepatitis (NASH) improvement, suggesting that fat infiltration in the skeletal muscle may be a relevant therapeutic target for patients with MAFLD.

Exercise-based interventions seem to be effective therapeutic approaches for MAFLD prevention and treatment (8). In our study of preadolescent children with overweight/obesity, we compared the effect of a 22-week family-based lifestyle and psychoeducation intervention with the same intervention plus supervised exercise and observed that only children participating in the group that exercised achieved a significant reduction in hepatic fat (nearly 20%) (9). Of note, reductions in hepatic fat were independent of body mass loss and changes in total and abdominal adiposity. These findings seem to support the role of myosteatosis as a mediator of exercise in hepatic fat reduction and as a therapeutic target of MAFLD; this hypothesis, however, still needs to be tested in children, in whom obesity and MAFLD prevalence are alarming. Therefore, the aim of this study was to explore whether the effects of a multicomponent intervention, including exercise, on hepatic fat reduction are mediated by changes on IMAAT.

RESEARCH DESIGN AND METHODS

Study Design and Study Participants

This study is under the umbrella of the Effect of Exercise on Hepatic Fat in Overweight Children (EFIGRO) project, a clinical trial designed to compare the effect of a family-based lifestyle and psychoeducational intervention (control group) with the same intervention plus supervised exercise (exercise group) on hepatic fat percentage in preadolescent children with overweight/obesity (9). Of 125 children assessed for eligibility, 116 (aged 8–12 years) were allocated to control (n = 57) or exercise (n = 59) groups. Detailed information about inclusion/exclusion criteria, methodology, design of the intervention program, etc., can be found elsewhere (9,10). In brief, children were eligible if they presented with overweight or obesity as defined by the World Obesity Federation (11), were 8–12 years of age, did not present any medical condition that limited their activity, and did not have diabetes or any other endocrine disorder.

All parents or legal guardians and their children gave consent to participate in the study. The study protocol was approved by the Euskadi Clinical Research Ethics Committee (Vitoria) and followed the ethical guidelines of the Declaration of Helsinki (revised version 2013).

Intervention Arms

Children were allocated to the control or exercise groups after baseline measurements. At baseline, there were no significant differences between the two groups for BMI, age, and puberty stage (9). The control group received a family-based lifestyle and psychoeducational intervention (two sessions a month, 45 min per session), which consisted of 11 sessions focused on dietary habits, physical activity, sleep hygiene, communication skills, and feelings and emotions. Sessions were given separately for parents and children (10).

The exercise group received the same family-based lifestyle intervention plus supervised exercise training (three sessions a week, 90 min per session) for 22 weeks. Briefly, the exercise intervention consisted of high-intensity (>76% heart rate peak) aerobic and resistance training. To encourage children to spend as much time as possible at high intensity, we used motivation strategies through games. Children were monitored during the sessions by heart rate monitors (Polar RS300X).

Hepatic Fat and Intermuscular Abdominal Fat Fraction Assessments

Hepatic fat percentage and IMAAT were assessed by MRI (MAGNETOM Avanto 1.5T, Siemens Healthineers, Erlangen, Germany). Images were acquired with breath-holding during expiration. Sagittal, coronal, and transverse abdominal localizers (from the diaphragm to the symphysis pubis) were used to determine the accurate location of each image with respect to the vertebral discs. For hepatic fat quantification, detailed information can be found elsewhere (10). Briefly, two different three-dimensional gradient-echo sequences were performed in breath-hold using syngo MR B17A software (Siemens Healthineers) according to the manufacturer's instructions (12). For IMAAT, fat segmentation was calculated at three axial slices (L2–L3, L3, and L4–L5), and the average was used for analyses. Data processing steps of the IMAAT images can be found in Fig. 1. Briefly, T1-weighted images were collected. Next, a two-point Dixon gradient-echo pulse sequence was used to separate the tissue water signal from the lipid signal, resulting in four different images: water only, fat only, in phase, and out of phase. Additionally, two images were calculated: fat fraction or parametric image and 2F − W image, where F is the image of the fat, and W is the image of the water. The Otsu thresholding algorithm was then used for analyses (13). Finally, a nonsupervised clustering (K-means) method was applied to the abdominal visceral compartment using the fat fraction image (14,15). The medical imaging group performed all the analyses and were blinded to participant groups.

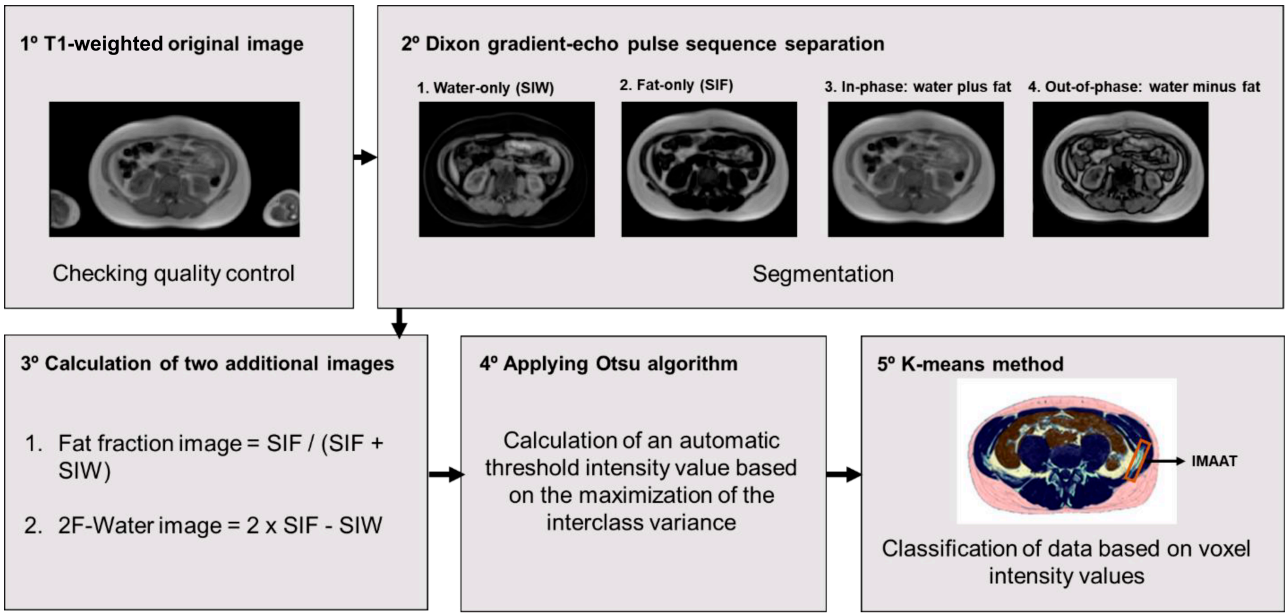

Figure 1—IMAAT processing steps. F, fat; SIF, signal intensities of fat; SIW, signal intensities of water.

Other Potential Contributors: Sensitivity Analyses

For exploratory purposes, we examined the mediating role of cardiometabolic and diabetes risk factors over the hepatic fat reduction at the end of the intervention. Serum triglycerides (mmol/L), HDL and LDL (mmol/L), insulin (IU/mL), fasting glucose (mmol/L), HOMA, and γ-glutamyl transferase (units/L) were measured from morning fasting blood samples collected at the hospital. Overall abdominal adiposity was measured by DEXA scan (Hologic QDR 4500 W).

Statistics

All data are presented as mean and SD unless otherwise specified. We assessed normality of the variables used in the analyses by visual (Q-Q plots) and statistical (Kolmogorov-Smirnov) tests, and therefore, parametric tests were used. To test whether the effects of the intervention on changes in hepatic fat were mediated by changes in IMAAT, mediation analyses were performed after adjusting for age, sex, and hepatic fat at baseline. The unstandardized B and standardized β-regression coefficients are presented for the following equations: *1*) regression of the mediator (i.e., change in IMAAT) based on the independent variable (i.e., group), *2*) regression of the dependent variable (i.e., change in hepatic fat) based on the independent variable (group), and *3*) regression of the dependent variable based on both the mediator and the independent variable. Indirect and total effects were also presented, and thus, the percentage of the total effect was calculated to explain how much of the total effect was explained by the mediation. As sensitivity analyses, we additionally explored whether other cardiometabolic and diabetes risk factors (i.e., triglycerides, HDL, LDL, insulin, glucose, HOMA, and γ-glutamyl transferase) could further contribute to hepatic fat reduction. The mediation analyses are in line with the A Guideline for Reporting Mediation Analyses statement (https://agrema-statement.org) (16) (Supplementary Material). Furthermore, to explore differences in changes of hepatic fat percentage between participants (irrespective of their assigned group) who experienced a meaningful change in IMAAT (i.e., responders in both groups, Cohen $d \geq 0.2$, $n = 59$) and those who did not (i.e., nonresponders in both groups, Cohen $d < 0.2$, $n = 39$) from baseline to postintervention, paired Student t test (within-group analysis) and one-way ANCOVA (between-group analysis) were applied.

The main analyses are presented based on the per-protocol principle for all participants who finished the intervention and attended at least 50% of the family-based lifestyle and psychoeducational sessions (in the exercise group, no minimum attendance of exercise sessions was required). The sensitivity analyses are presented based on a modified per-protocol principle for a minimum of 50% attendance of the exercise sessions. The intention-to-treat principle was based on missing values at postintervention obtained by multiple imputation. Imputation was performed using the pre- and postintervention values, age, sex, and intervention group. Intention-to-treat analyses are presented in the Supplementary Material.

All the analyses were performed using SPSS version 22.0 for Windows software (IBM Corporation, Chicago, IL) and its PROCESS macro. Mediation analyses were applied with a resample procedure of 10,000 bootstrap samples. The difference was considered significant when the indirect effect significantly differed from 0. For the rest of the analyses, the significance level was set as $\alpha < 0.05$. Figures were created using R version 4.0.3 software (https://cran.r-project.org).

RESULTS

Descriptive Characteristics of the Study Participants

Figure 2 shows the participant flow diagram of this study. Of 116 children initially allocated, 98 (10.5 ± 1.1 years, 56% girls) successfully completed the trial, attending at least 50% of the family-based lifestyle and psychoeducational intervention sessions, with no minimum attendance of exercise sessions for the exercise group

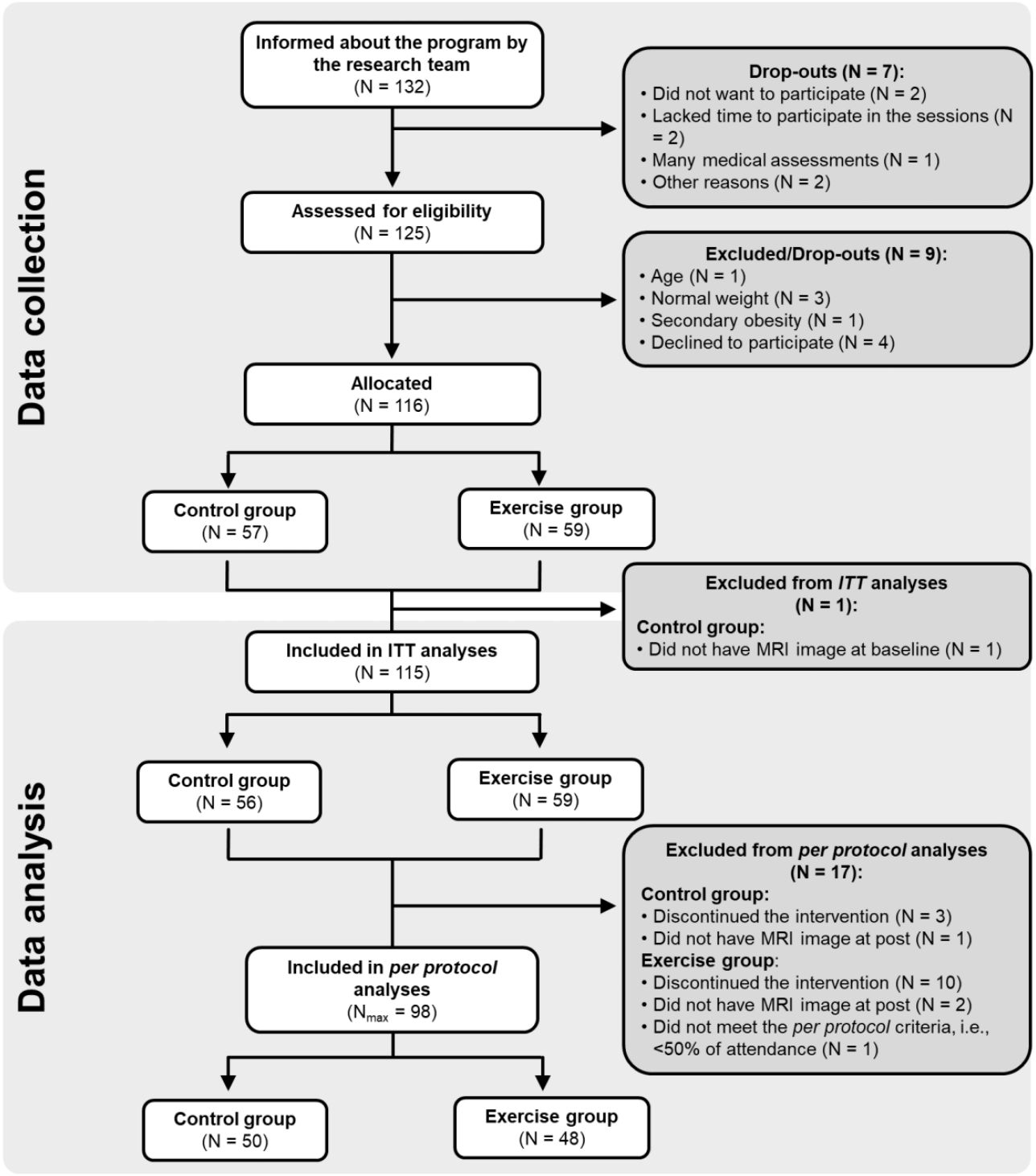

Figure 2—Flow diagram of the data collection and analysis of the study. The control group consisted on two family-based lifestyle and psychoeducational sessions a month. The exercise group focused on two family-based lifestyle and psychoeducational sessions a month plus three sessions per week of supervised high-intensity exercise. ITT, intention to treat.

(i.e., per-protocol analysis). There was no significant difference in terms of attendance at the lifestyle and psychoeducation program sessions between the control and exercise groups for either the parents/caregivers (86.4 ± 12.9% vs. 80.6 ± 15.3%, P = 0.334) or the children (87.2 ± 12.0% vs. 82.5 ± 14.6%, P = 0.496). The mean attendance rate of the children at the exercise program sessions was 72.0 ± 16.1%. No adverse events were observed as a consequence of the family-based lifestyle and psychoeducational intervention, while two participants showed exercise-related adverse events, including knee and ankle pain. Baseline characteristics of the study participants grouped by intervention groups (control vs. exercise) and by inter-individual variability (nonresponders vs. responders) can be found in Table 1 and Supplementary Table 1, respectively.

Linking Abdominal Muscle Fat and Hepatic Fat: Mediation and Responder Analyses

Figure 3 shows that the reduction of IMAAT explained 20.7% of the effect of the intervention on hepatic fat percentage at the end of the intervention (indirect effect β = −0.099 95% CI −0.210, −0.010). The intention-to-treat analysis showed similar findings (Supplementary Fig. 1). We also explored whether other cardiometabolic and diabetes risk factors (i.e., triglycerides, HDL, LDL, insulin, glucose, HOMA, and γ-glutamyl transferase) could further contribute to the hepatic fat reduction. The findings showed that these factors did not contribute to the effect of the intervention on hepatic fat percentage at the end of the intervention. The changes in hepatic fat percentage at the end of the intervention grouped by nonresponders and responders for IMAAT can be found in Fig. 4. In nonresponders for IMAAT (i.e., children whose reduction in IMAAT was Cohen *d* <0.2), there was no significant reduction of hepatic fat percentage (change −1.5%, *P* = 0.803). In contrast, hepatic fat percentage was significantly reduced in children categorized as responders for IMAAT (change −20%, *P* = 0.005). Between-group analysis showed that the reduction in hepatic fat percentage was significantly greater in responders for IMAAT than in nonresponders (−0.6% vs. −18.3%, age-, sex-, and baseline hepatic fat–adjusted *P* = 0.018). Interestingly, further adjustment with changes in overall abdominal adiposity did not substantially change the result (0.4% vs. −18.9%, *P* = 0.021). Likewise, we also explored whether the reduction of hepatic fat is independent from other adiposity depots, such as visceral, abdominal, and pancreatic adipose tissue fat fractions, and the results were similar (all $P \leq 0.026$). Similar findings were observed in the intention-to-treat analysis (Supplementary Fig. 2). In sensitivity analyses, we repeated the analyses by including only children with MAFLD (i.e., having >5% hepatic fat, *n* = 22 in the group of responders and *n* = 18 in the group of nonresponders) and observed similar results (−9.1% vs. −31.1%, *P* = 0.029).

Finally, we explored whether the effects of exercise on IMAAT and hepatic fat depended on the number of exercise sessions attended. We observed no significant correlation between the number of exercise sessions attended and the changes in IMAAT and hepatic fat in the exercise group (all $P > 0.05$). In sensitivity analyses using a modified per-protocol principle, we also included a minimum of 50% of attendance at the

Table 1—Baseline characteristics of the children participating in the study across intervention groups

	Control group (*n* = 57)			Exercise group (*n* = 59)		
	n	Mean (SD)	*n* (%)	*n*	Mean (SD)	*n* (%)
Age (years)	57	10.6 (1.1)		59	10.5 (1.0)	
BMI (kg/m^2)	57	25.2 (2.8)		59	25.8 (3.7)	
Hepatic fat (%)	56	5.3 (2.9)		59	6.0 (4.8)	
IMAAT (%)	57	7.0 (1.1)		59	7.2 (0.9)	
Girls			30 (52.6)		32 (54.2)	
Tanner stage						
Thelarche or gonadarche	55			53		
I			20 (36.4)			22 (41.5)
II			20 (36.4)			12 (22.6)
III			12 (21.9)			11 (20.8)
IV–V			3 (5.5)			8 (15.1)
Pubarche	55			53		
I			20 (36.4)			17 (32.1)
II			22 (40.0)			20 (37.7)
III			7 (12.7)			10 (18.9)
IV–V			6 (10.9)			6 (11.3)
MAFLD presence	56		23 (41.1)	59		28 (47.5)

The control group consisted of two family-based lifestyle and psychoeducational sessions a month. The exercise group consisted of two family-based lifestyle and psychoeducational sessions a month plus three sessions per week of supervised high-intensity exercise. MAFLD presence was defined as having >5% hepatic fat.

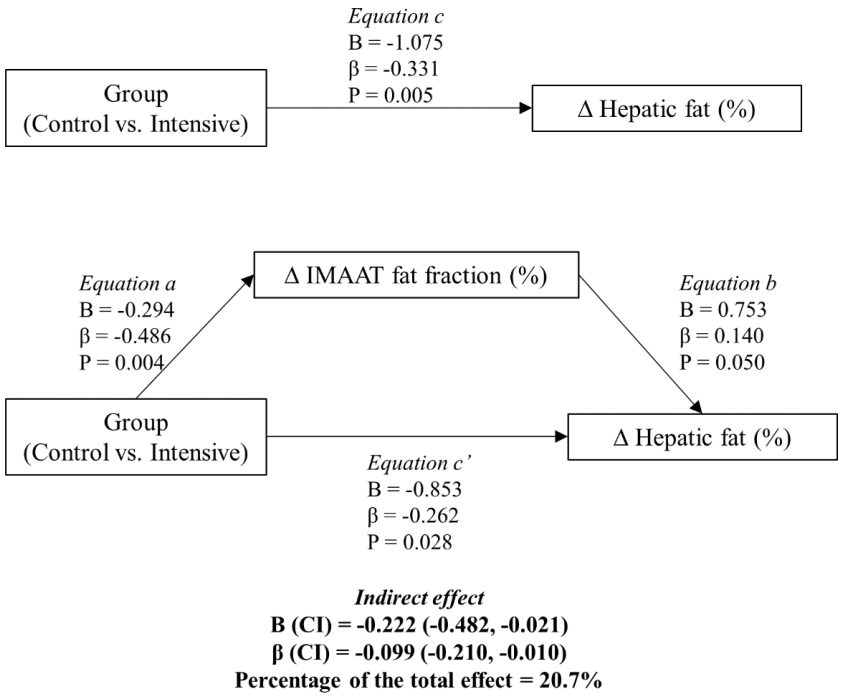

Figure 3—Mediation model to determine whether changes in IMAAT mediated changes in hepatic fat percentage. Data are presented according to the per-protocol analysis, i.e., attending at least 50% of the educational program sessions (in the exercise group, no minimum attendance of exercise sessions was required). Analyses were adjusted for baseline values, age, and sex. Delta (Δ) expresses the outcome at postintervention with respect to baseline.

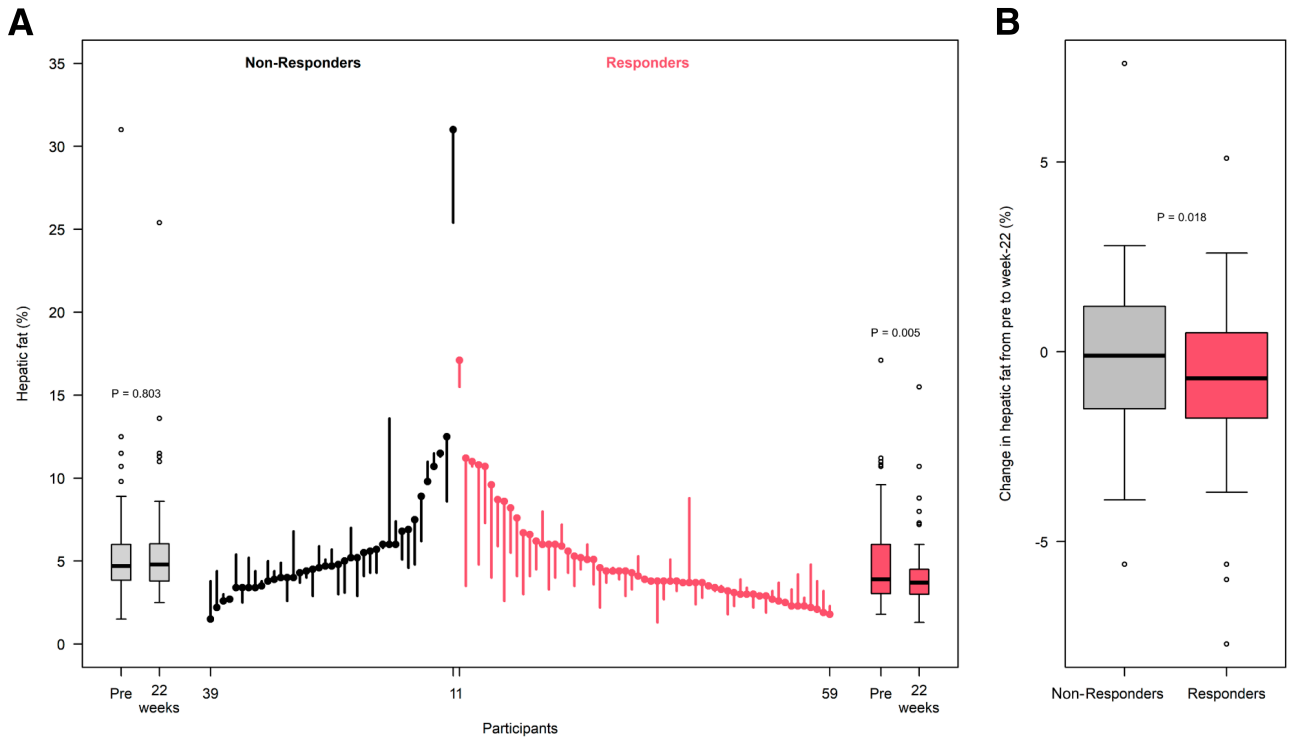

Figure 4—Changes in hepatic fat percentage in children who did not experience a meaningful IMAAT reduction (nonresponders) and those who experienced a meaningful IMAAT reduction (responders) after the intervention (per-protocol analysis). *A*: Box plots of hepatic fat percentage by IMAAT nonresponders (gray) and responders (pink) at baseline (pre) and after the 22-week intervention. The ends of the boxes are located at the first and third quartiles, with the line in the middle illustrating the median. Whiskers extend to the upper and lower adjacent values, the location of the farthest point within a distance of 1.5 interquartile ranges from the first and third quartiles. The parallel line plot contains one vertical line for each participant, which extends from their baseline to their 22-week value. Descending lines indicate a reduction in hepatic fat. Participants were classified as responders when they achieved a reduction of their IMAAT fat fraction with the intervention (Cohen $d \geq 0.2$), whereas nonresponders were categorized as participants who did not experience a reduction (Cohen $d < 0.2$). Pretest values are placed in ascending order for the nonresponder group (black) and descending order for the responder group (pink). *B*: Box plots of the change in hepatic fat percentage. Changes were calculated as postintervention − preintervention values. Analyses were adjusted for baseline values, age, and sex. Data analyses were conducted based on the per-protocol principle, i.e., attending at least 50% of the educational program sessions (in the exercise group, no minimum attendance of exercise sessions was required).

exercise sessions (four participants were excluded for not meeting this per-protocol criterion; thus, n = 94 participants). The results showed similar findings to the original per-protocol principle applied (e.g., changes in IMAAT explained 22.6% of the improvements in hepatic fat).

CONCLUSIONS

The current study shows the mediating role of the reduction of IMAAT in the improvement of hepatic steatosis after a multicomponent intervention in children with overweight/obesity. Indeed, only children who achieved a meaningful reduction in IMAAT at the end of the intervention had a reduction in their hepatic fat percentage, and this change was independent of abdominal fat loss. Our data thus suggest that abdominal muscle fat infiltration could be a therapeutic target of hepatic steatosis treatment in children with overweight/obesity.

In recent years, there has been growing interest in the physiopathological mechanisms linking the muscle-liver axis. Although most of the literature published on this topic is focused on thigh, psoas, or calf muscle fat, there is an emerging body of evidence focused on abdominal muscle fat (7,17). Today, the evidence is still very limited and focused on animal models (18) or the adult population (6,19,20). Our work is the first study to assess the role of abdominal muscle fat over hepatic fat after a multicomponent intervention in children with overweight/obesity. In agreement with our findings, Nachit et al. (6) observed that NASH improvement is associated with a significant decrease in psoas muscle fat content in patients with morbid obesity after two different interventions (i.e., 12 months of dietary intervention, bariatric surgery). In line with this, at a cross-sectional level, authors have shown a relationship between muscle fat content (measured at the thigh, psoas, or multifidus muscle level) and fatty liver disease in humans and animal models (6,19,20). Therefore, it seems that there is a generalized muscle-liver relationship independent of IMAAT area (21). Furthermore, our previous results in this cohort of children have provided new insights into the abdominal skeletal muscle-liver association; likewise, children with MAFLD had higher IMAAT than those without MAFLD (7). Taken together, it is biologically plausible that IMAAT reduction reflects an overall improved myosteatosis.

We previously reported that a multicomponent intervention program, which comprised exercise training in addition to a family-based lifestyle and psychoeducational intervention, is more effective at reducing hepatic fat percentage (−20%) than lifestyle intervention alone (0%) (9). In the current study, we have observed that the effects of the intervention are partially mediated by the

reduction of IMAAT. Our results suggest that the addition of exercise training to the intervention program could be a key factor for achieving abdominal muscle fat reduction and, thus, for reducing in hepatic steatosis in children with overweight/obesity. A previous study in adolescents with overweight/obesity showed that regular exercise was effective in reducing intermuscular adipose tissue at the fascia lata surrounding skeletal muscle and the adipose tissue area between muscle bundles, highlighting the usefulness of regular exercise as an important therapeutic strategy to reduce myosteatosis (22). In this regard, two previous systematic reviews observed that exercise and weight loss may directly decrease IMAAT and improve several cardiometabolic risk factors, such as insulin sensitivity and inflammation and muscle strength and quality (23,24). Our results, together with the reported anti-inflammatory effects of exercise training (23) and the effectiveness of physical activity on skeletal muscle metabolism (24), suggest that exercise (aerobic training, muscular training, or the combination) produces specific effects on abdominal muscle mass, reducing IMAAT independently of the effects on other fat depots. Indeed, skeletal muscle seems to be the major location for whole-body insulin-stimulated glucose disposal (25,26). In adults with obesity and type 2 diabetes, the increment of IMAAT is associated with insulin resistance (27,28). Overall, the causative effect of muscle and liver fat can be inferred from the present results and, therefore, we could state that myosteatosis contributes to MAFLD progression by the presence of peripheral insulin resistance and/or perturbation of the muscle metabolism and secretome associated with muscle fat (6,29–31). For example, in a preclinical model of mice, Nachit et al. (18) observed that severe myosteatosis was a consistent, specific, and early marker of NASH in MAFLD. Therefore, our findings in children, together with those reported in adolescents (22) and adults (6), reinforce the importance of reducing skeletal muscle fat infiltration, with a special emphasis on IMAAT, to improve liver health and insulin sensitivity.

Limitations and Strengths

This study has some limitations. The study design was not strictly randomized (i.e., 11 children/families were not available to attend the exercise sessions and, thus, were allocated to the control group), yet the participants allocated to both groups were comparable at baseline, and adjustments for potential baseline differences between the control and exercise groups were performed in the analyses. Moreover, we repeated all the analyses, excluding children/families who were not randomly assigned, and the findings obtained were similar to those presented in the main article.

The strengths of this study were its novelty in children with overweight/obesity and the relatively large number of participants with abdominal muscle and hepatic fat measurements based on MRI. The medical imaging group that analyzed the main outcomes (i.e., images from MRI) was entirely blinded to the intervention groups. Finally, the performance of family-based lifestyle and psychoeducational intervention plus supervised exercise training followed pediatric childhood obesity guidelines (32).

In summary, abdominal muscle fat plays a relevant role in the reduction on hepatic fat after a multicomponent intervention in children with overweight/obesity, regardless of abdominal fat loss. These data indicate that abdominal muscle fat infiltration in children could be a therapeutic target. Future studies are needed to corroborate or contrast our findings.

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Author Contributions. C.C.-S. contributed to the conception of the study, analyzed the data, and drafted the manuscript. F.I., R.C., A.V., B.R.-V., M.M., and M.O. contributed to the acquisition, analysis, and interpretation of the data and critically reviewed the manuscript. F.B.O. and J.R.R. contributed to the interpretation of the data and critically reviewed the manuscript. I.L. contributed to the conception of the study and analysis and interpretation of the data and critically reviewed the manuscript. All authors approved the final version of the manuscript. C.C.-S. and I.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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