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Serum Fatty Acid-Binding Protein 4 Levels in Adolescents: Effect of Insulin Resistance

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Abstract

Background: Fatty acid-binding protein 4 (FABP4) is an adipokine that plays a causative role in obesity and diabetes. In a stratified cross-sectional study with adolescents, we explored whether changes in FABP4 are already present in lean adolescents, provided they display elements of insulin resistance (IR).
Methods: Adolescents were divided in four groups according to body mass index and homeostasis model assessment-IR.
Results: In metabolically unhealthy lean (MUL) adolescents (MUL, lean with IR), FABP4 was 33% higher than in healthy counterparts (metabolically healthy lean [MHL]). Obese adolescents without IR (metabolically healthy obesity [MHO]) had 50% higher levels of FABP4 than their lean counterparts (MHL), while levels of FABP4 in obese adolescents with IR (metabolically unhealthy obese [MUO]) were 220% higher than those of MUL adolescents. The differences were significant at least with $P < 0.005$. MUO > MHO > MUL. Our data demonstrate that the known FABP4 defect in adults with obesity also occurs in youth and even in lean adolescents, suggesting an early association between impaired glucose metabolism and FABP4 irrespective of body weight. FABP4 was more sensitive in discerning each of our 4 subgroups than either adiponectin or leptin. Moreover, evidence for a putative early adiponectin resistance in MUL suggests a combined defect in these adolescents that call for early detection and prevention of the metabolic disturbance that should stay away from concentrating only in subjects with obesity.
Conclusions: Our data may serve to draw the considerable attention that is currently paid to FABP4 to the adolescent population, irrespective of the presence of obesity. Further studies with larger cohorts and analyses of visceral and liver fat are warranted.

Keywords: obesity, insulin resistance, adolescents, fatty acid-binding protein 4, TOFI

Introduction

Obesity represents an important public health problem, since it promotes and/or precedes insulin resistance (IR) and is associated with an increased risk of developing comorbidities such as metabolic syndrome (MetS), type 2 diabetes mellitus, and cardiovascular diseases (CVDs).[1] Adolescents with obesity are at high risk of obesity in adulthood, which is closely associated with an increased risk of these metabolic disorders.[2] However, it is less clear whether the problem lies only in the obesity or it is due to the ensuing IR.

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Indeed, recent studies in children and adolescents have uncovered a new phenotype of metabolically healthy obesity (MHO),[3] with very variable prevalence,[4] characterized by high body mass index (BMI) and high fat mass but *without* metabolic alterations. Adolescents in this group differ in body composition, inflammation profile, and cardiovascular risk.[5] They lack IR, dyslipoproteinemia, or high blood pressure (BP) in contrast to metabolically unhealthy obese (MUO), most likely due to the presence of excess subcutaneous adipose tissue (SAT) although with little accumulation of ectopic fat, mainly visceral (visceral adipose tissue [VAT]) or hepatic.[6] Also, on the other side of the spectrum, there is a subgroup of metabolically unhealthy lean (MUL) adolescents (with normal subcutaneous fat mass and low BMI) which still present metabolic disorders.[7]

They display increased ectopic fat, namely nonalcoholic fatty liver disease, visceral, intramyocellular, or epicardial fat.

Fatty acid-binding protein 4 (FABP4) is one of the most abundant proteins in adipocytes. It is crucial for homeostasis and endurance due to its role in adipocyte homeostasis, regulating lipolysis and adipogenesis through interactions with hormone-sensitive lipase and peroxisome proliferator activator receptor gamma, respectively. However, it becomes maladaptive in conditions of nutrient excess or chronic stress.[8]

Although the number of studies assessing adipokine profiles in the MHO phenotype is still limited, the observed associations between FABP4[9,10] and other adipokines as adiponectin,[11] leptin/adiponectin ratio,[12] and plasminogen activator inhibitor 1[6] with the MHO phenotype provide evidence that different adipokine profiles might contribute to the dissociation of the MHO and MUO phenotypes.[13] However, studies of these obesity phenotypes and their accompanying adipokine profiles are still lacking in the pediatric and adolescent populations.

We have recently studied lipoprotein changes in the four phenotypes and found evidence for lipoprotein lipase dysregulation and apoB48 increases in lean adolescents if they have IR.[14]

In this regard, one aim of this cross-sectional follow-up investigation is to study the status of FABP4, adiponectin, and leptin in those metabolically healthy and unhealthy adolescents with either obesity or normal weight to gain insight on the full spectrum of changes that may spur cohort longitudinal studies. A second aim is to ascertain whether, as we determined for lipoproteins, MUL adolescents also display adipokine changes associated with early IR to provide evidence that would help shift the prevalent unilateral focus on obesity *per se*, rather than in subjacent metabolic disturbances.

Methods

Subjects

The subjects in the present study were 127 adolescents aged 15–19 years (59% girls, $n=72$; 41% boys, $n=55$) recruited from High Schools of León Guanajuato, México, between August 2017 and May 2018. We included 55 normal weight and 72 adolescents with obesity (Fig. 1 displays the flowchart).

Informed consent was obtained from parents and participants and the research was approved by the Ethics Committee of the University of Guanajuato (CIBIUG-P24-2018), and the study complied with the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki.

Participants provided information on demographic, cigarette smoking, physical activity, and a family history of chronic diseases.

Anthropometric measures

The height and weight of the adolescents was measured using a SECA stadiometer and a SECA scales, respectively, and BP was measured on the nondominant arm while the subject was sitting with an Omron HEM-7320-LA electronic monitor (Omron Healthcare Co. Ltd, Kyoto, Japan) and the average of 3 measurements was recorded. BP standardized

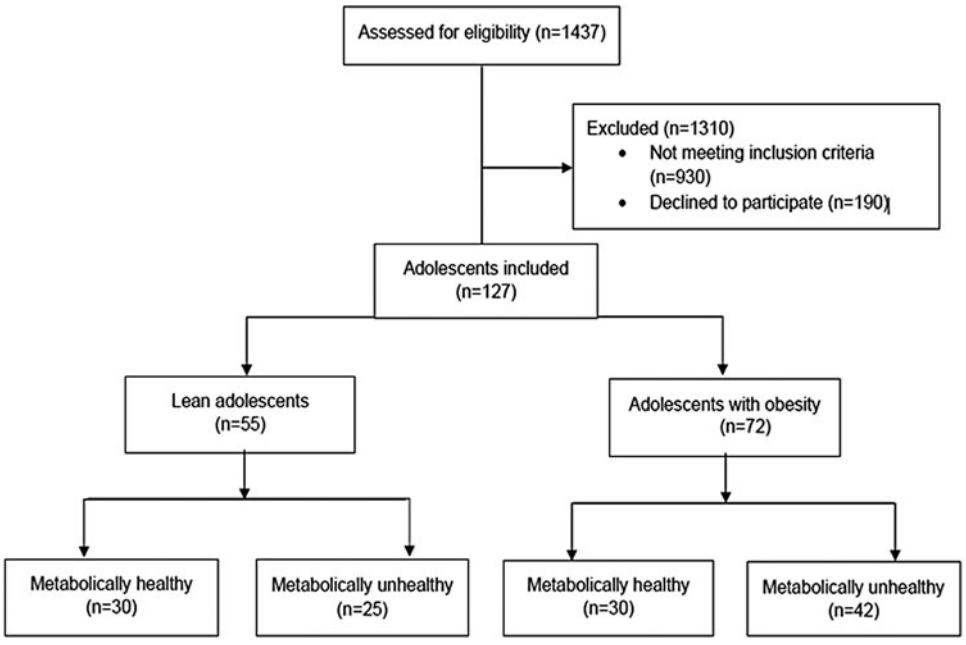

FIG. 1. Flow diagram of recruiting process.

scores and centiles were calculated using the definitions set by the Centre for Disease Control and Prevention techniques.[15] Adolescents were considered with obesity when the BMI for their age was more than 2 standard deviations (SDs) above the median established in the World Health Organization (WHO) Child Growth Standards.[16]

Definition of study groups

Study adolescents were divided in four categories based on BMI (normal weight and obesity for age- and gender-specific BMI cutoffs were as recommended by the WHO),[14,16] estimated IR, and/or hypertriglyceridemia. IR was measured by the homeostasis model assessment of insulin resistance (HOMA-IR), using the following formula: (insulin [mU/L] × glucose [mmol/L])/22.5. The HOMA-IR threshold ≥3.0 was used to diagnose IR). The cutoff of 3.0 for HOMA-IR was chosen to compare our data with those published by Aradillas-García et al.[17]

Hypertriglyceridemia, was defined by cutoff values triglycerides (TG) ≥130 mg/dL 10–19 years.[14,18] Therefore, the four categories were as follows: (1) metabolically healthy lean (MHL): nonobese adolescents with normal insulin and normal TG, (2) MUL: nonobese, with IR and/or hypertriglyceridemia, (3) MHO: adolescents with obesity without IR and normal TG, and (4) MUO: adolescents with obesity and IR and/or hypertriglyceridemia.

Laboratory measurements

All blood samples were obtained in the morning after a 12-hr overnight fast and serum samples were immediately stored at −80°C for subsequent assays. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and TG were measured on the same day using an automatic biochemical analyzer (TBA-2000FR; Toshiba Medical Systems, Japan). The glucose oxidase method was used to measure fasting plasma glucose levels.

Serum adipocytokines were measured using enzyme-linked immunosorbent assay (ELISA). Adiponectin was measured with Human HMW Adiponectin Quantikine ELISA Cat. No. DHWAD0. The intra- and interassay coefficients of variation were <3.7% and <8.6%, respectively. Serum leptin was measured using the Human Leptin Quantikine ELISA Cat. No. DLP00. The intra- and interassay coefficients of variation were <3.3% and <5.4%, respectively. FABP4 was measured using the Human Adipocyte FABP4 ELISA kit (RD191036200R; BioVendor R&D, Bruno, Czech Republic). The intra- and interassay coefficients of variation were 6.0% and 10.0%, respectively.

Statistical analyses

The distribution and normality of each variable was determined by the Kolmogorov–Smirnov test. Data are shown as mean ± SD for variables with normal distribution or as median and interquartile range for non-Gaussian distribution; difference between groups with and without obesity was calculated using *t* tests or Wilcoxon test according to the distribution of data; and the difference between the four groups of study was calculated using analysis of variance and for comparison between groups we used the *post hoc* analysis of Kruskal–Wallis test or Tukey-honest significant difference.

To correlate HOMA-IR with BMI systolic and diastolic BP, TG/HDL-C and TC/HDL-C index, and adipocytokine (adiponectin, leptin, and FABP4), we used the Spearman correlation analysis in the whole group. A significance level of <0.05 was considered. The statistical package IBM SPSS (SPSS Inc., Chicago, IL) statistics version 25 was used.

Results

Anthropometric and metabolic characteristics

As depicted in the flowchart (Fig. 1), in this cross-sectional study, we recruited 127 adolescents comprising 55 lean adolescents and 72 adolescents with obesity. The anthropometric and metabolic characteristics of the study subjects are depicted in Table 1. We then stratified them in four groups: 30 MHL, 25 MUL, 30 MHO, and 42 MUO according to the selected criteria described in Methods. The metabolic characteristics of the four subgroups were already reported in our previous study.[14] There was no difference in gender or age among the four groups. Both systolic and diastolic BP were higher in the MUO group.

Insulin resistance

We found an increase in insulin levels by 40% in the adolescents with obesity as well as a twofold increase in HOMA-IR.

Cardiometabolic dyslipidemia

Dyslipidemia in obese adolescents was characterized by a highly significant increase in TG (30%) accompanied, as expected, by reduced HDL-C by 11%, which translated in an increased TG/HDL-C ratio by 47%. Non-HDL-C and very LDL-C were also elevated. These data underscore the presence of dysfunctional triglyceride-rich lipoproteins catabolism associated with IR.

FABP4 is a marker of metabolic dysfunction and IR

Figure 2 shows the levels of FABP4 in our four groups. MUL displayed 33% increased levels compared with MHL. MHO levels were over twofold higher than those of MHL and 62% higher than MUL. MUO showed the highest levels (almost threefold compared to MHL). There appears to be a gradient of response. Both IR and obesity alone associate with increased FABP4, and when they occur together, the effect is larger.

Dissociation between changes in adiponectin and leptin levels

Paradoxical increased adiponectin levels in MUL. Figure 3a displays adiponectin levels in the four groups. As expected, MUO had the lowest levels of the four groups, 28% lower than MHL subjects. Conversely, adolescents with obesity without insulin resistance (MHO) did not differ from MHL, showing that IR is necessary to cause lower levels in adiponectin. Unexpectedly, the highest levels of adiponectin were not found in the MHL but in the MUL, where it was 25% higher. Due probably to high variability, the difference between MHL and MUL did not achieve statistical significance, but the trend suggests the possibility of an early adiponectin resistance when IR is present in lean adolescents.

Stepwise increase in leptin. Figure 4 displays leptin levels in the four groups. Also showing high variability, leptin was

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TABLE 1. DISTRIBUTION OF ANTHROPOMETRIC AND METABOLIC CHARACTERISTICS BY BODY MASS INDEX

Variable	*Lean adolescents* (n = *55*)	*Adolescents with obesity* (n = *72*)	P
Female/male	29/26	46/26	0.27
Age (years)	16.11 ± 1.08	16.40 ± 1.10	0.14
Weight (kg)	56.35 ± 7.73	86.94 ± 13.27	<0.00006
Height (cm)	1.65 ± 0.10	1.64 ± 0.076	0.91
Body mass index (kg/m^2)	20.75 ± 1.79	32.08 ± 3.88	<0.000001
Systolic blood pressure (mmHg)	106.15 ± 13.02	112.41 ± 10.65	0.009
Diastolic blood pressure (mmHg)	68.30 ± 6.42	74.20 ± 7.54	0.0001
Glucose (mg/dL)	90.60 ± 9.88	92.32 ± 10.36	0.35
Total cholesterol (mg/dL)	161.82 ± 33.07	170.11 ± 35.19	0.18
LDL-C (mg/dL)	96.84 ± 29.76	104.07 ± 29.97	0.179
HDL-C (mg/dL)	47.38 ± 10.58	42.03 ± 8.98	0.002
Non-HDL-C (mg/dL)	114.44 ± 32.14	128.08 ± 33.87	0.023
Very LDL-C (mg/dL)	17.36 ± 8.05	23.04 ± 11.86	0.003
TG (mg/dL)	87.07 ± 40.10	113.17 ± 60.34	0.006
TG/HDL-C	1.98 ± 1.14	2.91 ± 1.81	0.001
TC/HDL-C	3.55 ± 0.95	4.16 ± 0.99	0.0006
LDL-C/HDL-C (mg/dL)	2.15 ± 0.83	2.54 ± 0.79	0.007
Insulin mU/L[a]	7.50 (5.0–11.10)	16.36 (9.57–25.48)	<0.00001
HOMA-IR[a]	1.17 (1.01–2.46)	3.56 (2.18–6.0)	<0.00001
Creatinine[a] (mg/dL)	0.80 (0.70–0.90)	0.80 (0.70–0.90)	0.88

Data are shown as mean ± standard deviation for variables with normal distribution and the difference between groups was calculated using *t* tests for variables with normal distribution or data expressed as median and interquartile range for non-Gaussian distribution and was used Wilcoxon test.[a] Metabolic parameters were all measured after a 12-hr fast.

HDL-C, high-density lipoprotein cholesterol; HOMA, homeostatic model to assess insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

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3.4-fold higher in MUL versus MHL, indicating that leptin responses are not only due to obesity and suggesting a role for ectopic fat as the source of the added leptin. As expected, MHO showed levels that were 4.3-fold those of MHL. The highest levels were found in MUO amounting to 6.3-fold those of MHL and 45% higher than MHO.

Defect in FABP4 and leptin is more pronounced in females. To rule out possible differences due to gender, we conducted the appropriate analyses, which do not change the pattern previously shown for each group combined. This is shown in Table 2.

Spearman correlation analysis

Table 3 shows the correlations of HOMA-IR with clinical and metabolic parameters in the whole cohort. The tightest

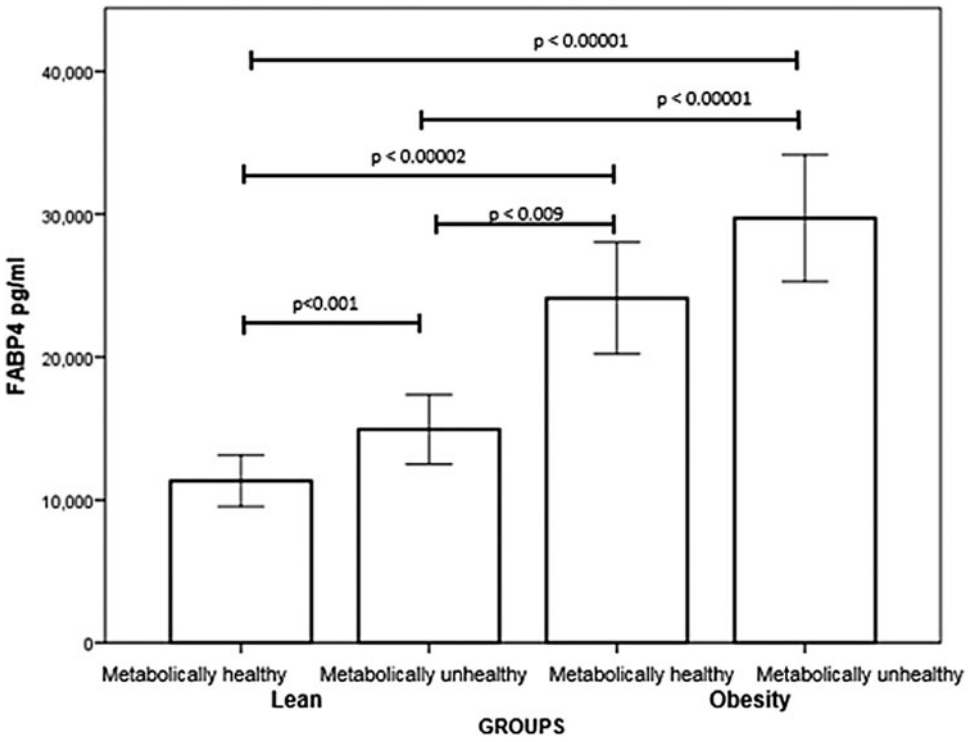

FIG. 2. FABP4 in adolescents of different categories of BMI and metabolic status. Metabolic status was defined by insulin resistance and/or hypertriglyceridemia and BMI. Data represent mean ± SD. BMI, body mass index; FABP4, fatty acid-binding protein 4; SD, standard deviation.

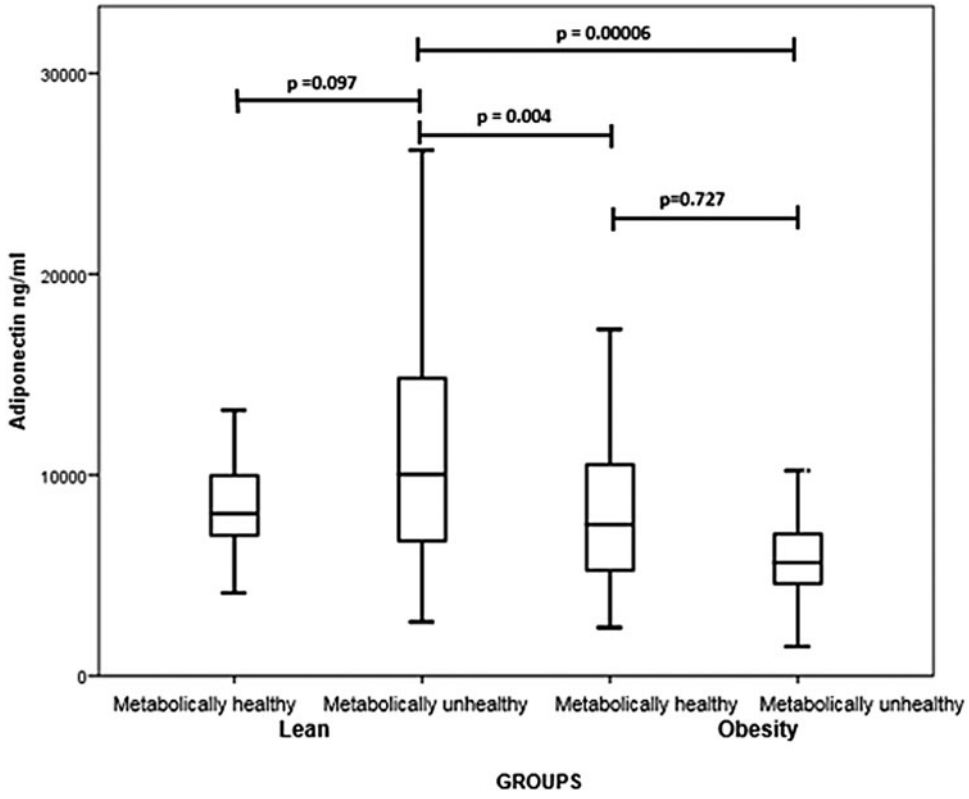

FIG. 3. Adiponectin in adolescents with different categories of BMI and metabolic status. Metabolic status was defined by insulin resistance and/or hypertriglyceridemia and BMI. Data represent mean ± SD.

correlations (Rho over 0.4) were displayed by BMI, TG/HDL-C, TC/HDL-C, leptin, and FABP4, which display the tighter correlation with fasting IR.

Discussion

This study originality resides in that, to our knowledge, it is the first to show the joint behavior of adipocytokines FABP4, adiponectin and leptin in lean adolescents, and adolescents with obesity, with and without IR. Our data show that (1) the FABP4 defect in obesity, so far shown in adults, already occurs in youth and (2) they suggest an early association between impaired glucose metabolism and FABP4 because lean adolescents with IR have significantly higher FABP4 levels than those without IR.

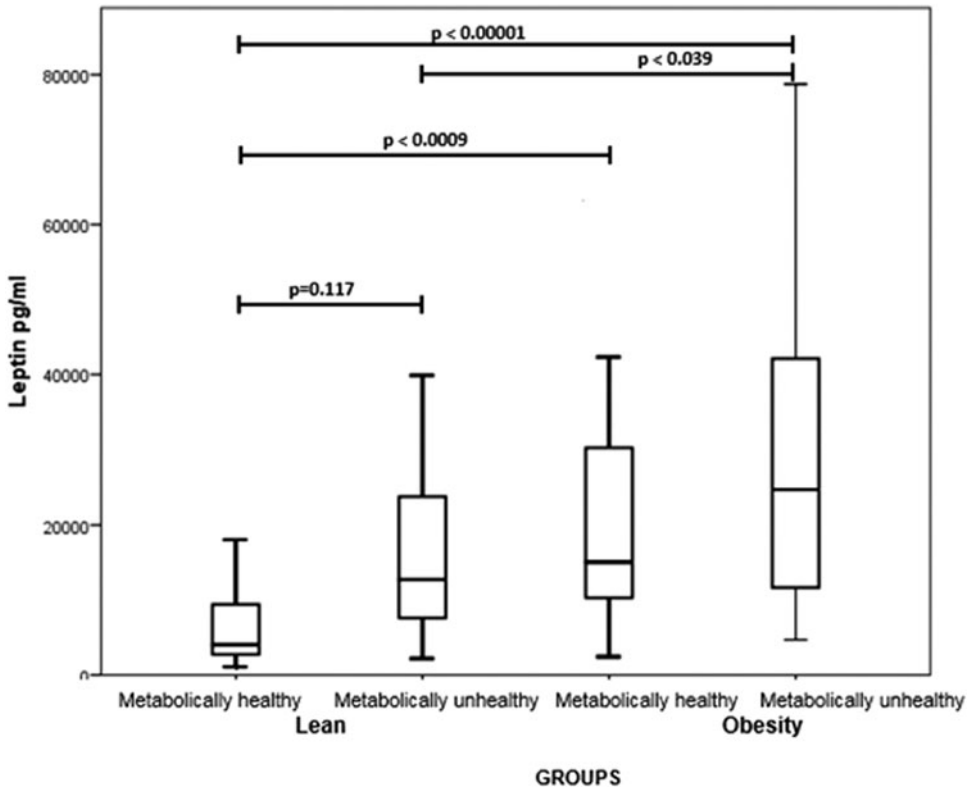

FIG. 4. Leptin in adolescents of different categories of BMI and metabolic status. Metabolic status was defined by insulin resistance and/or hypertriglyceridemia and BMI. Data represent mean ± SD.

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TABLE 2. ADIPOKINES STRATIFIED BY GENDER AND GROUPS

Male						
Groups	*Lean adolescents*		*Adolescents with obesity*			
Variable	*MHL* (n = *17*)	*MUL* (n = *9*)	*MHO* (n = *11*)	*MUO* (n = *15*)	P	Post hoc P *value*
Adiponectin (ng/mL)	9425.5 ± 3639.6	12,731.7 ± 6655.4[€]	8401.4 ± 4375.1	6432.3 ± 1971.6[€]	<0.007	€= 0.01
Leptin (pg/mL)	5469.9 ± 5237.0[¥]	6072.8 ± 4270.5[£]	22,253.1 ± 20,315.7	27,414.4 ± 22,577.3[¥,£]	<0.0007	¥= 0.002; £= 0.05
FABP4 (pg/mL/)	10,120.4 ± 4397.4[µ]	11,159.1 ± 4604.0[æ]	23,747.4 ± 10,708.4[µ,æ]	29,215.0 ± 9087.8 [µ,æ]	<0.00001	µ = 0.0007; 0.0002; æ = 0.005; 0.0002
Female						
Groups	*Lean adolescents*		*Adolescents with obesity*			
Variable	*MHL* (*n* = *13*)	*MUL* (n = *16*)	*MHO* (n = *19*)	*MUO* (n = *27*)	P	Post hoc P *value*
Adiponectin (ng/mL)	8927.9 ± 3296.4	11,606.8 ± 6692.3[ǂǂ]	8178.9 ± 3879.8	6202.0 ± 35,11.9[ǂǂ]	<0.003	ǂǂ = <0.005
Leptin (pg/mL)	8533.5 ± 5938.2[Ω]	22,732.1 ± 14,987.9	26,880.3 ± 22,409.9[Ω]	31,063.6 ± 18,595.3[Ω]	<0.003	Ω = <0.045; <0.009
FABP4 (pg/mL)	12,959.0 ± 5078.9[ɖ]	17,103.1 ± 5579.5[ƀ]	24,322.6 ± 10,618.8[ɖ,ƀ]	30,006.1 ± 16,608.8	<0.0002	ɖ = <0.003; ƀ = 0.01

FABP4, fatty acid-binding protein 4; MHL, metabolically healthy lean; MHO, metabolically healthy obese; MUL, metabolically unhealthy lean; MUO, metabolically unhealthy obese.

TABLE 3. SPEARMAN CORRELATION ANALYSIS IN THE WHOLE GROUP

HOMA-IR	*Rho*	P
Body mass index	0.56	<0.000001
Systolic blood pressure	0.24	0.01
Diastolic blood pressure	0.34	<0.0005
TG/HDL-C	0.51	<0.000001
TC/HDL-C	0.47	<0.000001
Adiponectin	–0.25	<0.005
Leptin	0.42	<0.000001
FABP4	0.44	<0.000001

FABP4 has come to the limelight arguably as the most promising adipose tissue hormone.[19] FABP4 is a secreted hormone that participates in glucose homeostasis. It functions at a critical junction in the crosstalk between energy storage sites and other organs that evolved to respond to life-threatening situations. Chronic engagement of FABP4 under maladaptive situations produce metabolic stress such as MetS or obesity. Most studies focus specifically on obesity and FABP4.[20–22] In our study, we show that, at least in adolescents, obesity aggravates, but is not necessary to produce higher levels of FABP4, it suffices to have IR (stemmed from the secretion profile of visceral and other ectopic fat). Indeed, a recent study in adults showed a strong negative correlation of FABP4 with the glucose clearance rate when performing hyperinsulinemic-euglycemic clamping and a positive correlation with insulin secretion during a food tolerance test[23]

Here, we show that MUL adolescents (MUL, lean with IR) showed 33% higher levels of FABP4 than healthy counterparts (MHL). MUL adults (also described as thin on the outside but fat on the inside), often display excess visceral adipose tissue and ectopic fat deposition, inflammation of adipose tissue, altered inflammatory profiles, and adipokines, reduced skeletal muscle mass and low cardiorespiratory fitness.[24] Future studies should be carried out to measure ectopic fat in adolescent populations and its association with FABP4. The higher levels of FABP4 secreted by visceral adipose tissue compared to SAT suggest a causal link between FABP4 and MetS.[19] Our data support this proposition. Obese adolescents without IR (MHO) had 50% higher levels of FABP4 than their lean counterparts (MHL), while levels of FABP4 in obese adolescents with IR (MUO) were 220% higher than those of MUL adolescents: MUO>MHO>MUL.

As expected, we observed a strong positive association of FABP4 with HOMA-IR. FABP4 as an adipokine may influence insulin sensitivity.[25]

In obesity and IR, which produce uncontrolled lipolysis, FABP4 is constantly compromised.[8] We found a gradual increase from MUL to MHO to MUO. Confronting with the sparse literature on adolescents, our data are in agreement with another study that found increased levels of FABP4 in obese children compared with normal-weight children.[26] Another study in adolescents showed that increased body fat and abdominal fat were associated with increased levels of FABP4.[27] The importance of FABP4 is highlighted by the fact that hundreds FABP4 inhibitors have been synthesized for the purpose of treating atherosclerosis and diabetes.

These pharmacologic studies may provide innovative diagnostic and therapeutic approaches for MetS, type 2 diabetes, obesity, and atherosclerosis.[28]

To have a more complete picture of the key adipokines, we went on to explore leptin and adiponectin. We found a stepwise increase trend in leptin in our four groups. Although it displays high variability, leptin was 3.4-fold higher in MUL versus MHL, indicating that leptin responses are not solely due to obesity and suggesting a role for ectopic fat as the source of the added leptin. As expected, MHO showed even higher than those of MHL. The highest levels were found in MUO amounting to 6.3-fold those of MHL and 45% higher than MHO, most likely showing the compounded effect of SAT and VAT sources of leptin and/or leptin resistance caused by hyperinsulinemia.

Although leptin resistance is a complex pathophysiological phenomenon, a chief overarching concept is that hyperinsulinemia *per se* compromises leptin signaling at hypothalamic level, which may provide a link for a feed-forward cycle of hyperinsulinemia and hyperleptinemia.[29] Leptin and insulin interact to modulate vascular function, and this interaction may result in vascular dysfunction.[30]

Our data in MUL versus MHL are in agreement with another study that showed that leptin levels are more important than waist circumference and are as important as BMI as a risk marker for CVD in children.[31]

Adiponectin is a pleiotropic organ-protective protein that is decreased in obesity, IR/type 2 diabetes, and CVD.[32] We observed that, unexpectedly and despite its high variability, the MUL group presented the highest levels of adiponectin. This suggests that some degree of adiponectin resistance is occurring when IR alone is present. Indeed, in children and adolescents without obesity, adiponectin has been associated with increased markers of abdominal obesity such as waist circumference.[33] Other studies showed a negative correlation between adiponectin and visceral fat in children and in adolescents.[34,35] In the whole cohort, as expected, we found a negative correlation of adiponectin with HOMA-IR. Finally, other studies showed lower levels of adiponectin in obese adolescents with IR.[36,37]

Care should be exercised in the interpretation of adiponectin levels, especially if the relative concentrations of trimmers, hexamers, and polymers are not reported.

We stratified further the groups by analyzing putative differences due to gender. The results do not change what was discussed above and shown in Figs. 2–4. Interestingly and probably due to the different fat distribution, certain differences between MHL and MUL adolescents are more marked for females than males: Leptin in MUL is 11% higher than in MHL for males and 266% higher for females ($P = 0.0001$); FABP4 in MUL is 10% higher than in MHL for males and 32% higher for females ($P = 0.001$). Although the sample size is low, these data suggest that females are more exposed to deleterious changes in FABP4 than males. This showcases the importance of studying both genders and calls for further research on this issue.

Our study has certain limitations, such as a small sample size and a cross-sectional design that does not allow for demonstration of causality, although it allows to infer a gradient of metabolic dysfunctions as adolescents progress from simple IR to obesity, in many cases. Another limitation is that, for methodological reasons, we did not assess visceral nor liver fat.

In conclusion, our stratified cross-sectional study shows for the first time, in a comprehensive design, an increase in circulating FABP4 that is present even in lean adolescents, provided they display elements of IR. Our data may serve to draw the considerable attention that is currently paid to FABP4 both as a marker and a mechanistic participant in metabolic disorders to the adolescent population, irrespective of the presence of obesity. Further studies with larger cohorts and analyses of visceral and liver fat are warranted.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by A.P.G., M.E.G.S., and A.G. The first draft of the article was written by A.P.G., M.E.G.S., and A.G. and all authors approved the final version.

Consent for Publication

All adolescents and their parents gave consent for the publication of their data anonymously.

Availability of Data and Material

Data and material are available by request.

Author Disclosure Statement

The authors declare that they have no conflict of interest.

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