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Title
Physical activity, growth, and inflammatory mediators in BMI-matched female adolescents.

Permalink
https://escholarship.org/uc/item/64f7506v

Journal
Medicine and science in sports and exercise, 39(7)

ISSN
0195-9131

Authors
Ischander, Mariam
Zaldivar, Frank
Eliakim, Alon
et al.

Publication Date
2007-07-01

DOI
10.1249/mss.0b013e318053e7a2

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Physical Activity, Growth, and Inflammatory Mediators in BMI-Matched Female Adolescents

MARIAM ISCHANDER[1,2], FRANK ZALDIVAR, JR.[1], ALON ELIAKIM[1,3], ELIEZER NUSSBAUM[1,2], GENEVIEVE DUNTON[4], SZU-YUN LEU[1], DAN MICHAEL COOPER[1], and MARGARET SCHNEIDER[1]

[1]Pediatric Exercise Research Center, University of California at Irvine, Irvine, CA; [2]Millers Children's Hospital, Long Beach, CA; [3]Meir Medical Center–Sackler School of Medicine, University of Tel Aviv, Tel Aviv, ISRAEL; and [4]Department of Preventive Medicine, University of Southern California, Los Angeles, CA

ABSTRACT

ISCHANDER, M., F. ZALDIVAR JR., A. ELIAKIM, E. NUSSBAUM, G. DUNTON, S. LEU, D. M. COOPER, and M. SCHNEIDER. Physical Activity, Growth, and Inflammatory Mediators in BMI-Matched Female Adolescents. *Med. Sci. Sports Exerc.*, Vol. 39, No. 7, pp. 1131–1138, 2007. **Purpose:** Physical inactivity is deleterious to health, but it has been difficult to determine the extent to which these effects are attributable to abnormal body composition or to factors related to physical activity alone. To begin to gauge independent effects of physical activity on health risk, we matched by BMI two groups of normal-weight adolescent females, one physically active (all participants in high school sports), and one sedentary. **Methods:** Thirty-seven sedentary and 37 physically active adolescent females (mean 15.5 yr) were matched for age and BMI percentile (mean = 58.8). Comparisons included fitness, body composition and bone mineralization (by DEXA), circulating inflammatory cytokines, growth factors, bone-turnover markers, leptin, and adiponectin. **Results:** Compared with the normal-weight sedentary girls, active girls had significantly ($P < 0.05$) higher fitness level (peak $\dot{V}O_2$ 35.5 ± 5.2 vs 24.4 ± 4.1 mL·kg^{-1}·min^{-1}), lean body mass (43.2 ± 4.4 vs 38.7 ± 3.6 kg), bone mineralization (spinal BMD z-scores 0.04 ± 0.88 vs −0.41 ± 0.85), and lower percent body fat (25.4 ± 04.6 vs 29.7 ± 03.7%). Additionally, active girls had lower inflammatory cytokines levels (e.g., TNF-α 1.7 ± 1.3 vs 2.6 ± 2.2 pg·mL^{-1}), and leptin (17.4 ± 11.2 vs 24.7 ± 14.7 ng·mL^{-1}), and higher bone-turnover markers (e.g. osteocalcin 12.6 ± 7.6 vs 7.8 ± 3.0 U·L^{-1}), IGFBP-3 (6416 ± 21280 vs 4247 ± 1082 ng·mL^{-1}), and adiponectin levels (11919 ± 3935 vs 9305 ± 2843 ng·mL^{-1}). **Conclusion:** The normal-weight, physically active group was fitter and had greater lean body mass, stronger bones, and lower levels of inflammatory markers than did the normal-weight, sedentary group. In adolescent girls, the choice of a lifestyle involving high school sports is characterized by a circulating mediator and body composition pattern that, if sustained, is associated with generally lower long-term risk of cardiovascular disease and osteoporosis. **Key Words:** FITNESS, INFLAMMATION, ADOLESCENCE, BONE MINERALIZATION, BODY COMPOSITION, GROWTH MEDIATORS

The grave health care consequences of obesity during childhood and adolescence are now very well recognized, and the preponderance of evidence suggests that physical inactivity plays a role in the development of obesity (typically determined by body mass index (BMI)). What remains enigmatic, however, are the specific roles of body fat and physical activity *per se*. The question—how would an active and inactive adolescent, each with the same BMI, compare in terms of health risk assessment?—has been difficult to approach and answer, for a number of reasons.

One problem has been a lack of understanding of the mechanisms that might link obesity during childhood with increased risk of impaired health later in life. Recently, discoveries in both children and adults showing that obesity is associated with elevated leukocytes (31) and certain circulating cytokines (e.g., IL-6 and C-reactive protein) suggest that a chronic low-grade inflammatory state is linked to subsequent impairment of cardiovascular status and insulin dysregulation (10). Moreover, exercise itself is now known to alter many of these inflammatory mediators in both children and adults (5,20). These insights provide a potentially novel means of distinguishing the effects of physical inactivity from that of obesity because levels of fitness, body composition, and circulating inflammatory markers are all measurable.

Therefore, the aim of the present study was to compare physical activity profiles, fitness, body composition (measured as DEXA-derived lean, bone, and fat mass), and the

adipose biomarkers adiponectin and leptin, and key markers of growth (IGF-I and IGFBP-3 (its predominate circulating binding protein)) and inflammation (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1 receptor antagonist (IL1-ra), and C-reactive protein (CRP)), in a group of sedentary, physically active, *normal-weight* adolescent girls who were matched by age and BMI. We focused on adolescent females because levels of physical activity decline markedly with maturation in this group (2), and we used naturally occurring factors in the real lives of adolescents (i.e., their participation or nonparticipation in high school sports) as part of our strategy to recruit physically active and sedentary participants.

We hypothesized that inflammatory markers would be lower in the physically active adolescent girls than in their BMI-matched sedentary coparticipants. Further, we hypothesized that lean body mass, circulating growth factors, bone mineralization (determined by DEXA), and bone-turnover markers (osteocalcin, bone-specific alkaline phosphatase (BSAP), and collagen-degradation factors), which are known to be influenced by physical activity (8), would also be higher in the active girls. Ultimately, these data would be important to determine the extent to which changes in physical activity, in addition to normalization of BMI, are necessary to mitigate the adverse health effects of childhood obesity. A better understanding of these physiological determinants would be useful in more precisely shaping the costly policy initiatives that are necessary to change the environmental, behavioral, and nutritional factors necessary to impact childhood obesity.

METHODS

Subjects. Seventy-four healthy young adolescent females between the ages of 14 and 17 yr old were recruited from two Southern Californian high schools. Our strategy was to recruit subjects exhibiting either sedentary or active levels of physical activity. In one set of recruitment materials, we advertised for adolescent females who were *not* members of any sports teams and who had low levels of physical activity. Sedentary behavior was then confirmed by self-report and was defined as no more than three 20-min bouts of vigorous physical activity per week and no more than five 30-min bouts of moderate physical activity per week. The criteria used for determining sedentary status reflect the definition commonly employed by the U.S. Centers for Disease Control and Prevention (27). Sedentary status was confirmed twice: once during the spring recruitment, and again during the summer when participants arrived at the clinic. Thus, sedentary status was stable across a 2- to 3-month period.

The active group responded to recruitment materials seeking adolescent females currently participating in a high school sponsored sports team (predominately endurance-type exercise and team sports such as soccer, basketball,

and track). Physical activity level was then confirmed by self-report and was defined as participating in an average of ≥ 60 min of vigorous physical activity per day. This level of activity exceeds the current recommendation recently published by the American Academy of Pediatrics (3). From a total of 194 subjects who responded and met the inclusion criteria for either the sedentary or active group, we then matched sedentary and physically active groups by age and BMI so that there were 37 girls in each group. We chose to match participants on BMI because this index is the most widely used indicator of body composition employed by clinicians in the pediatric setting. All girls were postmenarche and eumenorrheic, per self-report (> 10 menstrual periods per year). The UCI institutional review board approved this study, and written informed consent and assent were obtained from all participants and from their parent or guardian. The studies were conducted at the UCI general clinical research center (GCRC). Data on behavioral and attitudinal factors relating to habitual physical activity in some of these subjects have been published elsewhere (7).

Height, weight, BMI, body composition, and bone health. Standard calibrated scales and stadiometers were used to determine height, weight, and BMI (weight/ height^2). BMI percentile for each participant was calculated using the recently published standards from the U.S. Centers for Disease Control, National Center for Health Statistics (15).

Total-body composition was determined by DEXA using a Hologic QDR 4500 densitometer (Hologic Inc., Bedford, MA). DEXA was also used for the assessment of bone mass (i.e., bone mineral content (BMC; in grams) and bone mineral density (BMD; in grams per squared centimeters)) for various structural regions (i.e., whole body, lumbar spine, total hip, and femoral neck). Participants were scanned in light clothing while lying supine. DEXA scans were performed and analyzed using pediatric software. On the days of each test, the DEXA instrument was calibrated using the procedures provided by the manufacturer.

Physical activity. Physical activity level was measured using a 3-d physical activity recall (3DPAR) validated by Motl et al. (16). The 3DPAR provides a calculation of how many minutes a respondent expends in light (< 3 METs), moderate (3–6 METs), and hard (> 6 METs) activity as defined by the compendium of MET values published by Ainsworth et al. (1). The participants completed the 3DPAR on the day of their clinic visit. Visits were scheduled throughout the week, and participants were asked to recall their activity for the 3 d before their clinic visit. Participation in physical education was not included in the 3DPAR.

Cardiovascular fitness. Each subject performed a progressive ramp-type cycle ergometer exercise test to the limit of her exercise tolerance. Subjects were vigorously encouraged during the high-intensity phases of the exercise protocol. Gas exchange was measured breath-by-breath, and anaerobic (ventilatory/lactate) threshold and peak $\dot{V}O_2$

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(oxygen consumption) were calculated using a Sensor Medics metabolic system (6).

Blood sampling and analysis. Blood samples were drawn throughout the day using standard phlebotomy. Blood draws were performed on the same day as the exercise test and were always completed before any other clinical testing. Participants were instructed to eat a light meal before coming to the clinic. Blood samples were immediately spun at 3000 rpm, at 4°C for 20 min. The serum was aliquotted and stored at -80°C until analyzed.

Serum cytokines and growth factors. Circulating levels of serum cytokines were measured using commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kits manufactured by R&D Systems (Minneapolis, MN) and included *interleukin-6* (IL-6; intraassay CV 3.8–11.1%, interassay CV 9.9–16.5%, sensitivity 0.094 pg·mL^{-1}); *tumor necrosis factor alpha* (TNF-α; intraassay CV 5.3–8.8%, interassay CV 10.8–16.7%, sensitivity 0.12 pg·mL^{-1}); *interleukin-1 receptor antagonist* (IL-1ra; intraassay CV 3.1–6.2%, interassay CV 4.4–6.7%, sensitivity 22 pg·mL^{-1}).

Circulating levels of serum growth factors were analyzed using commercially available ELISA kits. The following assays were manufactured by diagnostic system laboratories (DSL, Webster, TX): *insulin growth factor–binding protein 3* (IGFBP-3; intraassay CV 7.3–9.6%, interassay CV 8.2–11.4%, sensitivity 0.04 ng·mL^{-1}); *C-reactive protein* (CRP; intraassay CV 1.7–3.9%, interassay CV 2.8–5.1%, sensitivity 1.6 ng·mL^{-1}); *Leptin* (intraassay CV 1.5–6.2%, interassay CV 3.3–5.3%, sensitivity 0.05 ng·mL^{-1}); and total circulating *insulin growth factor-1* (IGF-1; intraassay CV 4.5–7.1%, interassay CV 4.8–8.8%, sensitivity 0.03 ng·mL^{-1}). IGF-1 was extracted from IGF-I binding proteins using a modified acid–ethanol extraction method. Adiponectin was assessed using a kit manufactured by B-Bridge International, Inc. (Sunnyvale, CA), with an intraassay CV of 3.3%, an interassay CV of 7.4%, and sensitivity of 0.0234 ng·mL^{-1}.

Bone-turnover markers. Bone turnover was assessed by measuring the following circulating bone-turnover markers in serum using commercially available ELISA kits (QUIDEL inc, San Diego, CA). Measurement included *osteocalcin* (intraassay CV 4.8–9.8%, interassay CV 4.8–10%, sensitivity 0.45 ng·mL^{-1}); *bone-specific alkaline phosphatase* (BSAP; intraassay CV 5–8%, interassay CV 4–6%, sensitivity 0.7 U·L^{-1}); *C-terminal procollagen peptide* (CICP; intraassay CV 5–7%, interassay CV 5–7%, sensitivity 0.2 ng·mL^{-1}); and *deoxypyridinoline cross-links* (PYD; intraassay CV 9–12%, interassay CV 6–15%, sensitivity 0.4 M·L^{-1}).

Statistical analysis. The underlying distributions for basic characteristics, fitness level, and body composition are all normally distributed, and thus two-sample *t*-tests were applied to examine differences between the active and sedentary girls. For the physical activity variable, which was nonnormally distributed, the group comparison was

conducted using the Wilcoxon rank-sum test. Because the underlying distributions of growth and inflammatory mediators are not clearly understood and attempts to normalize the data by transformation were not successful, we decided to apply both parametric and nonparametric methods to study group differences; where the conclusions differed between the two tests, both results are presented and discussed. CRP was log$_{10}$-transformed because of the magnitude of the data. All data are presented with mean ± SD, and all tests were examined with 0.05 significance level. Owing to the exploratory nature of the work, each analysis was treated as a test of an individual hypothesis, and no corrections in the significance level were made for multiple comparisons.

As a *post hoc* analysis, all blood markers and bone density variables that were significantly different between active and sedentary adolescents were further examined with the analysis of covariance (ANCOVA) model to explore the activity effect while controlling for percent body fat.

RESULTS

Anthropometric, body composition, activity level, and fitness characteristics of the study participants are summarized in Table 1 and Figure 1. The total activity level of the active group was higher compared with the sedentary group, mainly due to time expended in vigorous activity. There were no significant differences between the groups in the time spent in light and/or moderate physical activity. As defined, the groups were matched for BMI and BMI percentiles. However, participants of the active group were significantly taller, had a significantly greater lean body mass (LBM), and had significantly lower percent fat mass. Fitness was significantly higher in the active group when presented as $\dot{V}O_2$ normalized to body weight (active 35.5 ± 5.2 vs sedentary 24.4 ± 4.1) as well as when $\dot{V}O_2$ was normalized to LBM (active 48.5 ± 7.1 vs sedentary 35.3 ± 6.0).

Bone mineral density measures and levels of circulating bone-turnover markers are summarized in Table 2 and Figure 2. Whole-body, spinal, hip, and femoral neck BMD *T* scores and spinal BMD *z*-scores were significantly greater in the active group compared with the sedentary group. Circulating levels of the bone-formation markers osteocalcin

TABLE 1. Anthropometric, body composition, and physical activity characteristics (mean ± SD) of the study participants.

	Sedentary	Active	*P*
Age (yr)	15.5 ± 0.69	15.5 ± 0.69	NS
Height (m)	1.62 ± 0.06	1.65 ± 0.06	0.016
Weight (kg)	56.2 ± 6.6	59.1 ± 6.4	NS
BMI (percentile)	58.6 ± 20.26	58.9 ± 19.81	NS
LBM (kg)	38.7 ± 36.2	43.2 ± 44.2	< 0.0001
Moderate activity (min·d^{-1})	138.1 ± 135.5	96.2 ± 78.4	NS
Vigorous activity (min·d^{-1})	23.2 ± 30.9	97.8 ± 68.2	< 0.0001

P values are from Wilcoxon rank-sum tests for moderate and vigorous activity and from two-sample *t*-tests for other measurements.
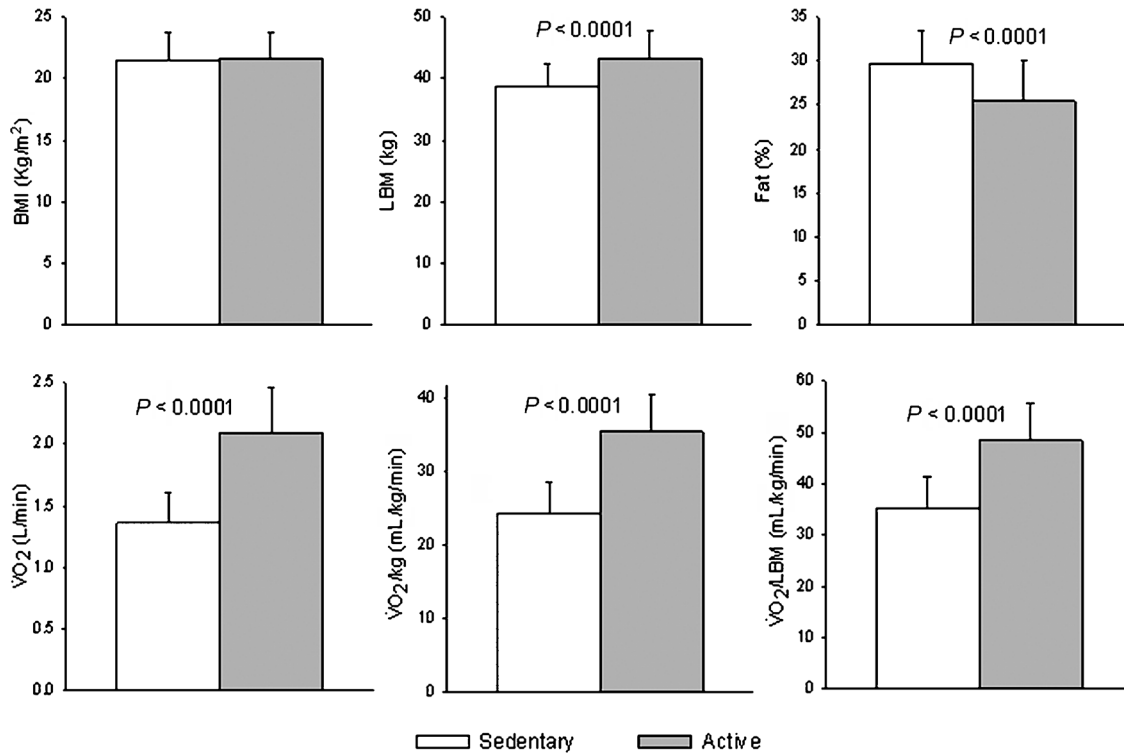
FIGURE 1—Comparison of body composition and fitness levels between active and sedentary adolescent girls. Groups were matched for BMI; active girls had significantly lower body fat and significantly higher lean body mass and fitness level. *P* values are from a two-sample *t*-test.

and BSAP were significantly higher in the active group compared with the sedentary group. There were no statistically significant differences in PYD level between the groups. CICP showed a significant difference using the Wilcoxon rank-sum test but a nonsignificant difference using a two-sample *t*-test. We found that the conflicting result was caused by one extreme outlier in the sedentary group, which produced a large variation. By removing this subject and her paired subject in the active group, the two-sample *t*-test did show a significant difference between these two groups ($P = 0.002$).

Circulating levels of the inflammatory mediators found to be significantly different between the two groups are shown in Figure 3. IL-6, IL-1ra, and TNF-α levels were significantly elevated in the sedentary group compared with the

active group. Log$_{10}$ (CRP) showed a significant group difference using a two-sample *t*-test ($P = 0.03$) but a nonsignificant difference using a Wilcoxon rank-sum test ($P = 0.08$). Inspection of the data did not reveal an explanation for these discrepant findings, so the findings related to CRP were considered inconclusive.

Circulating levels of growth factors, leptin, and adiponectin are summarized in Figures 3 and 4. Circulating IGFBP-3 level was significantly higher in the active group compared with the sedentary group. No significant differences were found in IGF-I levels between the groups. Leptin was significantly lower and adiponectin was significantly higher in the active group compared with the sedentary group.

The results from the *post hoc* ANCOVA showed that, after controlling for percent body fat, the activity effect remained significant for all of the bone and blood variables except for IL-6 ($P = 0.13$), L1ra ($P = 0.054$), and leptin ($P = 0.84$).

DISCUSSION

We used naturally occurring behavioral differences (i.e., participation in high school sports) within a group of normal-weight adolescent girls to begin to determine whether levels of physical activity *per se* were associated with circulating inflammatory mediators, growth factors, and anatomic indexes of body composition. The sedentary and physically active girls were matched for the most commonly used index of body composition (BMI) and, as

TABLE 2. Bone mineral density and circulating levels of bone-turnover markers of the study participants.

	Sedentary	Active	*P*
Spine BMD (*T* score)	−0.91 ± 0.75	−0.42 ± 0.86	0.010
Spine BMD (*z*-score)	−0.41 ± 0.85	0.04 ± 0.88	0.026
Hip BMD (T score)	−0.24 ± 0.77	0.68 ± 1.09	< 0.0001
Femoral neck BMD (*T* score)	−0.001 ± 0.89	0.750 ± 1.08	0.0016
CICP (ng·mL^{-1})[a]	119.9 ± 49.2	161.2 ± 60.6	< 0.005
PYD (U·L^{-1})	2.0 ± 0.36	1.9 ± 0.68	NS

Data presented as means ± SD.
P values are from two-sample *t*-tests and Wilcoxon rank-sum tests for C-terminal procollagen peptide (CICP) and deoxypyridinoline cross-links (PYD) and from two-sample *t*-tests for other measurements.
[a] $N = 36$ by dropping one matched pair of subjects, with extreme values in one of the subjects.
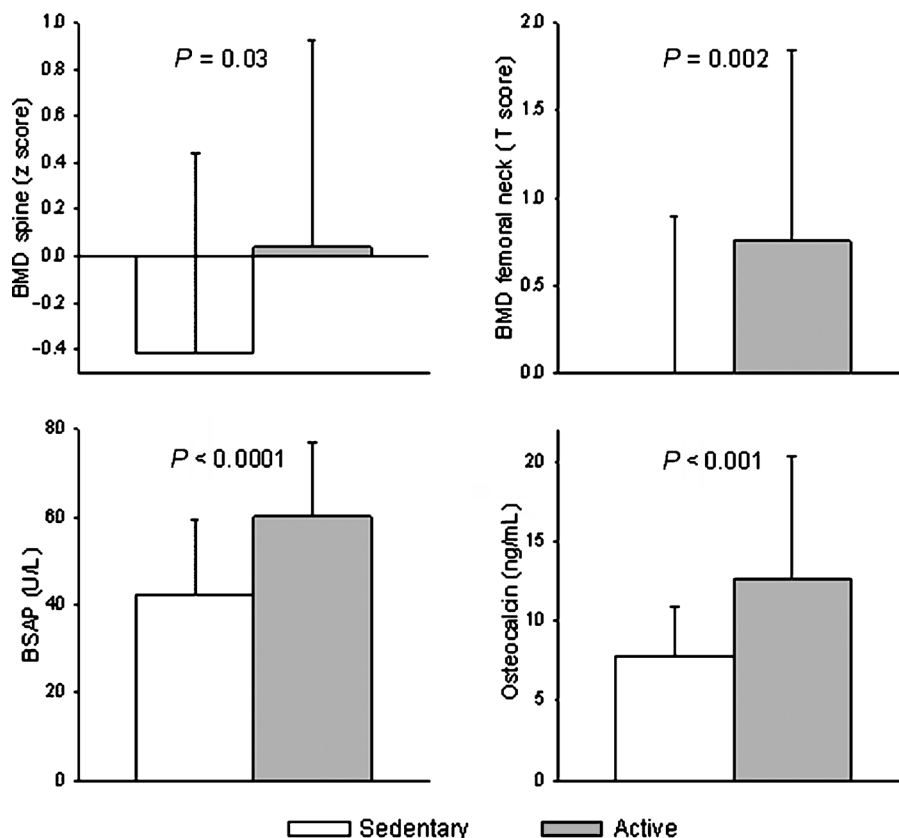
FIGURE 2—Comparison of bone mineral density and bone-formation markers between active and sedentary adolescent girls. BMD and bone-formation markers were significantly higher in the active girls. *P* values are from a two-sample *t*-test for BMD and are from a two-sample *t*-test and a Wilcoxon rank-sum test for bone-formation markers.

expected from our recruitment/selection strategy, differed substantially in physical activity profiles (Table 1). We found profound differences in circulating inflammatory mediators (Fig. 3), growth factors (Fig. 3), fitness (Fig. 1), and bone mineralization (Fig. 2) between the two groups. Moreover, despite their having the same mean BMI, small but significant differences in the distribution of lean and fat tissues were found between the two groups (Fig. 1). Thus, these data demonstrate that levels of physical activity are associated with inflammatory and growth mediators in adolescent girls and are related to body composition in a way that is not detectable by BMI alone.

We found lower values of the immune/stress mediators in the physically active girls (Fig. 3). It is known that brief bouts of exercise stimulate inflammatory/stress mediators (in particular, IL-6), but the long-term effect of exercise training in both children and adults seems to be an attenuation of basal levels of stress/immune activation (21,24). Thus, the lower levels of these factors in the fit children may reflect their increased levels of regular physical activity.

It is also known that in obese (usually physically inactive) adults and children inflammatory mediators are elevated, probably owing to the production of these factors by fat tissue (19,29). The participants in the sedentary group

were not obese. They did, however, have a small but significantly higher percent fat mass (Fig. 1). Thus, an alternative explanation might be that this relatively small difference could lead to higher levels of circulating stress/ inflammatory mediators in the sedentary girls. To determine whether or not circulating inflammatory mediators were *low* in the physically active group or, alternatively, *high* in the sedentary group, normal values for inflammatory mediators in childhood and adolescence would be needed. Unfortunately, reference values are not yet well developed. Sample sizes are often small, and factors such as gender, ethnicity, level of habitual physical activity, and adiposity are not taken into consideration. From the limited available data in previous studies of adolescent females (18,23), it does seem that the values we found in the physically active group were, indeed, lower suggesting that the predominant effect on inflammatory mediators was due to relatively greater levels of physical activity and not due to the small increase in percent body fat found in the sedentary girls.

Similarly, previous studies indicate that in adults, as levels of habitual physical activity and fitness increase, CRP levels decrease (12). However, in some studies, these relationships were no longer significant after adjustment for possible confounders like BMI (28). Far less is known about the relationship between CRP, body composition, and
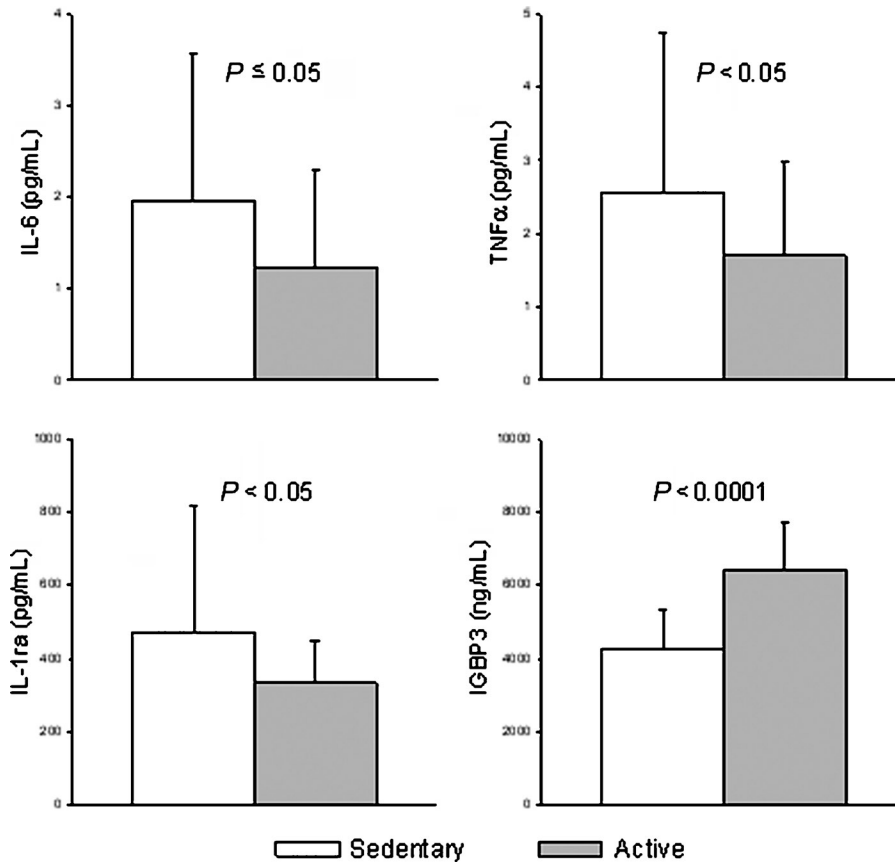
FIGURE 3—Comparison of circulating inflammatory mediators and growth factors between active and sedentary adolescent girls. Markers of inflammation were significantly higher and IGFBP-3 significantly lower in the sedentary girls. All P values are from a two-sample t-test and a Wilcoxon rank-sum test.

levels of physical activity in children, and the majority of the studies have been done in obese children. Isasi et al. (11) noted an inverse relationship between CRP and fitness in boys, but not in girls. Our findings related to CRP were inconclusive, as our two statistical methods yielded conflicting results.

Higher physical activity and fitness were associated with higher circulating bone-formation markers, as well as with greater BMD (Fig. 2). These results are consistent with previous cross-sectional and prospective studies demonstrating that increased physical activity and exercise training lead to a significant increase in circulating bone-formation markers and bone mineral density in young females (9,22,25). The link between physical activity and bone formation during adolescence is particularly salient as this is a developmental stage known to be particularly important to
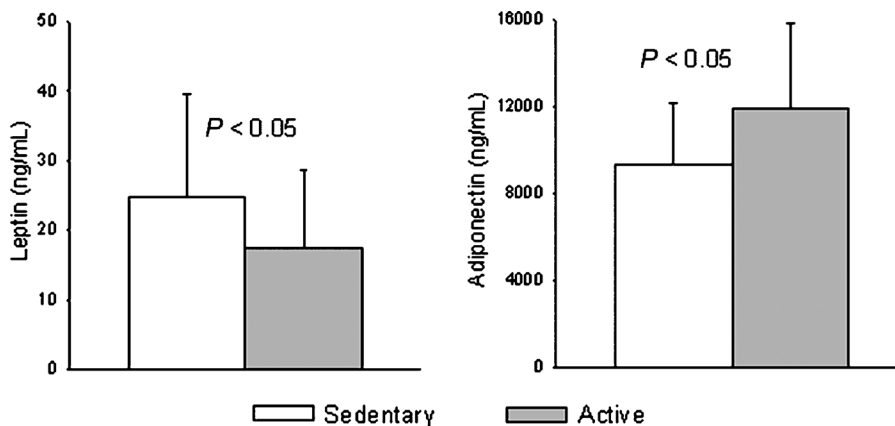

FIGURE 4—Comparison of circulating leptin and adiponectin levels between active and sedentary adolescent girls. Leptin was significantly higher and adiponectin was significantly lower in the sedentary girls. All P values are from a two-sample t-test and a Wilcoxon rank-sum test.

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a critical variable: peak bone mass. When we compared our values for bone-formation markers with established control values (26), we found, in general, that the levels were low in the sedentary group. These observations highlight the deleterious effect of a sedentary lifestyle during adolescence in girls.

Lean body mass was also greater in the physically active girls. In previous cross-sectional studies, LBM and muscle mass have been correlated with circulating levels of IGF-I in adolescent girls (8). In the present study, we did not find a difference in IGF-I between the two groups despite the difference in LBM. However, IGFBP-3 was higher in the physically active girls. IGFBP-3 is the predominant circulating binding protein of IGF-I, and there are data suggesting that IGFBP-3 may, under certain circumstances, act to enhance the biological effects of IGF-I (13). Exercise training can increase circulating levels of IGFBP-3 (14). Finally, a comparison of the IGFBP-3 levels in the present study to those previously measured in adolescent girls suggests (26) that these levels were normal in the sedentary group but higher in the physically active participants.

Adiponectin is a fairly recently discovered adipocytokine and is unique in that its circulating levels are inversely related to fat mass in both children and adults (19,29). Some investigators have suggested that higher levels of adiponectin may protect against adverse consequences of obesity such as insulin resistance (30). In our study, adiponectin was significantly higher in the physically active girls (Fig. 4). The difference in fat mass was significant but relatively small between the two groups, and we wondered whether or not the difference in adiponectin could be explained by the difference in fat mass. We compared expected values of adiponectin derived from fat mass from a previous study in our laboratory (19) and calculated that the predicted adiponectin would be $10,900 \text{ ng·mL}^{-1}$ in the physically active girls and $10,540 \text{ ng·mL}^{-1}$ in the sedentary girls. Thus, the physically active girls had higher circulating levels of adiponectin than predicted, and the sedentary girls had lower circulating levels of adiponectin than predicted.

Significant differences in the adipocyte-derived hormone leptin were also found between the physically active and sedentary girls (Fig. 4). In the case of leptin, the values in the normal-weight sedentary girls were much higher than references values (15.6 ng·mL^{-1} from Hackney et al. (9)). It is not clear to what extent levels of physical activity *per se* influence adiponectin (17) or leptin, but our results support the idea that there may be effects of physical activity on adiponectin and leptin that are independent of fat mass.

In *post hoc* ANCOVA, we found that most of the significant differences between the sedentary and active adolescents remained significant even after controlling for percent body fat. The exceptions were IL-6 and leptin, which were no longer significantly related to activity after controlling for percent body fat, and L1ra, which became marginally significant after controlling for percent body fat. We note that this finding suggests that even a small amount of fat can significantly alter the immune and endocrine systems, which can lead to significant downstream events.

In summary, normal-weight adolescent girls who participate in high school sports have markedly different profiles of inflammatory mediators, markers of bone formation, and growth factors, as well as anatomic correlates of bone mineral density and lean body mass, than do normal-weight sedentary girls. A novel observation of this study was that both a sedentary and a physically active behavior seemed to have some independent effects on each of these factors. Moreover, the differences that we observed between the two groups resulted from lifestyle choices within each participant's natural environment (i.e., the choice to participate in high school sports), rather than from an imposed experimental paradigm. Because there is mounting evidence supporting the idea that a variety of adult diseases originate from lifestyle patterns during childhood (4), our data support the notion that behavioral differences in childhood and adolescence influence mediators known to be mechanistically involved in the regulation of body composition and bone mineral density during this critical stage of human development.

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