Endocrinology & Metabolic Syndrome
ISSN: 2161-1017

Linares-Segovia et al., Endocrinol Metab Synd 2013, S2
DOI: 10.4172/2161-1017.S2-003

Research Article Open Access

Effect of an Exercise Program, on Hemodynamic, Metabolic and Inflammatory Markers in Obese Mexican Adolescents

Benigno Linares-Segovia[1,2]*, Juan Manuel Guízar-Mendoza[3], Norma Amador-Licona[4], Gloria Barbosa-Sabanero[1] and Juan Manuel Malacara[1]

[1]*Department of Medicine and Nutrition, Division of Health Sciences, Campus Leon, University of Guanajuato, Guanajuato, México*
[2]*PEMEX Regional Hospital Salamanca, Salamanca, Guanajuato, México*
[3]*University de LaSalle, Department of Research, Leon, Mexico*
[4]*Instituto Mexicano del Seguro Social, UMAE 1, Leon, Mexico*

Abstract

Background: Obesity prevalence has increased in Mexican adolescents. This disease is associated with a chronic inflammatory response, which has been proposed to have an important role in cardiovascular disease. The aim of this study was to evaluate the short term effect of a moderate-intensity physical activity program on hemodynamic, metabolic, and inflammatory markers in obese adolescents.

Findings: We performed a longitudinal study in 43 healthy obese adolescents (26 female and 17 male). The study was conducted at the Mexican Institute of Social Security in Leon, Mexico. Subjects were submitted to aerobic exercise training during 90 minutes for 16 weeks, 5 days per week. Before and after the intervention program, hemodynamic, metabolic and inflammatory parameters were measured. Body weight was reduced by 4%. Blood pressure, insulin, insulin resistance, C reactive protein, interleukine 6, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 serum levels significantly decreased independently of gender while adiponectin levels increased. In the multiple regression analysis, the increase in adiponectin levels and the decrease in body mass index were related to systolic blood pressure levels (R^2= 0.26; p=0.001), while final maximum O_2 consumption rate and final systolic blood pressure levels were related to decrease in C reactive protein levels (R^2= 0.79; p=0.0001).

Conclusions: A moderate-intensive exercise for 90 minutes a day at short term significantly diminished adiposity, hemodynamic, metabolic, and inflammatory markers in obese adolescents.

Keywords: Physical activity; Body fat; Cytokines; Adhesion molecules

Abbreviations: BMI: Body Mass Index; CRP: C Reactive Protein; (ICAM)-1: Intercellular Adhesion Molecule- 1; (IL1): Interleukine 1; (IL6): Interleukine 6; (METs): Metabolic Equivalents; (TNFα): Tumor Necrosis Factor-alpha; (VCAM)-1: Vascular Cell Adhesion Molecule

Introduction

Obesity is a prevalent metabolic disorder in large parts of the developing world. In 2004, the age adjusted rates of obesity and overweight reported in the third National Health and Examination Survey (NHANES III) was 16.0% for children [1]. In Mexico, the National Health and Nutrition Survey 2006 showed a 23.3% and 9.2% for overweight and obesity prevalence respectively in 12-19 years old [2]. This represents a relative increased of 7.8% and 33.3% in overweight and obesity respectively when compared with the National Nutrition Survey 1999 [3]. Obesity is associated with a chronic inflammatory response [4], which has been proposed to have an important role in cardiovascular disease. Furthermore, the Hispanics are one of the populations that are especially prone to develop obesity and metabolic complications [5].

A recent study found that controlled aerobic exercise program, without weight loss, reduced hepatic and visceral fat accumulation, and decreased insulin resistance in obese adolescents [6]. However, there is scarce information evaluating the short term effects of a moderate intensity physical activity program on hemodynamic, metabolic and proinflammatory markers in obese Mexican adolescents.

Materials and Methods

We performed a longitudinal study in 43 asymptomatic volunteers (26 female and 17 male) obese adolescents (BMI ≥ 95^{th} percentile according to the growth charts from the Centers for Disease Control and Prevention [7]). The sample size was estimated before the study. Forty adolescents would achieve an 80% power to detect a relative 25% decrease in C reactive protein (CRP) levels after the exercise maneuver considering a known mean and standard deviation of 6.0 ± 2.5 mg/L according to a α level of 0.05 using a simple-sided *t*-test [8].

Adolescents were recruited on the basis of age (12-15 years) from a public high-school. All of them were healthy non-smokers, without chronic illnesses, and none had participated in athletics or regular exercise before this study. The local ethical committee approved the study, and informed consent was obtained from all participants and at least one parent.

All subjects were submitted to aerobic exercise training during 90 minutes for 16 weeks, 5 days per week according to the European Youth Heart Study recommendations [9]. The exercise program used in this study was specifically designed by investigators (L.B. and G.J.), and it consisted of the following: 1) Warm up (10 minutes): Sports-specific callisthenics such as push-ups and sit-ups; 2) Moderate effort (30 minutes): The participants performed competition skills, including take-downs, escapes, running etc.; 3) Recreational activities

***Corresponding author:** Benigno Linares Segovia, Department of Medicine and Nutrition, University of Guanajuato, Guanajuato, México; Tel: +52 477 7145859 ext. 4627; E-mail: blinares70@yahoo.com.mx

Received February 08, 2013; **Accepted** February 25, 2013; **Published** February 28, 2013

Citation: Linares-Segovia B, Guízar-Mendoza JM, Amador-Licona N, Barbosa-Sabanero G, Malacara JM (2013) Effect of an Exercise Program, on Hemodynamic, Metabolic and Inflammatory Markers in Obese Mexican Adolescents. Endocrinol Metab Synd S2: 003. doi:10.4172/2161-1017.S2-003

(30 minutes): swimming, basket-ball, volley-ball, and foot-ball; 4) Flexibility (15 minutes) and 5) Stretching (5 minutes).

Physical activity was assessed by the International Physical Activity Questionnaire [10]. It is expressed as metabolic equivalents (METs) which represent the ratio of the energy expended during a specific activity to the resting metabolic rate. METs were assigned to each physical activity according to the Compendium of Physical Activities [11], as values of 2.5, 4.0, and 6.0 for low, moderate, and intense activity respectively. Overall fitness was assessed according to the 12-min walk-run test (12mWRt) [12], to estimate the maximal oxygen intake (VO_{2max}).

After 10 days of exercise according to the initial physical fitness assessment, all obese children were capable to perform a 90 min training session at 60-70% of maximal heart rate. Participation in the exercise training program averaged 88.4% of scheduled visits. Blood pressure was evaluated using a mercury sphygmomanometer with a cuff covering two thirds of the right arm. After 15 minutes in rest, two readings were made within a 5 minutes interval, and the average was registered. Body fat was measured by using a body fat analyzer (TANITA model BF682).

All adolescents were instructed to go on a weight-reduction diet by a standard appointment at the nutrition department. Dietary assessment was carried out by one experienced qualified dietitian to minimize inter-individual bias among different professionals. Food quantities were estimated using Nutrikcal a nutritional software package developed by Ogali (Mexico, D.F.)

Venous blood was obtained after overnight fasting to determine lipid profile, glucose, insulin, leptin, adiponectin, interleukine-1 (IL1), IL6, TNFα, CRP, ICAM-1, and vascular cell adhesion molecule-1 (VCAM-1) levels. All measurements were performed at baseline and after the intervention program.

Blood glucose concentration was measured using the glucose oxidase method (Ortho Clinical Diagnostics; Johnson-Johnson). The intra-assay coefficient of variation (CV), and inter-assay CV were 1.9% and 7.5% respectively.

Serum insulin was measured with a solid phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA). The intra-assay CV was 5.2%, the inter-assay CV was 7.3%, and the sensitivity limit was 1.2 µIU/mL.

Serum leptin was measured by immunoradiometric assay (Diagnostic Systems Laboratories, Inc., Webster, Texas). The intra assay CV was 3.7%, the inter assay CV was 5.2%, and the sensitivity limit was 0.10 ng/ml.

Adiponectin levels were measured by radioimmunoassay (Linco Research, St Charles, MO). The intra assay CV was 3.8%, the inter assay CV was 8.4%, and the sensitivity limit was 1.0 ng/ml.

IL1, IL6, PCR TNFα, VCAM-1, and ICAM-1 levels were measured by ELISA (Biosource International, California, USA).

Statistical Considerations

Results are expressed as mean ± SD or as median (95% CI) according to variables distribution. Differences between genders were assessed by χ^2 for proportions. The Mann-Whitney U test or Student´s *t*-test were used for continue variables displaying non-normal or normal distribution respectively. For comparison of continue variables before and after the exercise program we performed ANOVA test and Tukey honest significant difference as post-hoc test. In addition, we performed ANCOVA test considering gender as covariable. Considering that systolic blood pressure has been a better predictor risk of cardiovascular events than diastolic blood pressure levels [13], and that CRP levels have been considered as a useful inflammatory marker in clinical practice [14]; forward stepwise multiple regression analysis was used to study the clinic and biochemical predictors of change in these variables. We considered F value to enter and F value to remove set to p<0.05 and p<0.10, respectively. All data were analyzed using the STATISTICS software version 6.0 (Statsoft Inc. Tulsa OK).

Results

We included 43 adolescents, 5(11.6%) withdrew the study during the first month of follow-up. At baseline, female adolescents showed lower physical activity and VO_{2max}, while BMI, diastolic blood pressure, and leptin levels were higher than male adolescents (Table 1).

Median total energy intake significantly decreased after the intervention program (2077 ± 562 vs. 1639 ± 535 Kcal; p= 0.03) without difference in macronutrients distribution (51.8 ± 18.7% of carbohydrates, 14.0 ± 6.5% of proteins, and 31.0 ± 13.1% of fat) by gender or by the effect of the intervention program.

Following the program physical activity, run distance in 12 minutes and VO_{2max} significantly increased, while body weight only reduced 4%. BMI, body fat and blood pressure levels also decreased in all the group after the intervention program, and the statistical significance persisted independently of gender (Table 2).

Glucose, triglycerides, VLDL-cholesterol, insulin, insulin resistance, CRP, IL-1, IL-6, ICAM-1, and VCAM-1 serum levels also significantly decreased after the intervention program; however,

Variable	Female n= 24	Male n= 14	*p*
Age (years)	13.2 ± 0.7	12.8 ± 0.7	0.16
Weight (kg)	80.5 ± 11.7	74.9 ± 13.6	0.19
Height (m)	1.58 ± 0.06	1.58 ± .09	0.93
BMI (kg/m²)	32.0 ± 3.7	29.6 ± 3.3	0.04
SBP (mmHg)	127.5 ± 8.5	125.3 ± 7.7	0.44
DBP (mmHg)	86.6 ± 7.3	82.1 ± 5.0	0.04
Physical activity (mets/week)	1652 ± 254	1918 ± 290	0.005
Run distance (m/12min)	1313.6 ± 176.5	1456.1 ± 166.0	0.01
VO_{2max} (mL/kg/min)	16.3 ± 3.7	19.3 ± 3.5	0.01
Glucose (mmol/L)	5.0 ± 0.4	5.4 ± 0.4	0.02
Leptin (ng/mL)	24.3 (17.4-32.3)	19.9 (15.2-22.1)	0.08
Adiponectin (ng/mL)	12.7 (4.9-22.7)	6.3 (2.5-12.9)	0.16

Table 1: Baseline clinical and biochemical characteristics of obese adolescents according to gender.

Variable	Baseline n= 38	After exercise n= 38	*p*	*p**
Weight (kg)	78.4 ± 12.5	75.2 ± 13.6	<0.0001	0.004
BMI (kg/m²)	31.1 ± 3.6	29.5 ± 3.9	<0.0001	<0.0001
Body fat (%)	37.8 ± 6.0	35.5 ± 6.2	<0.0001	<0.0001
HR (beats/min)	97.9 ± 9.6	88.6 ± 11.3	0.0003	0.08
SBP (mmHg)	126.7 ± 8.2	117.3 ± 10.3	<0.0001	0.003
DBP(mmHg)	85.0 ± 6.8	67.6 ± 6.4	<0.0001	<0.0001
Physical activity (mets/week)	1750 ± 294	3445 ± 640	<0.0001	<0.0001
Run distance (m/12min)	1366 ± 184	1708 ± 287	<0.0001	<0.0001
VO_{2max} (mL/kg/min)	17.4 ± 3.9	24.7 ± 6.1	<0.0001	0.0002

*p value adjusted for gender

Table 2: Anthropometric, hemodynamic and overall fitness change after physical training program in all obese adolescents.

glucose and IL-1 levels lost significance after adjusting for gender. An increase in adiponectin and LDL-cholesterol levels was observed but LDL-cholesterol levels were dependent of gender (Table 3).

Eight (21.0%) adolescents did not show weight reduction during the program; however physical activity and VO_{2max} change, as well as hemodynamic and inflammatory markers were similar with the rest of the group (data not showed).

In the multiple regression analysis, we found that change in adiponectin levels and BMI were related to change in SBP levels (Table 4).

Final VO_{2max} (r= 63; p=0.004), change in BMI (r= 0.51; p=0.06), change in BF(r= 0.72; p=0.003), and final SBP (r= 0.47; p=0.07) were related to decrease in CRP levels. In the multiple regression analysis, only final VO_{2max} (β=0.63; p=0.0008) and final SBP levels (β=0.54; P=0.002) persisted in the model (R^2= 0.79; p=0.0001).

All the results of the multiple regression analysis were independent of change in energy intake evaluated by 24-h recall method.

Discussion

Hispanic adolescents seems to have a high risk of being obese [15], and considering that it is necessary to reduce the risk of cardiovascular disease in childhood, we report the effect of physical training program on hemodynamic, metabolic and inflammatory markers in obese adolescents. In our study, adiposity decreased in both genders and change in BMI was significantly related to diminish in systolic blood pressure. This can be explained by changes in hormonal production according to adipocytes size. Growth of adipose tissue mass involves both hypertrophia and hyperplasia of adipocytes. Fat cell size has been related to different adipokine production of adipose tissue. Long-term-steady-state weight reduction in obese subjects resulted in

Variable	Baseline n= 38	After exercise n= 38	*p*	p*
Glucose (mmol/L)	5.1 ± 0.5	5.1 ± 0.5	0.02	0.08
Triglycerides (mmol/L)	4.0 ± 1.4	2.8 ± 1.0	<0.0001	0.001
Total-Chol (mmol/L)	3.9 ± 0.6	3.9 ± 0.7	0.38	0.39
HDL-Chol (mmol/L)	0.9 ± 0.2	0.9 ± 0.2	0.47	0.49
LDL-Chol (mmol/L)	2.1 ± 0.5	2.3 ± 0.6	0.002	0.07
VLDL-Chol (mmol/L)	0.8 ± 0.2	0.5 ± 0.2	<0.0001	0.001
Insulin (pmol/L)	21.5 (17.9 - 27.9)	12.9 (7.8 -17.2)	0.001	0.01
HOMA-IR	0.65 (0.51 - 0.92)	0.38 (0.24 - 0.59)	0.002	0.02
Leptin (ng/mL)	21.0 (18.2 - 22.8)	16.5 (12.9 -20.1)	<0.0001	0.003
Adiponectin (ng/mL)	10.5 (4.7 - 13.5)	19.0 (12.9 - 32.7)	<0.0001	0.0006
CRP (mg/L)	7.4 (3.1 -10.1)	3.3 (2.1 – 4.4)	0.009	0.01
TNFα (pg/mL)	6.8 (5.7 - 11.0)	5.1 (4.2 - 5.9)	<0.0001	0.005
IL-1 (ng/mL)	0.07 (0.03 - 0.09)	0.05 (0.03 - 0.05)	0.004	0.05
IL-6 (pg/mL)	3.0 (2.2 - 3.4)	1.5 (1.1 - 1.8)	<0.0001	0.0007
ICAM-1(ng/mL)	598.7 ± 115.7	452.4 ± 130.0	<0.0001	<0.0001
VCAM-1 (ng/mL)	2728 (1919 - 3044)	1482 (1143 -1924)	0.0001	0.0005

*p value adjusted for gender

Table 3: Biochemical variables before and after physical training program in obese adolescents.

Variable	β	p
Change in adiponectin levels	-0.45	0.0002
Change in BMI	-0.30	0.04

R^2= 0.26, intercept -8.07; Standard Error 2.68; p= 0.001 for the model

Table 4: Multiple regression analysis for factors associated to change in SBP levels.

marked decreases in fat cell volume, leptin secretion, and serum leptin concentrations compared with control subjects, despite similar percent body fat [16]. Furthermore, exercise reduces adipocyte hypertrophy and up-regulation of PPAR(gamma) in rats with metabolic syndrome [17], which could explain at least in part the reduction in inflammatory markers, leptin, and the increase in adiponectin levels in our study.

The decrease in ICAM-1 levels after the intervention program independently of gender is a relevant end point. ICAM-1 determine a variety of lymphocyte functions but, perhaps more importantly in the context of cardiovascular disease, it also plays a pivotal role in the "trafficking" of leucocytes through tissues, interacting with $beta_2$ integrins on white cells [18]. Even more, increased amounts of soluble ICAM-1 and E selectin have been found in patients with atherosclerosis [19].

Adiponectin levels were negatively associated with SBP levels in multiple regression analysis, this supports the hypothesis that adiponectin reduces the inflammation status of vasculature, and in turn blood pressure levels [20]. It has been reported that adiponectin dose dependently produces inhibition of the expression of adhesion molecules VCAM-1, ICAM-1 and E-selectin, reducing monocyte´s phagocytic activity and decreasing the accumulation of modified lipoproteins in the vascular wall [21]. Weight loss is a potent inducer of adiponectin levels; however they are affected by many other factors including gender, age, and lifestyle [22]. So, the increase in physical activity even in those children without weight loss during follow up could explain the increase in adiponectin levels.

Other inflammatory and metabolic markers also improved after the intervention program. According with our results, Ziccardi et al. [23], in obese women found reductions in IL6, VCAM-1 and ICAM-1 following weight loss of 10 kg; however, we demonstrated reductions in these and other parameters after only a 3.2 kg of weight reduction, and results in the multiple regression analysis were independent of change in energy intake.

Evidence exists that leptin levels are reduced in physical active individuals independent of BMI [24], and that leptin in associated with CRP levels [25]. Consequently, physical activity could decrease IL-6 and TNF-alpha levels and, ultimately, CRP production, by reducing obesity and leptin and increasing adiponectin and insulin sensitivity [26]. Even more, some of these effects may be mediated by modification of cytokine production from other sites, besides adipose tissue, such as skeletal muscles.

How exercise training reduces inflammation and suppresses markers of inflammation is not well defined. Dufaux et al. detected that the difference in CRP concentrations depended on the type of sports performed, and the proportion of aerobic endurance activities seems to be related to the degree of CRP reduction [27]. Milani et al. analyzed 12 the effects of a phase II cardiac rehabilitation program on plasma levels of hs-CRP; they reported a significant 36% reduction after the 3-month intervention independently of weight reduction [28]. This finding implies that adipose tissue is not the only source of proinflammatory cytokines.

Obesity and sedentary physical activity are important cardiovascular risk factors [29]. The American Heart Association concluded that primary prevention is the key to decreasing obesity and limiting its societal impact, particularly since the prevalence of obesity is increasing in children and adolescents [30]. In our study, all obese adolescents showed low physical activity and VO2max levels according to charts for Spanish children [29]. However; they improved their exercise capacity and aerobic energy metabolism, which have been associated with reduction in local inflammatory activation.

The main strengths of this study were the high performance of a training program, according to the proposed by the European Youth Heart Study [9], and the evaluation of hemodynamic, metabolic, anthropometric and inflammatory markers together, considering that clustering of cardiovascular disease risk factors has recently proved a better measure of cardiovascular health in children than single risk factors [31]. However a limitation of this study is the small sample size and that we did not have control group.

In conclusion, a 16 weeks programme involving 90 minutes of aerobic exercise 5 days per week significantly diminished adiposity, hemodynamic, metabolic, and inflammatory markers in Hispanic obese adolescents who are specially prone to develop metabolic and hemodynamic complications.

Acknowledgments and Funding

This study was supported by FOFOI and CONCYTEG grants (IMSS FP-2005/116 and GTO-2005-18792) respectively.

References

1. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, et al. (2004) Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. JAMA 291: 2847-2850.
2. Olaiz-Fernández, Rivera-Dommarco J, Shamah-Levy T, Rojas R, Villalpando-Hernández S, et al. (2006) Encuesta Nacional de Nutrición 2006. Cuernavaca, Morelos, México: Instituto Nacional de Salud Pública.
3. Rivera DJ, Shamah LT, Villalpando HS, González de Cossío T, Hernández PB, et al. (1999) Encuesta Nacional de Nutrición 1999. Estado de niños y mujeres en México. Cuernavaca, Morelos, México: Instituto Nacional de Salud Pública.
4. Wellen KE, Hotamisligil GS (2005) Inflammation, stress, and diabetes. J Clin Invest 115: 1111-1119.
5. Mirza NM, Kadow K, Palmer M, Solano H, Rosche C, et al. (2004) Prevalence of overweight among inner city Hispanic-American children and adolescents. Obes Res 12: 1298-1310.
6. van der Heijden GJ, Wang ZJ, Chu ZD, Sauer PJ, Haymond MW, et al. (2010) A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. Obesity (Silver Spring) 18: 384-390.
7. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, et al. (2000) CDC growth charts: United States. Adv Data : 1-27.
8. Browner WS, Black D, Newman T, Hulley SB (1993) Estimación del tamaño de la muestra y de la potencia In: Hulley SB, Cummings SR, editors. Diseño de la investigación clínica. Barcelona, España: DOYMA. 15
9. Andersen LB, Harro M, Sardinha LB, Froberg K, Ekelund U, et al. (2006) Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). Lancet 368: 299-304.
10. Booth M (2000) Assessment of physical activity: an international perspective. Res Q Exerc Sport 71: S114-120.
11. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, et al. (1993) Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 25: 71-80.
12. Cooper KH (1968) A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. JAMA 203: 201-204.
13. Strandberg TE, Pitkala K (2003) What is the most important component of blood pressure: systolic, diastolic or pulse pressure? Curr Opin Nephrol Hypertens 12: 293-297.
14. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, et al. (2003) Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107: 499-511.
15. Patrick K, Norman GJ, Calfas KJ, Sallis JF, Zabinski MF, et al. (2004) Diet, physical activity, and sedentary behaviors as risk factors for overweight in adolescence. Arch Pediatr Adolesc Med 158: 385-390.
16. Löfgren P, Andersson I, Adolfsson B, Leijonhufvud BM, Hertel K, et al. (2005) Long-term prospective and controlled studies demonstrate adipose tissue hypercellularity and relative leptin deficiency in the postobese state. J Clin Endocrinol Metab 90: 6207-6213.
17. Zhu Z, Zhang L, Wang L (2005) Exercise reduces adipocyte hypertrophy and up-regulation expression of Peroxisome proliferators activated receptor (gamma) in rats with metabolic syndrome. Arterioscler Thromb Vasc Biol 25:e103.
18. Adams DH, Shaw S (1994) Leucocyte-endothelial interactions and regulation of leucocyte migration. Lancet 343: 831-836.
19. Blann AD, McCollum CN (1994) Circulating endothelial cell/leukocyte adhesion molecules in atherosclerosis. Thromb Haemost 72: 151-154.
20. Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, et al. (2004) Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. Biochem Biophys Res Commun 314: 415-419.
21. Kougias P, Chai H, Lin PH, Yao Q, Lumsden AB, et al. (2005) Effects of adipocyte-derived cytokines on endothelial functions: implication of vascular disease. J Surg Res 126: 121-129.
22. Tilg H, Moschen AR (2006) Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 6: 772-783.
23. Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, et al. (2002) Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation 105: 804-809.
24. Tomaszewski M, Charchar FJ, Przybycin M, Crawford L, Wallace AM, et al. (2003) Strikingly low circulating CRP concentrations in ultramarathon runners independent of markers of adiposity: how low can you go? Arterioscler Thromb Vasc Biol 23: 1640-1644.
25. Shamsuzzaman AS, Winnicki M, Wolk R, Svatikova A, Phillips BG, et al. (2004) Independent association between plasma leptin and C-reactive protein in healthy humans. Circulation 109: 2181-2185.
26. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, et al. (1998) Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. JAMA 279: 669-674.
27. Dufaux B, Order U, Geyer H, Hollmann W (1984) C-reactive protein serum concentrations in well-trained athletes. Int J Sports Med 5: 102-106.
28. Milani RV, Lavie CJ, Mehra MR (2004) Reduction in C-reactive protein through cardiac rehabilitation and exercise training. J Am Coll Cardiol 43: 1056-1061.
29. Ortega FB, Ruiz JR, Castillo MJ, Moreno LA, González-Gross M, et al. (2005) [Low level of physical fitness in Spanish adolescents. Relevance for future cardiovascular health (AVENA study)]. Rev Esp Cardiol 58: 898-909.
30. Eckel RH, Krauss RM (1998) American Heart Association call to action: obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. Circulation 97: 2099-2100.
31. Andersen LB, Wedderkopp N, Hansen HS, Cooper AR, Froberg K (2003) Biological cardiovascular risk factors cluster in Danish children and adolescents: the European Youth Heart Study. Prev Med 37: 363-367.

This article was originally published in a special issue, **Obesity consequences & Weight Management** handled by Editor. Dr. Weihong Pan, Pennington Biomedical Research Center, USA