Original Article

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Association between Cardiovascular Fitness and Inflammatory Markers in Boys Aged 11-14 Years

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Abstract

Objective: It is reported that some inflammatory markers are predictive factors for atherosclerosis in childhood and adolescence and cardiovascular disease in adulthood. We investigated whether markers of inflammation including: cytokine [Interleukin-6 (IL-6)], acute-phase reactant [C-reactive protein (CRP)], white blood cell (WBC) count and its subgroups are associated with maximal oxygen consumption (VO_{2max}) in overweight and normal children.

Methods: Subjects were 26 boys aged 11-14 years included in two groups of overweight (n=10) and normal weight (n=16) children. VO_{2max} was measured employing an incremental graded exercise test. IL-6 and CRP levels as well as WBC count were measured. Multivariable regression was employed to evaluate whether inflammatory markers were associated with VO_{2max}.

Findings: Mean VO_{2max} for all subjects (n=26) was 36.35±10.42 ml/kg/min. This rate was lesser for overweight subjects (25.77±5.04) than in normal weight children (41.54±5.96). Log IL-6, log CRP, and WBC count were correlated with VO_{2max}. Also subgroups of WBC including Leukocytes, Lymphocyte, Neutrophils, Monocytes and Eosinophils associated with VO_{2max}.

Conclusion: IL-6, CRP and WBCs were inversely associated with aerobic or cardiorespiratory fitness levels measured by VO_{2max} in children. This was independent of BMI of the subjects.

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Key Words: Inflammatory markers; VO2 max; Children;Obesity; C-Reactive protein; Interleukin-6

Introduction

It is reported that systemic inflammation is a predictor for cardiovascular diseases [1]. It is suggested that inflammatory processes play an essential role in the pathogenesis of atherosclerosis and its complications[2].

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Several investigators reported that low-grade inflammation is involved in early stage of atherogenesis in that there is an impairment of endothelial function [3]. Also low-grade inflammation is involved in the formation of fatty streaks and plaque[4] as well as in the thrombotic events leading to myocardial infarction and strokes[5]. Inflammatory factors including C-reactive protein (CRP), and interleukin-6 [IL-6], as well as white blood cell (WBC) count and its subgroups have been reported as important risk factors for atherosclerosis that could predict future cardiovascular events[6,7]. Moreover, these inflammatory factors are involved in other diseases, e.g. CRP and IL-6 levels are reported as predictors for development of type 2 diabetes, and also there is a positive relation between these factors and obesity[8,9]. CRP is reported to be reason for some of obesity co-morbidities[1]. In the process of inflammation a characteristic step is adhesion of leukocytes, neutrophils, and monocytes to the endothelium that is induced by cell adhesion molecules which will be followed by migration of these cells across the endothelium[8]. WBC count has been reported as a predictor for cardiovascular events[10]. It is reported that prevalence of obesity, metabolic syndrome and related diseases both in adults and children is increased in Iran [11]. This is important because obesity during childhood is reported as a independent risk factor for morbidity and mortality in adulthood [12].

Cardiorespiratory fitness that is shown by ability of a person to perform aerobic exercise is an important factor associated by lower rates of several clinically important outcomes such as stroke, metabolic syndrome, myocardial infarction, and other cardiovascular diseases [13,14] Theoretically, low cardiorespiratory fitness could be due to atherosclerotic changes in the peripheral vasculature or coronary arteries. The increased levels of CRP and the related atherosclerosis could lead to these pathological changes[15]. A positive relation has been reported between aerobic or cardiorespiratory fitness and a lower risk of coronary heart disease (CHD) in healthy adults that was independent of measured adiposity[16]. VO_{2max} is an accurate predictor of exercise capacity, and a strong predictor of cardiovascular outcomes[16].

Early-stage atherosclerosis has been reported in children[17], but data on inflammatory factors in obese children were not known as well as the adults. Kullo et al [16] have shown that inflammatory markers are inversely associated with levels of VO_{2max} in adults. According to Marcell et al[18] a moderate to intense exercise program did not reduce levels of chronic inflammation markers including CRP and adiponectin. However, this program leads to improved levels of participants' fitness. Data on children and inflammatory factors is rare, especially on association of inflammation markers with cardiovascular fitness in overweight children.

Therefore, the purpose of the present study was to examine the association between cardiovascular fitness and inflammatory factors including CRP, IL-6 and WBCs in overweight and normal weight children.

Subjects and Methods

Subjects: Twenty six subjects including 10 overweight and 16 normal weight children were enrolled in this study. They were randomly selected from 265 voluntary students who studied in the Javad-ol-Aemmeh school in Tehran.

Subjects had no history of cardiovascular disease, diabetes, or any other medical conditions that disqualified them from participating in exercise sessions. All subjects provided an informed consent including their parent's testimonial. The subjects' height was measured by a standard meter to the nearest centimeter. The weight was measured by a calibrated balance scale to the nearest 0.1 kg. Body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Being overweight was defined as having BMI more than 85th and less than 95th percentile of BMI for age and sex[19].

Percentage of body fat was measured by a bioelectric impedance machine (Imbody 30, Korea). This study was approved by the ethical committee of the Tehran University of Medical Sciences.

Maximal exercise test: A maximum cycle-ergometer test was conducted to evaluate the cardiorespiratory fitness levels of the subjects, as described by Hansen et al[20]. The protocol started by a 10 minutes warm up period in that subjects pedaled on a ergometer cycle at a speed of 4 km/h, and load of 20 watt. Then every 3 minutes the load was increased by the subject height×0.16 until exhaustion. Techno-jim Bikerace, H30 600, Italy, was employed in this study.

Heart rate of the subject was recorded continuously using a telemetry belt (Polar Grey, f11, Pepper, Kempele, Finland). Criteria for exhaustion and termination of the test were a) heart rate ≥185 beats/min, b) failure to maintain a pedaling frequency of at least 30 revolutions per min, and c) the subject could not continue even after vocal encouragement. It was a subjective judgment by the researcher. The power output was calculated to be equal to W1 + (W2 t/180), (W1 = work rate at fully completed stage), W2 = work rate increment at the last incomplete stage, t = time in sec at the last incomplete stage).

Maximum oxygen consumption (VO_{2max} ml/min) was calculated by employing the Hansen formula (VO_{2max} = 12 x calculated power output plus 5 x body weight in kg)[20].

Cardiorespiratory fitness was reported as VO_{2max}/kilogram of body mass.

Laboratory tests: After an overnight fasting, vein blood samples were taken from the subjects while in supine position. Serum concentrations CRP, IL-6, WBC and its subgroups were measured. All analyses were performed at the Shariati Hospital in Tehran. High sensitivity CRP concentrations were measured employing an immunometric assay ELISA kit (RANDOX, England) with Hitachi 902 Automatic Analyzer (Roche, Germany). The lower functional sensitivity of the assay was 0.1 mg/l. The coefficient of variation (CV) intra- and interassay was 1.5% and 2.5% respectively. Plasma Int-6 was measured by sandwich enzyme immunoassay technique. This assay had a sensitivity of 0.70 pg/mL, intra- and interassay CV of less than 1.6% and 3.3% respectively. Plasma CBC was determined by a cell counter employing Isotone soluble technique (Kx21 System).

Statistics: Frequencies, means, and standard deviations were calculated for each variable. Bivariate associations and Pearson correlation coefficient for continuous variables were analyzed. Mean CRP levels were calculated for each fitness level, and linear trend was assessed using linear regression analysis. In all analyses, CRP levels were log transformed (natural logarithm) to approximate normality.

Statistical calculation was carried out by Statistical Package for Social Sciences software (SPSS v 11.5, Chicago, Ill) and the level of significance was set at $P<0.05$. All variables were checked for normality of distribution before analysis, and appropriate trans formations were applied when necessary. Association between CRP, IL-6 and WBC in individual variables and cardiovascular fitness were assessed by Pearson's correlation coefficient.

Findings

The subjects (n=26) were aged 12.6 (±0.8) years (range 11–14 yr) (Table 1). Ten (38.5%) subjects were categorized as overweight. Sixteen (61.5%) subjects had normal weight. CRP levels and WBC counts in normal and overweight subjects are presented in Table 1. Mean CRP level in overweight children was greater than that in normal weight subjects (Table 1). Over-weight children had lower VO_{2max} level than normal weight children (25.77±5.04 vs 41.54±5.96 ml/kg/min). Both IL-6 and CRP were significantly correlated with VO_{2max} levels.

Also in all children WBC and subgroups (Leukocytes, Neutrophils, Monocytes, Eosinophils) count were significantly correlated with VO_{2max} (Table 2). Subgroups of WBC were associated with VO_{2max} in normal and

Table 1: Baseline characteristics of 26 children (16 normal, 10 overweight)

Variables (Mean ± SD)	Overweight (n=10)	Normal weight (n=16)	All children (n=26)
Age(years)	12.7 (0.1)	12.6 (0.8)	12.6 (0.8)
Weight (kg)	81.4 (15.8)	46.9 (5.9)	60.1 (20.1)
Height (cm)	167.0 (8.3)	156.0 (7.9)	160.0 (9.5)
Body mass index	29.2 (3.0)	19.3 (1.9)	22.1 (5.4)
Body fat (%)	32.2 (4.2)	17.1 (5.9)	22.6 (9.0)
VO_{2max}(ml/kg/min)*	25.8 (5.0)	41.5 (6.0)	35.5 (9.6)
CRP(mg/l)#	1.2 (0.7)	0.5 (0.4)	0.8 (0.6)
IL-6 (pg/ml)†	2.2 (0.5)	1.4 (0.2)	1.7 (0.5)
WBC ‡ (cumm) (×10³/µl)	16.1 (2.5)	12.5 (2.4)	13.9 (0.3)
Leukocytes	8.0 (1.2)	6.3 (1.2)	6.9 (1.5)
Lymphocytes	3.4 (0.6)	2.8 (0.7)	3.1 (0.7)
Neutrophils	4.3 (0.8)	3.3 (0.7)	3.7 (9.1)
Monocytes	0.12 (0.04)	0.06 (0.02)	0.87 (±0.04)
Eosinophils	0.15 (0.08)	0.08 (0.03)	1.09 (0.06)

* VO_{2max}: Maximum oxygen consumption
# CRP: C-reactive protein
† IL-6: interleukin-6
‡ WBC: white blood cell

overweight subjects (Table 1 and 2). In a multivariable regression analysis that included all three markers of inflammation, WBC count (r=-0.760, P<0.001), IL-6 (r=-0.775, P<0.001) and CRP (r=-0631, P=0.011), remained significantly associated with VO_{2max}.

Table 2: Correlation (Pearson) of inflammatory factors, body mass index, and body fat, with VO_{2max} in overweight, normal weight and in all children

Factors	Normal weight (n=16)	*P* value	Overweight (n=10)	*P* value	Total (n=26)	*P* value
Body mass index	-0.62	0.01	-0.86	0.001	-0.89	<0.001
Body Fat(%)	-0.69	0.003	0.48	0.2	-0.85	<0.001
CRP*(mg/l)	-0.70	0.003	-0.64	0.04	-0.77	<0.001
IL-6†(pg/ml)	-0.60	0.01	-0.20	0.6	-0.73	<0.001
WBC (cumm) (×10³/µl)	-0.22	0.4	-0.49	0.1	-0.63	0.001
Leukocytes	-0.21	0.1	-0.48	0.2	-0.62	0.001
Lymphocytes	-0.06	0.4	-0.49	0.1	-0.41	0.04
Neutrophils	-0.38	0.1	-0.38	0.2	-0.65	<0.001
Monocytes	-0.48	0.06	-0.37	0.9	-0.64	<0.001
Eosinophils	-0.28	0.3	-0.23	0.5	-0.59	<0.001

* CRP: C-reactive protein; † IL-6: interleukin-6; ‡ WBC: white blood cell

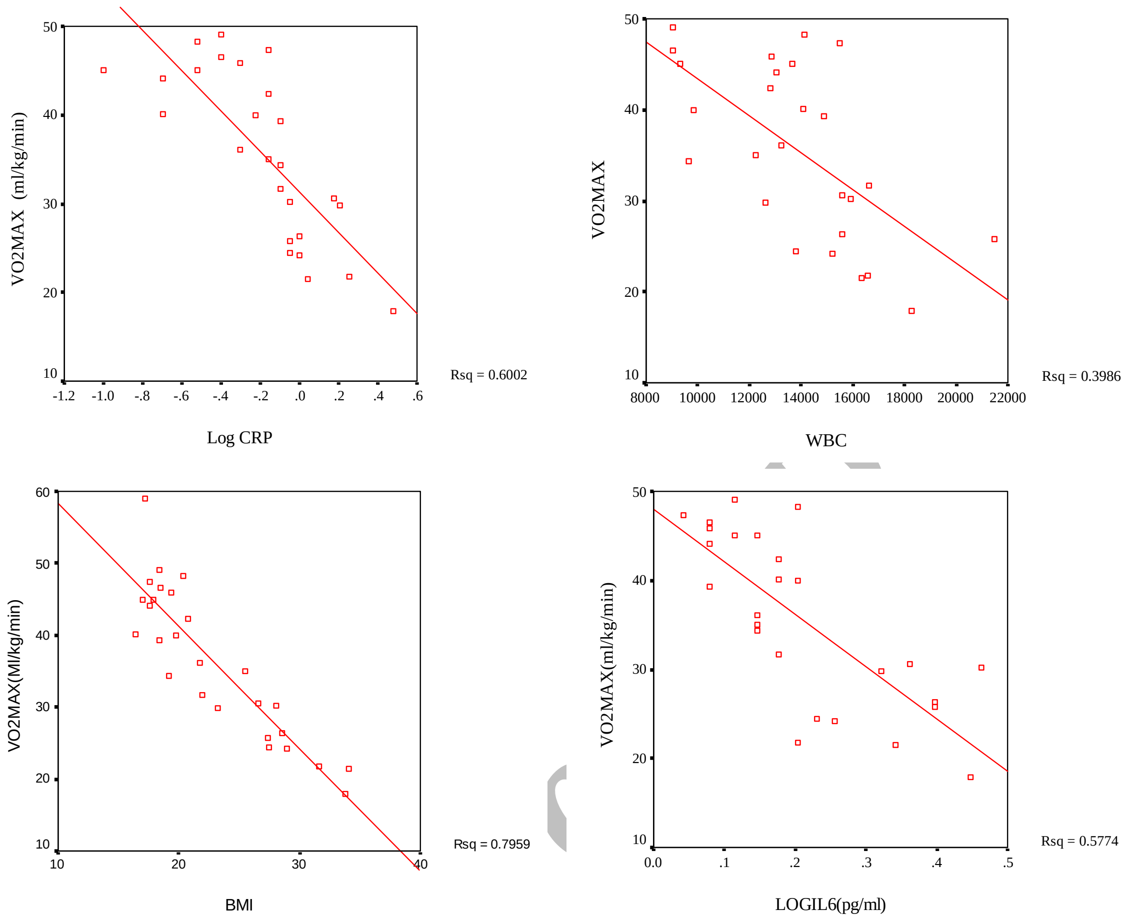

Fig 1: Scatter plots indicate correlation between log C-reactive protein, IL-6, WBC count and BMI with maximal oxygen consumption (VO_{2max})

There are a significant correlations between log IL-6 (r=-0.76, *P*<0.001), log CRP (r= -0.77, *P*<0.001), WBC count (r= -0.63, *P*=0.001) and BMI (r= -0.892, *P*<0.001) with VO_{2max} (Fig 1).

In all children, the three markers of inflammation, log IL-6 (*P*=0.001), log CRP (*P*<0.001), WBC count (*P*<0.001) and subgroups of WBC including Leukocytes (r=-0.61, *P*<0.001), Lymphocytes (r=-0.40, *P*=0.03), Neutrophils (r=-0.65, *P*<0.001), Monocytes (r=-0.64, *P*<0.001) and Eosinophils (r=-0.58, *P*=0.002) remained significantly inversely related to VO_{2max}. Multivariable regression model with stepwise elimination for predictors of VO_{2max} indicates that only BMI associated (*P*<0.001, R2=0.796) with VO_{2max}, a unit increase in BMI was associated with a decrease of 1.3-1.91 ml/kg/min in VO_{2max} (Table 3).

Discussion

The main finding of this study was that the cytokine IL-6, acute-phase reactants (CRP), WBC and its subgroups count were inversely related to VO_{2max} in children, even after adjustment for potential confounders such as age and BMI. Previous studies have suggested an inverse association between inflammatory markers and cardiorespiratory fitness in adults [16,21]. Studies on physical fitness and

Table 3: Multivariable regression model with stepwise elimination (predictors of VO_{2max})

	B-Coeff	*p*	R Square (partial)
BMI§	-0.909	<0.001	0.796
Body fat(%)	-0.291	0.138	-0.312
CRP* (mg/l)	-0.213	0.118	-0.328
IL-6† (pg/ml)	-0.112	0.427	-0.170
WBC‡ (cumm) ($\times10^3$/µl)	-0.133	0.243	-0.248

§ BMI: Body mass index; * CRP: C-reactive protein; † IL-6: interleukin-6; ‡ WBC: white blood cell

CRP in children are limited. The present study is the first one to demonstrate an independent association between a cytokine (IL-6), CRP and WBC and its subgroups count with VO_{2max} in overweight and normal weight children.

In studies that evaluate the association of inflammatory markers and cardiorespiratory fitness, adiposity and physical activity are main confounders. Adipose tissue is an essential source of IL-6[22]. High adiposity is reported to be associated with lower cardiorespiratory fitness. Also, low physical activity levels and reduced cardiorespiratory fitness are associated with higher levels of IL-6, CRP, and WBC[23].

Some studies have reported that CRP was negatively associated with the levels of aerobic fitness in adult subjects[24,25]. Our findings in children are consistent with the results of these studies.

Also subgroups of WBC were inversely associated with VO_{2max} levels both in normal and overweight children. Michishita et al[26] reported that monocyte and neutrophil counts were higher in women with low level of $\dot{V}O_{2max}$ compared to the women with high VO_{2max}. Morover, univariate regression analysis pointed out that VO_{2max} was related to both monocyte and neutrophil counts, but it was not related with HS-CRP (High Sensitivity C-Reactive Protein) levels. Our results suggest that VO_{2max} is a factor that shows inflammatory status in children and might support cardiovascular protective effects of cardiovascular fitness in this group. Geffken et al[27] showed that in elderly in more physically active subjects the level of CRP is lower.

Likewise, our results showed that CRP and WBC and its subgroups in the children with more physical fitness levels were lower. Some studies have reported no association between WBC count and VO_{2max} [2]. In our study, WBC count was inversely associated with $VO_{2\ max}$.

Some researchers focused on monocytes as the main inflammatory cells involved in atherosclerosis [29]. Some others noted that neutrophil is also a major cell in this regard[29]. Also, a study showed that various types of leukocytes might be important in this area[30].

In our study both monocyte and neutrophil counts were associated with $\dot{V}O_{2max}$. However, the results of our multivariate analysis suggest that monocyte counts may have a greater association with aerobic capacity.

The protective effects of physical activity and physical fitness on the cardiovascular risk factors are well documented in adults[31].

According to the results of this study and association between inflammatory markers, CRP, IL-6 and WBC count and onset of atherosclerosis in childhood, it could be suggested that emphasis on physical activity and cardiovascular fitness of children is an important factor for prevention of cardiovascular disease in adulthood.

Therefore, as it has been suggested, a school-based physical activity program might be beneficial to prevent atherosclerosis in children[32].

Our results have several clinical implications for use in pediatric population. Concentrations of CRP could be used to predict cardiorespiratory fitness levels in children. Also some studies reported elevated levels of inflammatory markers as predictors of functional disabilities [33]. In our study also mean level of CRP was grater in overweight children.

There is a controversy about the effects of physical fitness on inflammation and its markers. Several studies reported that physical activity is closely related with markers of inflammation [27,34,35]. On the other hand, some studies did not find such an association [35,36]. Our study is consistent with those studies that reported a significant association between CRP and other markers of inflammation with VO_{2max}.

Our results also showed that overweight children have higher level of CRP, IL-6 and WBCs and lower fitness levels than normal weight children. It still remains unclear how physical activity and aerobic fitness affect the inflammation process.

The main limitation of this study is the small number of the subjects. It has been reported that the intra-individual variation in CRP measured in adults is significant and therefore several measurements could more accurately show the levels of CRP[37]. We measured the CRP and other inflammatory factors in one occasion. However, frequently researches performed a single measurement of CRP and other inflammatory markers in their studies [15,16].

Conclusion

In conclusion, IL-6, CRP and WBCs were inversely associated with aerobic or cardiorespiratory fitness levels measured by VO_{2max} in children. This was independent of BMI levels of the subjects. Also subgroups of WBC including Lymphocyte, Neutrophil, Monocyte and Eosinophil counts were inversely associated with VO_{2max} and were higher in the low VO_{2max} group compared to the high VO_{2max} group. Our results suggest that VO_{2max} could predict the inflammatory status of children. Also our results indirectly suggest that aerobic exercise in overweight and normal weight children might have cardiovascular protective effects. This finding has implications for public health.

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