Original Article

Insulin Resistance Is Associated with Arterial Stiffness Independent of Obesity in Male Adolescents

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To determine the relationship between insulin resistance (IR) and arterial stiffness independent of obesity in male adolescents, we evaluated body fat, lipid parameters, indices of IR (fasting insulin, and the homeostasis model assessment of insulin resistance [HOMA-IR]), indices of insulin sensitivity (IS) (fasting glucose/fasting insulin [GF/IF], and the quantitative insulin sensitivity check index [QUICKI]), and lifestyle parameters in 256 male adolescents. We divided the study group into the following four subgroups based on the median value of HOMA-IR and obesity: non-obese with IS, non-obese with IR, obese with IS, and obese with IR. In order to estimate arterial stiffness, we measured brachial ankle pulse wave velocity (baPWV). Despite having a high body mass index (BMI), obese-IS adolescents showed a significantly lower fasting insulin and baPWV, but had higher IS indices than non-obese-IR adolescents. After an adjustment for age, BMI, waist-to-hip ratio, mean blood pressure, heart rate, total cholesterol level, triglyceride, alanine aminotransferase (ALT) level, physical activity, and television and computer usage, multiple regression models showed that baPWV was independently correlated with IR and IS indices. In conclusion, our results demonstrate an association between IR and baPWV independent of weight, suggesting that IR is a risk factor for the development of early atherosclerosis. Interventions that decrease IR in addition to weight reduction may be necessary to alter the early development of cardiovascular risk. (*Hypertens Res* 2007; 30: 5–11)

***Key Words*: insulin resistance, obesity, arterial stiffness, adolescent**

Introduction

It is now well recognized that atherosclerosis begins early in life as an asymptomatic disease (*1*, *2*) with uncertain preclinical determinants. A recent question in the field is whether insulin resistance (IR) or obesity is the greater cardiovascular risk factor in obese patients (*3*, *4*). The results of studies attempting to answer this question have been inconclusive (*5*, *6*). Because IR depends on body fat mass (*7*), the effects of IR and obesity on cardiovascular risk factors are difficult to distinguish. Despite the association between IR and obesity, obesity alone does not fully explain the development of IR because IR is not present in all obese individuals (*8*).

Non-obese, non-diabetic, healthy individuals can be insulin resistant (*9*), and type 2 diabetes occurs in non-obese individuals (*10*). Yet the question of why some obese children develop cardiovascular disease and others do not, still remains. Furthermore, although it is well established that obesity is correlated with metabolic and cardiovascular disease, a recent study has suggested that IR is more strongly correlated with metabolic and cardiovascular disease (*6*).

Arterial stiffness, a reflection of early arteriosclerosis, can be assessed by measurement of the pulse wave velocity

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(PWV). Decreased arterial elasticity is an independent risk factor for cardiovascular disease (*11*). Traditionally, carotid femoral PWV is measured by applanation tonometry to detect arterial stiffness, but it requires accurate placement of the transducers over the arteries (*12*). Brachial-ankle PWV (baPWV) has recently been utilized as a simple and reliable marker to screen the general population for prevention of cardiovascular disease (*13–15*). Yamashina *et al*. (*13*) found that baPWV correlated well with aortic PWV and a recent study demonstrated that an increased baPWV is linked to parameters reflecting both early atherosclerosis and cardiac diastolic function (*16*).

Studies have suggested that there is an association between IR and arterial stiffness (*17*, *18*). However, these studies contain no obvious evidence for the involvement of hyperinsulinemia and IR in the development of arterial stiffness during adolescence. Therefore, we tested the hypothesis that IR is associated with arterial stiffness independent of obesity in adolescents. We compared metabolic indices and baPWV among four subgroups defined by weight and the homeostasis model assessment of insulin resistance (HOMA-IR) median value: non-obese with insulin sensitivity (non-obese-IS), non-obese with insulin resistance (non-obese-IR), obese with insulin sensitivity (obese-IS), and obese with insulin resistance (obese-IR).

Methods

Subjects

School-based volunteers were recruited by a public advertisement written by the educational institution. A total of 256 healthy male adolescents ranging in age from 12 to 18 years were included. Upon examination, all participants were apparently healthy and had no history or evidence of 1) cardiovascular disease, 2) syndromal obesity, 3) diabetes, 4) moderate to severe hypertension (resting blood pressure, 170/100 mmHg), 5) dyslipidemia, 6) a body weight fluctuation of more than 5 kg in the previous 6 months, 7) endocrine disorders, 8) any known infectious disease, 9) medication that could affect cardiovascular function or metabolism, or 10) smoking. All adolescents and their parents gave informed consent. This study was approved by the institutional review board of the Yongdong Severance Hospital.

Methods

We took anthropometric measurements of each subject wearing light clothing and no shoes. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, using an automatic height-weight scale. Body mass index (BMI [kg/m^2]) was calculated as weight divided by height squared. Obese adolescents were classified according to the international BMI cut-off points for obesity. These international parameters are based on six nationally representative cross-sectional samples, classified by sex between the ages of 2 and 18 years, and calculated up to a BMI of 30 kg/m^2 for an age of 18 years (*19*). Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. Hip circumference was measured at the widest part of the hip region. Thigh circumference was measured 10 cm proximal to the superior patella border. To reduce measurement variation throughout the study, one person conducted all the anthropometric parameter measurements. Fat-free mass (FFM) and the percent body fat were determined using bioelectrical impedance analysis (Inbody 3.0; Biospace, Seoul, Korea) (*20*).

baPWV was measured using a volume-plethysmographic apparatus (PWV/ABI; Colin Co., Komaki, Japan). This device records the phonocardiogram, electrocardiogram, volume pulse form, and arterial blood pressure at both the left and right brachia and ankles. We applied brachial blood pressure as the follow-up blood pressure in this study. The mean blood pressure was calculated as follows: diastolic blood pressure + [(systolic blood pressure − diastolic blood pressure)/3]. baPWV was calculated by time-phase analysis between the right brachial and volume waveforms at both ankles. The distance between the right brachium and the ankle was estimated based on body height. In addition, because a significant correlation existed between the right and left baPWV, we used the mean baPWV for analysis (*21*). The coefficient of variation for inter-observer reproducibility was 8.4% while the intra-observer reproducibility was 10.0% (*22*).

After an 8-h overnight fast, blood samples were obtained from the antecubital vein of each subject into vacutainer tubes. Fasting serum glucose, total cholesterol, triglyceride, high density lipoprotein (HDL)–cholesterol, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured by enzymatic procedures using an autoanalyzer (Bayer, Terrytown, USA). Low density lipoprotein (LDL)–cholesterol was calculated from the Friedewald equation if the serum triglyceride level was below 400 mg/dl (*23*). High sensitivity C-reactive protein (hs-CRP) was measured by a latex-enhanced immunoturbidimetric assay using an ADVIA 1650 Chemistry system (Bayer). The inter-assay and intra-assay reproducibilities were 2.70±1.13% and 2.55±1.0%, respectively. Fasting insulin was measured by a chemiluminescence immunoassay (Roche, Indianapolis, USA).

IR was estimated by HOMA-IR (*24*), while insulin sensitivity was estimated by the ratio of fasting glucose to fasting insulin (GF/IF) and by the quantitative insulin sensitivity check index (QUICKI) (*25*). The calculations used for these estimations were as follows: HOMA-IR = (fasting insulin (μIU/ml) × fasting glucose (mmol/l)/22.5); GF/IF in mg/dl for glucose and μIU/ml for insulin; QUICKI = 1/[log (fasting insulin (μIU/ml)) + log (fasting glucose (mg/dl))].

Adolescents were divided into four groups according to the median HOMA-IR value and BMI: the non-obese-IS

Table 1. Characteristics of the Study Population

Characteristic	Non-obese-IS (N=101)	Non-obese-IR (N=29)	Obese-IS (N=31)	Obese-IR (N=95)
Age (years)	14.2±1.3	15.0±1.5[b]	14.4±1.5	15.3±1.6[b,e]
Anthropometry				
Body mass index (kg/m^2)	22.9±3.9	26.4±2.0[b]	29.4±2.0[b,d]	31.2±2.7[b,d,e]
Waist circumference (cm)	77.1±11.9	90.3±7.0[b]	89.9±5.7[b]	98.3±7.6[b,d,e]
Hip circumference (cm)	94.2±10.2	102.8±5.4[b]	105.1±5.6[b]	110.3±5.8[b,e]
Thigh circumference (cm)	47.4±8.1	52.5±4.6[b]	59.5±13.3[b,d]	58.5±6.1[b,d]
Waist-to-hip ratio	0.81±0.07	0.88±0.05[b]	0.86±0.05[b]	0.89±0.04[b,e]
Waist-to-thigh ratio	1.64±0.16	1.73±0.17	1.56±0.26	1.69±0.19
Body impedance				
Total body fat (%)	22.7±8.6	32.1±6.6[b]	34.7±6.3[b]	37.0±5.9[b]
Total fat mass (kg)	15.1±7.9	23.3±6.2[b]	28.2±5.2[b]	35.0±8.1[b,d,e]
Total lean mass (kg)	32.9±10.8	27.5±5.9	35.0±11.6	36.0±7.1[c]
Metabolic variables				
Mean BP (mmHg)	78.8±8.3	83.3±9.8	84.6±8.3[b]	89.9±8.6[b,d,e]
Heart rate (beats/min)	76.4±10.4	78.1±13.2	78.2±13.3	81.4±11.4[a]
Fasting glucose (mg/dl)	82.4±6.8	89.6±10.5[b]	80.8±8.9[d]	85.7±9.5[b,e]
Total cholesterol (mg/dl)	161.1±29.1	180.6±33.6[b]	179.7±34.9[b]	177.4±29.6[b]
Triglyceride (mg/dl)	77.7±35.5	118.4±65.9[b]	107.4±45.0	138.8±84.0[b]
HDL-cholesterol (mg/dl)	46.1±8.4	44.0±6.5	44.7±6.8	42.8±8.1[a]
LDL-cholesterol (mg/dl)	99.5±25.2	112.9±30.0	113.5±29.6	106.9±28.2
Fasting insulin (μIU/ml)	8.7±3.7	21.8±7.9[b]	9.9±4.2[d]	27.6±14.3[b,d,e]
GF/IF	13.2±16.6	4.4±0.9[b]	14.4±19.6[d]	3.6±1.2[b,e]
HOMA-IR	1.76±0.74	4.95± 2.43[b]	1.96±0.83[d]	5.93±3.39[b,e]
QUICKI	0.16±0.02	0.13±0.01[b]	0.16±0.02[d]	0.13±0.01[b,e]
ALT (IU/l)	19.1±9.4	38.6±27.0[b]	31.9±18.5	62.0±49.3[b,d,e]
AST (IU/l)	21.8±4.9	24.9±9.8	26.2±9.2	34.0±19.3[b,d,e]
hs-CRP (mg/dl)	0.10±0.22	0.24±0.56	0.17± 0.34	0.13±0.14
Sleep (h/day)	7.0±0.9	6.7±1.2	6.9±1.3	6.9±1.5
Walking (min/day)	58.4±43.9	57.4±28.5	67.8±61.8	65.6±54.0
TV and computer (h/week)	5.5±4.7	6.7±8.0	7.7±7.5	6.8±5.3
Physical activity (day/week)	3.5±1.8	4.0±1.6	3.4±1.8	3.4±1.7

Data are shown as the mean±SD. p-values are calculated by an ANOVA test. [a]$p<0.01$; [b]$p<0.001$ *vs*. non-obese-IS; [c]$p<0.01$; [d]$p<0.001$ *vs*. non-obese-IR; [e]$p<0.001$ *vs*. obese-IS. Mean BP, mean blood pressure=(systolic blood pressure + 2 diastolic blood pressure)/3; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low density lipoprotein cholesterol; GF/IF, the ratio of fasting glucose (mg/dl) to fasting insulin (μIU/ml); HOMA-IR, homeostasis model assessment insulin resistance; QUICKI, 1/[log (fasting insulin (μIU/ ml)) + log (fasting glucose (mg/dl))]; ALT, alanine aminotransferase; AST, aspartate aminotransferase; hs-CRP, high-sensitivity C-reactive protein; Sleep, the average number of hours spent sleeping in the most recent month; Walking, the average walking time (min) on weekdays; TV and computer, the hours of watching TV or using the computer for the week except during school hours; Physical activity, the number of days in the most recent week with continuous physical activity for more than 30 min and at an "above-medium-degree" intensity.

(HOMA-IR value <3), non-obese-IR (HOMA-IR value ≥3), obese-IS, and obese-IR groups.

Subjects were asked to fill out questionnaires regarding lifestyle (sleep pattern, physical activity, and television and computer usage). We surveyed the average amount of sleep in recent months and also recorded the TV and computer usage for 1 week outside of school hours. The amount of physical activity was determined by the average weekday walking time (min) and any recent, continuous "above-average-intensity" physical activity that lasted for more than 30 min. We defined "above-average-intensity" physical activity as any activity causing shortness of breath and visible perspiration (badminton, ping pong, swimming, skating, house cleaning, jogging, basketball, soccer, skipping, mountain climbing, *etc*.).

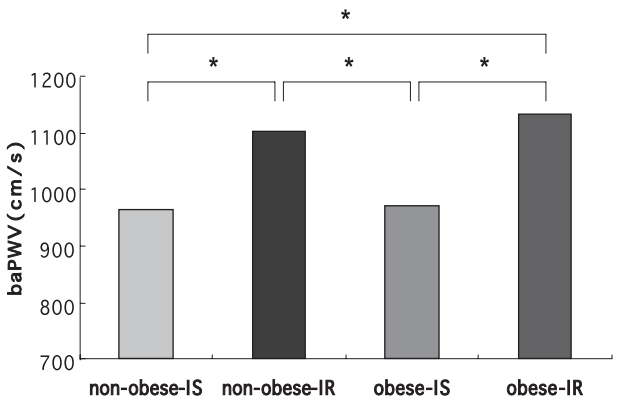

Fig. 1. *Brachial-ankle pulse wave velocity (baPWV) values of the four groups. Adolescents were divided into four groups according to median HOMA-IR values and obesity: the non-obese-IS (HOMA-IR value < 3), non-obese-IR (HOMA-IR value ≥3), obese-IS, and obese-IR groups. Values of* $p < 0.001$ *were considered to indicate statistically significant differences among the four groups.* *$p < 0.001$ *between groups by one-way ANOVA.*

Statistical Analyses

Data are expressed as the mean±SD. All data were analyzed using the statistical program SAS 9.1 (SAS Institute, Cary, USA). Clinical characteristics were compared among the four groups using a one-way ANOVA. When significant differences were found, a Tukey's post-hoc test was performed to assess the magnitude of these differences. Pearson's correlation coefficients were calculated to evaluate the relationship of baPWV with cardiovascular risk factors and lifestyles in this study. A multiple linear regression analysis was performed to determine the correlations of baPWV with IR (fasting insulin, HOMA-IR) and insulin sensitivity indices (GF/IF, QUICKI), after adjusting for potential confounders (age, BMI, waist-to-hip ratio [WHR], mean blood pressure, heart rate, cholesterol, triglyceride levels, ALT, physical activity, and television and computer usage). Significance was defined at the 0.05 confidence level.

Results

Table 1 and Fig. 1 show the characteristics of the four subject subgroups. Average age, anthropometric measurements, body composition measured by body impedance, mean blood pressure, heart rate, fasting glucose level, cholesterol level, HDL-cholesterol level, triglyceride level, fasting insulin level, GF/IF, QUICKI, ALT and mean baPWV were all significantly different among the four groups. The results show that the non-obese-IR group had significantly higher WHR, body fat, fasting glucose level, cholesterol level, triglyceride level, fasting insulin level, ALT, and baPWV than the non-obese-IS group. However, the non-obese-IR group had a significantly lower GF/IF and QUICKI level than the non-obese-IS group. Despite the high GF/IF and QUICKI level, the obese-IS group had significantly lower WHR, body fat, mean blood pressure,

Table 2. Correlations of baPWV with Body Composition, Cardiovascular Risk Factors, and Lifestyle

	Pulse wave velocity	
	r	*p*-values
Anthropometry		
Body mass index (kg/m^2)	0.416	<0.001
Waist circumference (cm)	0.403	<0.001
Waist-to-hip ratio	0.313	<0.001
Waist-to-thigh ratio	0.164	0.009
Body impedance		
Total body fat (%)	0.388	<0.001
Total fat mass (kg)	0.456	<0.001
Total lean mass (kg)	−0.006	0.937
Cardiovascular risk factors		
Age (years)	0.479	<0.001
Mean blood pressure (mmHg)	0.624	<0.001
Heart rate (beats/min)	0.197	0.001
Fasting glucose (mg/dl)	0.064	0.309
Fasting insulin (μIU/ml)	0.380	<0.001
GF/IF	−0.258	<0.001
HOMA-IR	0.347	<0.001
QUICKI	−0.447	<0.001
Total cholesterol (mg/dl)	0.203	0.001
LDL-cholesterol (mg/dl)	0.101	0.106
HDL-cholesterol (mg/dl)	−0.112	0.073
Triglyceride (mg/dl)	0.333	<0.001
ALT (IU/l)	0.318	<0.001
AST (IU/l)	0.189	0.002
hs-CRP (mg/dl)	0.108	0.084
Life style		
Sleep (h/day)	−0.069	0.287
Walk (min/day)	0.035	0.587
TV and computer (h/week)	0.188	0.004
Physical activity (day/week)	−0.097	0.129

Coefficients (*r*) and *p*-values are calculated by the Pearson correlation model. GF/IF, the ratio of fasting glucose (mg/dl) to fasting insulin (μIU/ml); HOMA-IR, homeostasis model assessment insulin resistance; QUICKI, 1/[log (fasting insulin (μIU/ ml)) + log (fasting glucose (mg/dl))]; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; hs-CRP, high-sensitivity C-reactive protein; Sleep, the average sleeping hours for the nearest month; Walking, the average walking time (min) on weekdays; TV and computer, the number of hours watching TV or using computer for the week, except during school hours; Physical activity, the number of days in the most recent week with continuous physical activity for more than 30 min and an "above-medium-degree" of intensity; baPWV, brachial-ankle pulse wave velocity.

Table 3. Independent Associations of baPWV with Indices of Insulin Resistance and Indices of Insulin Sensitivity

	baPWV		
	Regression coefficient	SD	*p*-values
Model 1: age adjusted			
Insulin	3.771	0.551	<0.001
GF/IF	−1.859	0.565	0.001
HOMA-IR	15.738	2.350	<0.001
QUICKI	−2,582.663	383.517	<0.001
Model 2: Model 1 + BMI adjusted			
Insulin	3.350	0.626	<0.001
GF/IF	−1.437	0.563	0.011
HOMA-IR	13.798	2.638	<0.001
QUICKI	−2,267.339	429.460	<0.001
Model 3: Model 2 + waist-to-hip ratio, mean BP, HR, TG, cholesterol, ALT adjusted			
Insulin	2.603	0.584	<0.001
GF/IF	−1.081	0.495	0.030
HOMA-IR	10.676	2.451	<0.001
QUICKI	−1,685.461	392.832	<0.001
Model 4: Model 3 + physical activity, watching TV and computer usage adjusted			
Insulin	2.736	0.611	<0.001
GF/IF	−1.071	0.508	0.036
HOMA-IR	11.298	2.585	<0.001
QUICKI	−1,733.973	409.357	<0.001

Values were calculated by a multiple regression model using the mean baPWV as the dependent variable. GF/IF, the ratio of fasting glucose (mg/dl) to fasting insulin (μIU/ml); HOMA-IR, homeostasis model assessment insulin resistance; QUICKI, 1/[log (fasting insulin (μIU/ml)) + log (fasting glucose (mg/dl))]; BMI, body mass index; Mean BP, mean blood pressure=(systolic blood pressure + 2 diastolic blood pressure)/3; HR, heart rate; TG, triglyceride; ALT, alanine aminotransferase; baPWV, brachial-ankle pulse wave velocity.

fasting glucose level, fasting insulin level, ALT and mean baPWV than the obese-IR group. Furthermore, the obese-IS group had significantly lower fasting glucose level, fasting insulin level, and mean baPWV level than the non-obese-IR group, but had significantly higher GF/IF and QUICKI level.

baPWV was positively correlated with the following: BMI, waist circumference, WHR, waist-to-thigh ratio (WTR), total body fat mass, age, mean blood pressure, heart rate, fasting insulin, HOMA-IR, total cholesterol, triglyceride, ALT, and television and computer usage. In contrast, baPWV was inversely correlated with GF/IF and QUICKI. In addition, although the association was not statistically significant, baPWV was negatively correlated with HDL-cholesterol (Table 2).

After adjustment for age, BMI, WHR, mean blood pressure, heart rate, total cholesterol, triglyceride, ALT, physical activity, and television and computer usage, multiple regression models showed that baPWV was independently correlated with the IR (fasting insulin, HOMA-IR) and insulin sensitivity (GF/IF, QUICKI) indices (Table 3).

Discussion

Many studies in adults and children have demonstrated that IR and obesity are associated with dyslipidemia, hypertension, and cardiovascular risks (*26*, *27*). Although a high prevalence of impaired glucose tolerance is found among obese adolescents (*28*), factors other than obesity must also be responsible, because a recent study reported that the correlation between obesity and IR was as low as 0.26 in early adolescents (*7*).

The key finding of our study was that arterial stiffness in male adolescents consistently increased with higher IR. The presence of obesity did not have a significant impact on the relationship between baPWV and IR. Further, our study shows that not all obese adolescents are necessarily insulin resistant. Despite their obesity, some obese adolescents display normal peripheral insulin sensitivity and have baPWV and cardiovascular characteristics similar to non-obese adolescents. In addition, obese-IS adolescents have favorable metabolic factors and a lower mean baPWV than non-obese-IR adolescents.

The mechanism underlying the relationship between IR and arterial stiffness is unknown, and this cross-sectional study cannot identify the causative factor. However, there are a number of possible mechanisms by which IR may contribute to arterial stiffness. First, IR exerts vascular effects through hyperinsulinemia and increased glycemia with which it is often associated. The effects of hyperinsulinemia on the vascular system may include the promotion of sodium reabsorp-

tion (*29*), stimulation of the sympathetic nervous system (*30*), and promotion of vascular smooth muscle cell growth (*31*), all of which might contribute to increased arterial stiffness. High plasma glucose levels might cause the glycosylation of arterial wall proteins, and these proteins have been associated with organ damage and atherosclerosis (*32*). Second, in the insulin-resistant state, the potent vasodilator effects caused by an insulin-induced and endothelium-derived nitric oxide release (*33*) are reduced, thus increasing the possibility for injury to the vessel wall and vessel wall stiffening. This vascular dysfunction in adolescents may be an early step in the development of atherosclerosis (*1*, *2*).

Our study is limited by its cross-sectional design, which did not enable us to draw causal relationships between IR and arterial stiffness. In addition, the subjects were not sampled randomly. For these reasons, some as-yet-undetermined factors could have been responsible for our main observation that arterial stiffness was consistently increased with increasing IR in male adolescents. Further prospective studies are necessary to clarify these pathophysiological aspects of the relationships between IR and baPWV. In addition, we used the median value of the HOMA-IR to divide the metabolically distinct subgroups into insulin resistant and insulin sensitive groups, but this value is not a precise determinant of IR. The gold standard method for measuring insulin sensitivity is the hyperinsulinemic-euglycemic clamp (*34*). However, since this procedure is invasive and labor-intensive, we used simple surrogate measures that have been correlated to the clamp procedure (*35*). Furthermore, our median HOMA-IR (3.0) value was similar to a previous finding in an unselected control population (*36*). We also used BMI values to assess the degree of obesity. In order to reflect body composition better, we adjusted for the percent body fat or fat mass instead of using BMI, and used the WHR (an indicator of upper *vs*. lower adiposity). Even with these body composition adjustments, baPWV demonstrated a constant correlation with IR and insulin sensitivity indices in multiple regression models (data not shown). In addition, although baPWV is a simple measurement and has high validity and reproducibility (*12*–*14*), it only represents the stiffness of the central and peripheral arteries. Further studies are needed to facilitate accurate interpretation of the baPWV measurements. Despite these limitations, our study is the first comprehensive examination of the relationship between IR and baPWV in adolescent males.

In conclusion, improving IR by a combination of changes in diet and physical activity (*37*, *38*) seems to be important in the prevention of early atherosclerosis independent of weight reduction in adolescents. Further research is necessary to clarify the roles of hyperinsulinemia and/or IR in the progression of arterial stiffness and to assess the effect of improved insulin sensitivity on decreasing arterial stiffness.

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