

Treatment of Childhood Syndrome X

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ABSTRACT. *Objective.* Hyperinsulinemia, hyperlipidemia, hypertension, and coronary artery disease comprise a quartet known as Syndrome X. This syndrome was first described in adults, but has recently been described in children and adolescents. The purpose of our study was to determine if diet or exercise is able to change the clinical profile of Syndrome X in children.

Study Design. We recruited 36 obese (% ideal body weight = 170.3 ± 31.1), children (9 to 12 yrs old) known to have high fasting cholesterol levels (177.5 ± 33.5 mg/dL). Each participated in a 6-week protocol in one of three groups: control (C), diet (D), or exercise (E). Twenty-five of the patients completed the study with full compliance. At the beginning and end of the study, we measured weight, height, blood pressure, serum insulin, and a lipid profile including: cholesterol, low density lipoprotein, high density lipoprotein (HDL), triglycerides, and apolipoprotein A (ApoA). All subject groups were similar before the study. The D group had the greatest attrition (40%) and all of the E group completed the study.

Results. After the 6-week study period, there was no significant weight loss or change in body mass index for any group. There was no significant change in blood pressure and there was no significant decline of fasting cholesterol or low density lipoprotein levels in any of the groups. HDL levels were low in all groups and did not significantly change with treatment. There was a significant decline in the triglyceride levels in both the diet and exercise groups after the study (preD = 150 ± 60 ; postD = 122 ± 50 ; preE = 165 ± 50 ; postE = 116 ± 39). Both the D and E groups also demonstrated a significant decrease in ApoA levels (preD = 174 ± 33 ; postD = 142 ± 24 ; preE = 200 ± 50 ; postE = 161 ± 23). Most impressively, fasting insulin levels significantly decreased with both diet and exercise, but did not change in controls during the 6 weeks (preC = 52 ± 19 ; postC = 53 ± 21 ; preD = 54 ± 23 ; postD = 15 ± 8 ; preE = 48 ± 21 ; postE = 9).

Conclusions. The findings of this study are consistent with previous studies describing the presence of Syndrome X in childhood. Both diet and exercise were effective in lowering triglyceride, ApoA levels, and insulin levels. However, due to the large rate of noncompliance in the diet group, exercise seems to be the best treatment for improvement in Syndrome X in children. *Pediatrics* 1997;100(2).

URL: <http://www.pediatrics.org/cgi/content/full/100/2/e5>; Syndrome X, insulin resistance, hyperlipidemia, children.

ABBREVIATIONS. CAD, coronary artery disease; BMI, body mass index; D, diet; E, exercise; VO₂ max, maximal aerobic capacity; C, control; SBP, systolic blood pressure; DBP, diastolic blood pressure; ApoA, apolipoprotein A.

Syndrome X, a clinical quartet of hyperinsulinemia, hypercholesterolemia, and hypertension with subsequent coronary artery disease (CAD), was initially described by Reaven¹ and has since been described by others.^{2,3} Some⁴ consider obesity to be a component of Syndrome X, although obesity is not part of Reaven's original description. Recently, Syndrome X has been described in children⁵ and adolescents.⁶

The heralding defect in Syndrome X is believed by many to be hyperinsulinemia,⁷ and one could propose that reduction of insulin levels would improve the other symptomatology. Decreasing dietary fat intake improves cholesterol levels and weight loss in type II diabetics (noninsulin-dependent diabetes mellitus) and is associated with lower fasting insulin levels.⁸ Exercise promotes weight loss and improves insulin sensitivity.⁹ The purpose of this study was to describe the effects of diet or exercise on the clinical manifestations of Syndrome X in children.

METHODS

Subjects

We recruited 36 obese children (ages 9 to 12, Tanner I, body mass index [BMI] >25, 17 girls, 19 boys), who had previously been found to have high fasting cholesterol levels (greater than 170 mg/dL),¹⁰ to participate in our study. Some of the subjects reported a positive family history of hypercholesterolemia; however, many were unsure if any family member had ever had a cholesterol level measured. All volunteers were Hispanic and were recruited from the San Jose Pediatric Clinic, Houston, Texas. The clinic is a primary care facility in an urban Hispanic neighborhood where the patients are of Mexican descent. Approximately 5% are Medicaid eligible, the remainder are uninsured. Each subject self-selected enrollment in one of three groups: control, exercise, or diet. The study lasted 6 weeks and was conducted during the summer school break. Characterizations of each subject group are described in Table 1. Approval for this study was obtained from the Committee for the Protection of Human Subjects at the University of Texas.

Description of Treatment Groups

The diet group (D) received individual dietary analysis from a registered dietician and recommendation for an individually-tailored diet designed to reduce fat intake to less than 30% of the total daily food intake. Although calorie restriction per se was not part of our dietary recommendation, some patients may have

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TABLE 1. Subject Characteristics

Subjects	Body Weight (kg)	Body Mass Index	Systolic Blood Pressure	Diastolic Blood Pressure	Fasting Insulin (mU/mL)	Fasting Cholesterol (mU/dL)	Fasting Glucose (mg/dL)
Control n = 7	56.6 ± 15	27.2 ± 2.7	111 ± 12	61 ± 10	47 ± 23	150 ± 39	81 ± 70
Diet n = 9	60.9 ± 14	29.9 ± 2.4	106 ± 13	62 ± 13	54 ± 23	170 ± 40	81 ± 112
Exercise n = 9	61.1 ± 17	27.9 ± 3.2	109 ± 10	64 ± 10	47 ± 38	167 ± 29	88 ± 9
Subject mean m = 25	59.8 ± 15	28.3 ± 1.4	109 ± 12	63 ± 11	51 ± 15	162 ± 36	82 ± 90

reduced calorie intake secondary to reduction of dietary fat. All dietary instruction was provided in Spanish and the sessions lasted 45 to 60 minutes. Dietary compliance was encouraged by phone consultation with the dietitian every week and a total of two in-office visits (transportation was provided) during the study. Compliance with the diet was monitored by review of a dietary food journal kept 3 days per week. Dietary content (% fat, % protein, % carbohydrate, and kilocalories) was determined by the Nutritionist IV nutritional assessment software program (Hearst Corp, San Bruno, CA).

The exercise group (E) participated in moderate aerobic exercise (to raise heart rate to 75 to 80% of maximum) for 1 hour three times per week at the University of Texas recreation center, under the guidance of an exercise physiologist. Compliance with exercise was encouraged by providing transportation to and from the sessions. The E group received additional measurement of maximal aerobic capacity (VO₂ max) at baseline and at the study's conclusion. The control group (C) received no intervention.

Study Measurements

Height, weight, and Tanner staging was assessed for all subjects at baseline and at the study's conclusion. Height for each time point is reported as the average of three measurements obtained using a wall-mounted Harpenden stadiometer. Weight is reported in kilograms and was obtained utilizing the same log and beam scale for each patient. Height and weight measurements were used to calculate BMI for each subject at each time point (BMI = weight/height²). Additionally, blood pressure was measured using a cuff sphygmomanometer. Results from the mean of three measurements taken in the sitting position are reported as systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as mean arterial blood pressure.

At baseline and at the end of the study, after an 8- to 10-hour fast, each patient had blood drawn for the following laboratory analyses: fasting insulin, cholesterol, triglyceride, very low density lipoprotein, high density lipoprotein, and apolipoprotein A (ApoA).

In Vitro Methods

Serum insulin was measured by radioimmunoassay (Coat-A-Count, Diagnostic Products Corp, Los Angeles, CA). Cholesterol, low density lipoprotein, triglyceride, and high density lipoprotein were measured by a photometric technique (COBAS MIRA analyzer, Roche, Somerville, NJ) after daily calibration. Control serum samples were used to check for precision and accuracy. ApoA levels were measured by radioimmunodiffusion assay (Bind-a-RID, The Binding Site, London, UK).

Statistical Analysis

All results are reported as the mean ± standard deviation. Statistical significance was determined by analysis of variance at a *P* level less than .05.

RESULTS

Of the initial 36 patients, 25 subjects completed the study with full compliance. Although more children initially selected the D group, this group had the highest rate of noncompliance and the largest drop-out rate (combined attrition of 40%). There was no significant difference between the subjects who completed the diet, those who were noncompliant, and those who dropped-out from the D group. All children who requested the E group completed the

study. The final number of children in each subgroup included: C group, 3 boys, 4 girls; D group, 4 boys, 5 girls; E group, 5 boys, 4 girls. Results for each treatment group are reported from the final subject number. At baseline, there was no significant difference between the subgroups. There was a tendency for the C group to have a lower body weight (kilograms) than the other two groups, but this difference was not statistically significant. Additionally, there was no difference in the lipid profiles from the children with a positive family history of hyperlipidemia, and those children who did not know their family history.

The average pretreatment total cholesterol for all of the patients was 178 ± 34 mg/dL, which is considered moderately high for age.¹⁰ ApoA levels were high when compared with age-matched normal values.¹¹ In all patients, the average pretreatment SBP and DBP measurements were at the 75th to 95th percentile for age. The mean pretreatment fasting insulin level for all subjects was 50.5 ± 15 (normal, <20 μU/mL). Clearly the pretreatment data suggest that the clinical findings of these children is consistent with Syndrome X.

Dietary history was obtained from the D group only. We believe the pretreatment dietary history from this group is probably representative of the diets for most of our study children. As assessed from the pretreatment dietary history, the diet of these children is comprised as 38% fat, 12% protein, and 50% carbohydrate. The D group who successfully completed our study, shifted their dietary intake to 29% fat, 15% protein, and 56% carbohydrate.

After 6 weeks of treatment, there was no significant difference between the pretreatment and post-treatment values, or between the treatment groups for height, BMI, and percent ideal body weight. Likewise, SBP, DBP, and mean arterial pressure did not change with treatment in any group. All of the children who participated in the D group lost weight (0.7 to 2.2 kg); however, the mean group weight loss was not statistically significant. Posttreatment, total body cholesterol, and low density lipoprotein levels were not significantly different between any of the treatment groups; however, triglyceride levels significantly decreased in the D and E groups. ApoA levels decreased significantly in both the D and E groups, but did not change in the C group. The lipid profiles before and after treatment are listed in Table 2.

The most significant finding of the study, is the marked decrease in the fasting insulin levels of the D and E groups after 6 weeks of treatment. These findings are illustrated by Fig 1.

TABLE 2. Lipid Profiles

Subject Group	Cholesterol (mg/dL)	High-density Lipoprotein (mg/dL)	Low-density Lipoprotein (mg/dL)	Apolipoprotein A (mg/dL)	Triglycerides (mg/dL)
Control					
Pre	161 ± 39	35 ± 3	85 ± 32	164 ± 23	162 ± 40
Post	150 ± 39	35 ± 5	103 ± 23	146 ± 30	161 ± 38
Diet					
Pre	194 ± 38	36 ± 6	102 ± 32	174 ± 33	150 ± 60
Post	170 ± 40	37 ± 5	136 ± 36	142 ± 24*	122 ± 50*
Exercise					
Pre	183 ± 32	37 ± 4	98 ± 27	200 ± 50	165 ± 50
Post	167 ± 28	41 ± 2	116 ± 29	161 ± 23*	116 ± 39*

* Indicates significant difference following treatment.

DISCUSSION

The findings of this study support previous reports⁵ that suggest that Syndrome X begins in childhood. Furthermore, our study suggests that the predominant feature of hyperinsulinism can be successfully treated by either diet or exercise. Although both diet and exercise were successful at lowering serum insulin levels, blood pressure did not change and only some components of the lipid profile changed. No subject group had significant weight loss, although all members of the D group lost weight.

The most significant limitation of our study is that we allowed the patients and/or their parents to select the treatment group. We accepted this limitation at the study's outset because we realized that families desired a particular treatment and to choose for them might adversely affect participation. Initially there were less children who selected the C group. Two of these patients did not return for the final blood work, thus the C group is slightly smaller than the D or E groups. Children who selected the D group tended to be the heaviest and had the worst lipid profiles.

The results from the D group suggest that even a modest reduction of fat intake for a short amount of time can result in decreased triglyceride and ApoA levels, as well as a small amount of weight loss, in children. Although these results are encouraging, the large percentage of drop-outs and noncompliant patients in this group tempers our enthusiasm. Our diet plan was aimed at reducing fat intake to age-recommended normal intake and therefore was not very restrictive. We also provided more contact and indi-

vidualized dietary management than is often provided to obese patients. It is reasonable to hypothesize that even greater numbers of children would not follow a more restrictive, less-personalized diet plan. However, if our subjects continued the diet for a longer period of time, we may have seen greater improvement in the lipid profiles, or demonstrated significant weight loss.

Our exercise program was successful in part because we offered transportation, and in part, because the children who chose this treatment group were interested in exercise. Although the mean VO₂ max did not statistically improve for the group, all patients improved his/her VO₂ max during the 6 weeks of exercise. Both diet and exercise resulted in improved triglyceride and ApoA levels. High serum triglyceride levels are associated with coronary heart disease.¹² High ApoA levels have been found in Type II diabetes and are also associated with CAD.¹³ Reduction in triglyceride and ApoA levels with only 6 weeks of treatment suggests that children can improve their risk for both diabetes and CAD with small changes in lifestyle.

High fasting insulin levels are associated with insulin resistance,¹⁴ a hallmark of type II diabetes.¹⁵ High-fasting serum insulin levels is believed to be the underlying cause of many of the clinical problems noted in Syndrome X; for example, hypertriglyceridemia and CAD.⁷ Our study demonstrates that both diet and exercise successfully decrease high insulin levels in children. Some researchers believe hyperinsulinism is a result of obesity,¹⁶ yet our treatment groups successfully lowered fasting insulin levels without reducing body weight or BMI. Perhaps lower insulin levels precede the weight loss that occurs with diet or exercise. Although our study does not evaluate future development of disease, it seems plausible that sustained reduction of fasting insulin levels would lower the future risk for development of both diabetes and coronary heart disease.

In summary, results of this study suggest that Syndrome X is an entity that begins in childhood and can be treated by either diet or exercise. However, given the large percentage of the D group who were noncompliant, exercise is probably a better treatment choice in children. Prolonged diet or exercise may be necessary to unmask the full effect of these treatments in childhood Syndrome X.

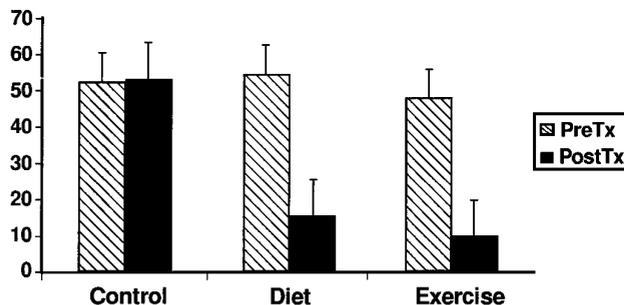


Fig 1. Fasting insulin levels before and after treatment. This figure depicts fasting insulin levels from each treatment group. Although the insulin levels from controls did not change, both the D and the E group demonstrated a significant decrease in their insulin levels after the 6-week treatment period.

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