

Low-Saturated Fat Dietary Counseling Starting in Infancy Improves Insulin Sensitivity in 9-Year-Old Healthy Children

The Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study

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OBJECTIVE — Insulin resistance is promoted already in childhood by obesity and possibly by high-saturated fat intake. We examined the effect of infancy onset biannually given dietary counseling on markers of insulin resistance in healthy 9-year-old children.

RESEARCH DESIGN AND METHODS — Healthy 7-month-old infants ($n = 1,062$) were randomized to the intervention ($n = 540$) and control ($n = 522$) groups. Each year, two individualized counseling sessions were organized to each intervention family. The purpose of counseling was to minimize children's exposure to known environmental atherosclerosis risk factors. Homeostasis model assessment of insulin resistance (HOMA-IR) index, serum lipids, blood pressure, and weight for height were determined in a random subgroup of 78 intervention children and 89 control children at the age of 9 years.

RESULTS — Intervention children consumed less total and saturated fat than the control children ($P = 0.002$ and < 0.0001 , respectively). The HOMA-IR index was lower in intervention children than in control children ($P = 0.020$). There was a significant association between saturated fat intake and HOMA-IR. In multivariate analyses including saturated fat intake, study group, and other determinants of HOMA-IR (serum triglyceride concentration, weight for height, and systolic blood pressure), study group was, whereas saturated fat intake was not, significantly associated with HOMA-IR. This suggests that the beneficial effect of intervention on insulin sensitivity was largely, but not fully, explained by the decrease in saturated fat intake.

CONCLUSIONS — The long-term biannual dietary intervention decreases the intake of total and saturated fat and has a positive effect on insulin resistance index in 9-year-old children.

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Insulin resistance, defined as an inadequate metabolic response to plasma insulin at normal concentrations (1,2), is promoted by obesity and high intake of

saturated fat (3–5), and up to 30% of overweight or obese individuals develop insulin resistance (6). Although the prevalence of the insulin resistance syndrome,

i.e., a cluster of metabolic abnormalities associated with reduced insulin sensitivity, increases with age, it exists already in childhood (7,8). In adults, the insulin resistance syndrome is associated with type 2 diabetes and cardiovascular disease (1). Preventing obesity and sedentary lifestyle and supporting a healthy lifestyle are important preventive measures, particularly if started in childhood.

The aim of the present study was to evaluate the effect of individualized repeatedly given dietary counseling aimed at a low-saturated fat low-cholesterol diet from the age of 7 years on serum insulin values and some other markers of the insulin resistance syndrome in 9-year-old healthy children.

RESEARCH DESIGN AND METHODS

The study design of the ongoing prospective randomized Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) study, which began in 1990, has been published in detail (9,10). Briefly, 1,054 volunteer families with 1,062 healthy 7-month-old infants were recruited to the study by nurses at the well-baby clinics in the city of Turku, Finland. The children were randomized to an intervention group ($n = 540$, 284 boys) or a control group ($n = 522$, 266 boys). At the age of 7 years, a time-restricted subsample of 200 children from both intervention and control groups was taken for more detailed laboratory measurements. In practice, to this cohort, we took those consecutive children who came to their 7-year annual STRIP visit (50 intervention boys, 50 intervention girls, 50 control boys, and 50 control girls) beginning January 1997 and ending November 1997. Selection bias did not occur. The participants of this present study comprised all 167 children of those original 200 who had blood samples available from their 9-year STRIP visit (78 intervention children, 35 boys; 89 control children, 47 boys).

Twice a year, the intervention group

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Abbreviations: apo, apolipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; PAI-1, plasminogen activator inhibitor type 1; STRIP, Special Turku Coronary Risk Factor Intervention Project for Children.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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received individualized dietary counseling given by a team consisting of a physician and a dietitian. The families recorded the child's food consumption for four optional consecutive days, including at least one weekend day, close (within 3 weeks) to each follow-up visit (11). A dietitian checked the food records and suggested appropriate changes to the diet. From the beginning of the study, the intervention group was supported to adopt a healthy low-saturated fat low-cholesterol diet, which was designed to meet the Nordic Dietary Recommendations (12). Since the age of 3 years, the recommended intakes comprised protein 10–15 E% (percentage of energy), fat 30 E% (saturated fat ≤ 10 E%), and carbohydrate 55–60 E%.

The control children have received the basic health education given at the Finnish well-baby clinics. During their STRIP visits, they received no detailed dietary counseling.

The study was approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital. Informed consent was obtained from all parents.

Anthropometric measurements

Weight was measured with an electronic scale (S10; Soehnle, Murrhardt, Germany) to the nearest 0.1 kg. Standing height was measured with a wall-mounted stadiometer (Harpender Stadiometer, Holtain, Crymych, U.K.) to the nearest 0.1 cm. Both measurements were taken in the fasting state, with the subject dressed in light clothing without shoes. The weight, weight for height (deviation of weight in percentages from the mean weight of healthy Finnish children of the same age, height, and sex), and height were recorded (13). Waist (midway between iliac crest and the lowest rib at the midaxillary line) and hip (maximum width over the greater trochanters) circumferences were measured with a flexible measuring tape to the nearest 0.5 cm. All children except 11 girls (4 intervention and 7 control girls) were prepubertal, i.e., at Tanner stage 1 (14). These 11 girls were all at Tanner stage 2, and none of them had had menarche.

Laboratory methods

Fasting serum total and HDL cholesterol, apolipoprotein (apo)A-1, apoB, and triglyceride concentrations were measured as described (10). The Friedewald formula (15) was used to calculate serum LDL cholesterol concentration. Blood

samples for determination of serum glucose and insulin concentrations were obtained after an overnight fast. The samples were centrifuged immediately, and 15 μ l of the enzyme inhibitor Antagosan was added to the 0.5-ml serum insulin sample. Samples were stored at -20°C for 2 months at the most. Serum glucose was measured by the glucose dehydrogenase method (Merck Diagnostica, Darmstadt, Germany) and serum insulin by radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). The intra-assay of insulin variations was 2.89% at the average concentration of 16.5 mU/l and 3.12% at the level of 142 mU/l. The interassay variations were 3.89 and 3.91%, respectively. Plasminogen activator inhibitor type 1 (PAI-1) was assessed by a chromogenic assay kit based on two-stage indirect enzymatic assay (Spectrolyse/PL PAI; Biopool International, Ventura, CA). The intra-assay variations were 2.8% at the concentration of 17.5 units/ml and 2.3% at the concentration of 28.7 units/ml. The interassay variations were 4.8 and 8.6%, respectively. The homeostasis model assessment of insulin resistance (HOMA-IR) method was used to estimate insulin resistance as described [(fasting insulin mU/ml \times fasting glucose mmol/l)/22.5] (16). The analyses were performed in the laboratory of the Research and Development Unit of Social Insurance Institution (Turku, Finland).

Statistical analysis

Two-way ANOVA was used to compare the means of anthropometric measurements, serum lipid values, markers of insulin resistance, blood pressure, and dietary intakes between the intervention and control groups and between sexes.

ANCOVA was used to determine correlates of the HOMA-IR index. First, because of the interdependency between various anthropometric variables, between serum lipid values, between energy nutrient intakes, and between systolic and diastolic blood pressure, one variable within each of these four variable groups was selected for the ANCOVA analyses based on their known associations with insulin resistance (1,2,4,7). These selected variables were as follows: weight for height, serum triglyceride concentration, saturated fat intake, and systolic blood pressure.

Serum insulin and triglyceride concentrations, plasma PAI-1 concentration, HOMA-IR values, and weight and weight for height values were log-transformed

for the analyses. The results are presented as means \pm SD unless otherwise stated. In all tests, $P \leq 0.05$ was considered significant. Statistical analyses were performed using SAS System for Windows, release 9.1.3 (SAS, Cary, NC).

RESULTS—Weight, height, weight for height, waist circumference, blood pressure, and intakes of monounsaturated fat and sucrose did not differ between groups or sexes (Table 1). Intakes of total and saturated fat were lower, and intake of polyunsaturated fat was higher in intervention children than in control children. Intake of carbohydrate was higher in the intervention group than in the control group, but the intervention effect was divergent in boys and girls (Table 1). Intervention girls had a higher intake of carbohydrate than control girls. Girls had greater hip circumference and lower intakes of total energy and polyunsaturated fat than boys.

Serum glucose concentration was slightly higher and insulin concentration was clearly lower in intervention children than in control children (Table 2). Boys had higher glucose concentrations than girls, but their insulin and PAI-1 concentrations were lower than in girls. HOMA-IR was lower in intervention children than in control children and lower in boys than in girls. Serum total and LDL cholesterol and apoA-1 and apoB concentrations did not differ between groups. LDL and apoB concentrations were lower in boys than in girls. Serum HDL cholesterol concentration did not differ between groups but was higher in boys than in girls. Serum triglyceride concentration was lower in intervention children than in control children and lower in boys than in girls. The 11 girls who had reached Tanner stage 2 did not differ in their basic anthropometric variables, blood pressure, energy nutrient intakes, insulin resistance markers, or serum lipid variables from prepubertal girls, except that apoB concentration was slightly higher in pubertal girls (0.76 vs. 0.66 mmol/l, $P = 0.043$).

We performed separate analyses to examine possible factors explaining insulin resistance in general and to determine the mechanisms of how intervention leads to decreased insulin resistance. Study group, sex, saturated fat intake, serum triglyceride concentration, weight for height, and systolic blood pressure were associated with HOMA-IR (Table 3). Saturated fat intake was associated

Table 1—Anthropometric variables, blood pressure, and energy nutrient intakes of intervention and control children

	Intervention boys (n = 35)	Control boys (n = 47)	Intervention girls (n = 43)	Control girls (n = 42)	Two-way ANOVA		
					Sex	Group	Interaction
Weight (kg)*	31.5 ± 5.7	30.3 ± 4.8	31.7 ± 5.7	32.3 ± 6.8	NS	NS	NS
Height (cm)	136.8 ± 6.7	135.6 ± 5.6	136.3 ± 6.0	136.3 ± 6.6	NS	NS	NS
Weight for height (%)*	1.78 ± 11.28	0.51 ± 13.00	3.70 ± 11.58	5.42 ± 14.54	NS	NS	NS
Waist circumference (cm)	58.9 ± 5.0	57.7 ± 4.9	57.7 ± 6.0	58.8 ± 6.0	NS	NS	NS
Hip circumference (cm)	69.4 ± 5.8	68.6 ± 5.1	70.2 ± 5.6	72.0 ± 7.3	0.028	NS	NS
Systolic blood pressure (mmHg)	100.1 ± 7.3	99.8 ± 7.6	100.3 ± 7.0	100.5 ± 8.3	NS	NS	NS
Diastolic blood pressure (mmHg)	58.3 ± 5.4	58.7 ± 5.6	58.6 ± 6.5	59.1 ± 6.2	NS	NS	NS
Total energy intake (kcal)	1,834 ± 324	1,815 ± 250	1,646 ± 258	1,696 ± 317	0.001	NS	NS
Total fat intake (E%)	30.8 ± 3.9	31.8 ± 4.3	29.1 ± 4.6	32.6 ± 4.4	NS	0.002	0.07
Saturated fat intake (E%)	11.2 ± 1.9	12.8 ± 2.1	11.2 ± 2.8	14.2 ± 2.3	NS	<0.001	0.07
Monounsaturated fat intake (E%)	11.59 ± 1.79	10.83 ± 1.75	10.39 ± 1.62	11.06 ± 1.95	NS	NS	0.013
Polyunsaturated fat intake (E%)	6.03 ± 1.12	5.39 ± 1.20	5.49 ± 1.19	4.80 ± 1.02	0.002	0.0003	NS
Carbohydrate intake (E%)	52.8 ± 4.4	53.0 ± 4.4	54.5 ± 4.7	51.3 ± 5.0	NS	0.039	0.013
Sucrose intake (E%)	9.6 ± 2.6	11.2 ± 4.1	9.8 ± 3.8	9.9 ± 3.8	NS	NS	NS

Data are means ± SD. *Weight and weight for height values were log-transformed for the analyses. E%, percentage of energy.

strongly with the intervention group ($P < 0.0001$). We included saturated fat intake in the ANCOVA analyses including study group and other determinants of HOMA-IR to examine whether the effect of intervention is so strongly explained by reduced saturated fat intake that the difference between groups in HOMA-IR would disappear. However, in the final multivariate model including study group, saturated fat intake was no more significantly associated with HOMA-IR, whereas study group was still significantly related to HOMA-IR. In the final multivariate ANCOVA model, significant explanatory variables for the HOMA-IR index were study group, serum triglyceride concentration, weight for height, and systolic blood pressure. The effect of weight for height was stronger in intervention children than in control children

and in girls than in boys (Table 3, final multivariate model).

CONCLUSIONS— Insulin resistance, hypertriglyceridemia, elevated blood pressure, and obesity are closely related (1,17). The present study showed that repeatedly given dietary counseling with onset in infancy, aimed at permanently low intake of saturated fat, seems to improve insulin sensitivity in 9-year-old children. At the dietary intake level, intervention was effective because intervention children consumed less total and saturated fat and more carbohydrate and polyunsaturated fat than control children.

High intake of saturated fat seems to associate with insulin resistance (3,4,18). When saturated fatty acid intake is excessive, triglycerides accumulate in many tis-

sues, e.g., in liver and muscle leading to cellular damage and dysfunction and eventually causing hyperinsulinemia to compensate for insulin resistance (19). In our study, high-saturated fat intake was a significant explanatory variable of HOMA-IR when children from both study groups were analyzed together. However, when study group was included as a covariate in the model, the significance of saturated fat intake disappeared. This indicates that our finding of decreased HOMA-IR in intervention children is to a large extent due to their lower saturated fat intake. However, as the study group remained as a significant determinant of HOMA-IR after multiple adjustments, other unmeasured factors, such as possible altered exercise habits, may partly explain our intervention effect on HOMA-IR. Hypertriglyceridemia in-

Table 2—Serum glucose and insulin, plasma PAI-1, HOMA-IR, serum lipid values, and apolipoproteins in intervention and control children

	Intervention boys (n = 35)	Control boys (n = 47)	Intervention girls (n = 43)	Control girls (n = 42)	Two-way ANOVA		
					Sex	Group	Interaction
Glucose (mmol/l)	4.66 ± 0.31	4.62 ± 0.24	4.60 ± 0.26	4.48 ± 0.26	0.014	0.037	NS
Insulin (mU/l)*	3.94 ± 1.33	5.00 ± 1.90	5.23 ± 2.00	5.76 ± 2.06	0.0003	0.005	NS
PAI-1 (units/ml)*	6.79 ± 2.65	8.33 ± 3.46	9.84 ± 5.69	9.57 ± 5.13	0.017	NS	NS
HOMA-IR*	0.82 ± 0.29	1.03 ± 0.41	1.08 ± 0.45	1.15 ± 0.44	0.003	0.020	NS
Total cholesterol (mmol/l)	4.30 ± 0.66	4.49 ± 0.85	4.55 ± 0.65	4.64 ± 0.65	NS	NS	NS
LDL cholesterol (mmol/l)	2.71 ± 0.48	2.78 ± 0.76	2.95 ± 0.61	2.97 ± 0.56	0.027	NS	NS
HDL cholesterol (mmol/l)	1.33 ± 0.25	1.37 ± 0.28	1.24 ± 0.20	1.30 ± 0.24	0.037	NS	NS
Triglycerides (mmol/l)*	0.57 ± 0.21	0.75 ± 0.38	0.79 ± 0.36	0.83 ± 0.29	0.001	0.018	NS
apoA-1 (g/l)	1.47 ± 0.22	1.52 ± 0.22	1.42 ± 0.15	1.48 ± 0.20	NS	NS	NS
apoB (g/l)	0.66 ± 0.13	0.74 ± 0.21	0.81 ± 0.17	0.80 ± 0.17	0.0002	NS	NS

Data are means ± SD. *Serum insulin and triglyceride concentrations, plasma PAI-1 concentration, and HOMA-IR values were log-transformed for the analyses.

Table 3—Determinants of HOMA insulin resistance index in 167 healthy study children

Variables explaining HOMA-IR*	P value for type 3 test	Model parameter estimate†
Each variable separately		
Study group	0.028	0.132 ± 0.060‡
Sex	0.004	0.173 ± 0.059‡
Saturated fat intake	0.003	0.035 ± 0.011
Triglycerides*	<0.0001	0.376 ± 0.069
Weight for height	<0.0001	0.014 ± 0.002
Systolic blood pressure	<0.001	0.018 ± 0.004
Final multivariate model (ANCOVA)		
Study group	0.025	−0.113 ± 0.051§
Sex	0.25	0.059 ± 0.051
Triglycerides*	<0.0001	0.264 ± 0.063
Weight for height	<0.0001	0.003 ± 0.003
Systolic blood pressure	0.011	0.009 ± 0.004
Weight for height and study group interaction¶	0.047	0.008 ± 0.004§
Weight for height and gender interaction#	0.021	0.009 ± 0.004

Data are means ± SE or P. In the final multivariate model, all variables significantly associating with HOMA-IR were tested together. Model inclusion criteria, $P < 0.1$; saturated fat intake dropped out from the final model because it was strongly associated with the study group. *HOMA-IR values and serum triglyceride concentrations were log-transformed for the analyses. †Model parameter estimate expresses change in logarithm of HOMA-IR per unit change of a variable. ‡Variable is dichotomous, and therefore estimated mean difference ± SE is calculated instead of the model parameter estimate. §Parameter estimates calculated for intervention group (0 for control group). ||Parameter estimates calculated for girls (0 for boys). ¶Mean ± SD weight for height was $2.84 \pm 11.42\%$ in intervention group and $3.13 \pm 13.98\%$ in control group. #Mean ± SD weight for height was $4.60 \pm 13.16\%$ in girls and $1.10 \pm 12.17\%$ in boys.

creases the amount of free fatty acids, which are known to promote insulin resistance (20). In the KANWU Study (4), insulin sensitivity was significantly impaired after a 3-month consumption of a high-saturated fat diet, while it remained unchanged on a monounsaturated fatty acid diet. In the Finnish Diabetes Prevention Study, a 3-year individualized lifestyle intervention reduced the intake of both total and saturated fat, and as a consequence, the incidence of diabetes in these overweight originally nondiabetic adults diminished (21). In the present study, study group and serum triglyceride concentration were significant explanatory variables for HOMA-IR index in the multivariate ANCOVA model study group. This suggests that the observed difference in HOMA-IR between intervention and control groups, most probably due to reduced saturated fat intake in intervention children, cannot solely be explained by mechanisms related to higher triglyceride levels in control children.

Adiposity in childhood may be the strongest predictor of the metabolic syndrome in adulthood (22), and overweight children are at increased risk of becoming obese adults (23,24). In a previous study on Finnish children, fasting serum insulin

concentrations correlated positively with BMI in 9-year-old boys and girls (25). In accordance with that and other previous studies (8,26–29), we also observed a strong connection between children's body composition and HOMA-IR. It is highly likely that obesity and insulin resistance have adverse subclinical cardiovascular consequences already in childhood. According to autopsy studies, BMI relates to the existence of fibrous plaques and fatty streaks in coronary arteries and aorta already in young children (30,31). A noninvasive ultrasound study of 10-year-old children revealed that obese girls have increased stiffness of abdominal aorta (32). In the study by Raitakari et al. (33), BMI and blood pressure in childhood correlated positively with the intima-media thickness of the common carotid artery in adulthood.

In the present study, sex was not associated with the HOMA-IR index in the multivariate model including study group. However, boys had lower HOMA-IR as well as serum triglyceride, LDL cholesterol, and apoB concentrations than girls. Total and saturated fat intakes did not differ between sexes, but boys had higher polyunsaturated fat intake than girls. Physical exercise improves insulin sensitivity (34) and affects serum lipid

values favorably (35). Unfortunately, the level of physical activity was not accurately measured in the present study. However, in another Finnish study, boys under 12 years of age were physically more active than girls (36). Thus, it is probable that boys in the present study were more active than girls, which may explain the more favorable lipid pattern and lower HOMA-IR index in boys.

In conclusion, the 9 years of biannual nutrition counseling aimed at diminished intake of saturated fat seems to protect children from the development of insulin resistance. Clear-cut explanatory factors for higher insulin resistance index were (in addition to belonging to the control group having high-saturated fat intake) body composition, serum triglyceride concentration, and systolic blood pressure. Our results, if sustained for future decades, thus suggest that development of insulin resistance and subsequently possibly also atherosclerosis may be delayed or prevented by introducing relevant dietary and lifestyle habits already in early childhood. Further follow-up studies with continuing counseling sessions in our trial will show whether the observed beneficial effects of intervention will continue over puberty into early adulthood.

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