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Effects of regular exercise on obesity and type 2 diabete mellitus in Korean children: improvements glycemic control and serum adipokines level

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Abstract. [Purpose] The aim of the study was to clarify the effects of regular exercise on lipid profiles and serum adipokines in Korean children. [Subjects and Methods] Subjects were divided into controls (n=10), children who were obese (n=10), and children with type 2 diabetes mellitus (n=10). Maximal oxygen uptake (VO_2max), body composition, lipid profiles, glucagon, insulin and adipokines (leptin, resistin, visfatin and retinol binding protein 4) were measured before to and after a 12-week exercise program. [Results] Body weight, body mass index, and percentage body fat were significantly higher in the obese and diabetes groups compared with the control group. Total cholesterol, triglycerides, low-density lipoprotein cholesterol and glycemic control levels were significantly decreased after the exercise program in the obese and diabetes groups, while high-density lipoprotein cholesterol levels were significantly increased. Adipokines were higher in the obese and diabetes groups compared with the control group prior to the exercise program, and were significantly lower following completion. [Conclusion] These results suggest that regular exercise has positive effects on obesity and type 2 diabetes mellitus in Korean children by improving glycemic control and reducing body weight, thereby lowering cardiovascular risk factors and adipokine levels.
Key words: Leptin, Resistin, Visfatin

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INTRODUCTION

Historically, type 2 diabetes mellitus (T2DM) has been considered an adult disease. However, recent epidemiological studies have reported an increase incidence of T2DM in children and adolescents in a number of countries[1, 2)]. Data from the 2007 US National Diabetes Fact Sheet indicate that 7.8% of the population and 0.22% of those aged ≤ 20 years have diabetes[1)]. T2DM has, also been associated with the growing pre valence of childhood obesity[2)]. In addition, increases in childhood obesity have been accompanied by an increased incidence of type 2 diabetes in youth[3, 4)]. In Asia the prevalence of T2DM has increased raidly in recent decades and is characterized by a younger age and lower body mass index (BMI) at onset compared with Western countries[5)].

Early treatment of T2DM in children is essential to slow or delay disease progression and prevent complications. Lifestyle modifications (e.g., dietary adaptations) are required, and many pediatric patients also require glucose lowering medication to achieve satisfactory glycemic control[6)]. Increased physical activity must be also considered as part of treatment: based on mounting evidence of the benefits of regular exercise on abdominal obesity in adults[7)]. There is also evidence in children suggesting that engaging in regulatory exercise is associated with a lower waist circumference and reduced visceral fat[6)].

Leptin, visfatin, resistin and retinol binding protein 4 (RBP4) are important adipokines that are involved in inflammation, insulin resistance, obesity and cardiovascular disease[8–12)]. They may also have a role in the pathogenesis of metabolic syndrome relating to obesity and insulin resistance[13)].

Despite this evidence, diet control and regular exercise are still lacking in children. This study was designed to examine the effects of a regular exercise program on serum adipokine levels and glycemic control in children who were obese or who had T2DM.

SUBJECTS AND METHODS

The 1998 Children and Adolescent Physical Growth Standard proposed by The Korean Society of Pediatrics was used in the assessments of subjects. Ten overweight

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Table 1. Descriptive characteristics of the study participants

Variable	CO		OB		T2DM	
	pre	post	pre	post	pre	post
Height (cm)	162.00±1.06	162.35±1.08	166.35±1.93	167.28±2.10	161.60±2.25	161.65±2.23
Weight (kg)	55.74±2.33	55.80±2.19	73.52[a]±2.66	69.16[ab]±2.64	63.98[a]±4.43	62.93[a]±4.19
BMI (kg/m^2)	21.18±0.72	21.13±0.70	26.56[a]±0.58	24.65[ab]±0.62	24.28[a]±1.27	23.88[ab]±1.20
%fat (%)	16.77±2.19	16.85±2.17	30.54[a]±1.11	26.96[ab]±0.87	28.97[a]±1.90	27.94[ab]±1.69
VO_2max (mL/min/kg)	33.17±1.41	33.98±1.04	28.05[a]±1.12	31.16[ab]±1.36	30.12[a]±1.61	33.57[b]±1.31

Values are mean ± SE; [a]p<0.05 vs. CO, [b]p<0.05 vs. pre
CO: control group; B: obese group; T2DM: type 2 diabetes mellitus group; BMI: body mass index

children with BMI > 95% or an obesity index > 120% were assigned to the obese group (OB, mean±standard error age, 16.7±0.19 years), ten children with normal weight were assigned to the healthy control group (CO, 15.0±0.01 years), and ten children were assigned to the T2DM group (16.8±0.22 years; metformin therapy: n=6, repaglinide therapy: n=2) The thildren in the T2DM group were D University Hospital inpatients with a 2-h glucose tolerance test ≤ 140 mg/dL, blood sugar level ≥ 200 mg/dL and no other complicating diseases. The participants and their caregivers submitted written informed consent prior to enrolment. The study recruited via poster advertisements and the internet and was approved by the D University Hospital Institutional Review Board after medical examination and diagnosis by medical specialists.

Aerobic exercise (modified from Roberts et al. [6]) was conducted for 40–60 minutes per session four times a week, for 12 weeks. Participants achieved 50% of their oxygen consumption through the VO_{2max} test. In weeks 1–4, participants engaged in 30–40 minutes of aerobic exercise walking/running) at a school field under the supervision of a professional trainer. Participants were monitored using a Polar System (Polar Electro, Kempele, Finland) that calculated heart rate reserve (HRR). In weeks 5–12, participants exercised in a similar manner but for 40–50 minutes at a HRR equivalent to 60% of VO_{2max}. Each session was preceded and followed by a 5-minute warm-up and cool-down[6].

Body composition testing was performed by measuring height, weight, body fat and BMI with the use of a Venus 5.5 impedance analyzer (Jawon Medical, Seoul, Korea). An exercise loading test was performed using an Inter track 6025 treadmill (Taeha, Seoul, Korea) and a Quark b_2 gas analyzer (Cosmed, Rome, Italy) using the lowest grade for physical activity for children in the modified Balke treadmill protocols. Criteria for determining maximal exercise included: i) the intensity of exercise was increased when the oxygen intake was < 2.0 mL/kg/min, ii) heart rate was not increasing, iii) Borg rating of perceived exertion was > 17, iv) category ratio scale (CR10) was > 7, and v) respiratory exchange rate was > 1.15[14].

All blood samples were collected at our laboratory at 08:00 following a 12-hour overnight fast. After a 10-minute rest in a comfortable chair, fasting blood was collected from the median cubital vein into a plain tube. Each blood sample was centrifuged at 3,000 g for 10 minutes at 4 °C and stored at −70 °C until required for analysis.

Lipid profiles (TC, TG, HDL-c and LDL-c) were quantified using commercial, enzyme-based kits (Asan, City, Korea). Plasma (2 uL) and the enzyme solution (300 uL) were rotated and incubated in a water bath at 37 °C for 5 minutes for color development. Optical density was determined using a UVmini-1240 spectrophotometer (Shimadzu, Tokyo, Japan) with the blank as a control. Glycemic control in the fasting state was determined by the homeostasis model assessment (HOMA-IR): [fasting glucose (mg/dL) × fasting insulin (μU/mL)] / 405

All serum samples were submitted for a solid phase sandwich enzyme-linked immunosorbant assay (ELISA) measurement of RBP4 (Sino Biological company location) using the standard curve method with a dilution series of a provided human RBP4. Leptin, resistin, visfatin, insulin and glucagon were measured using a Bio-plex 200 human serum adipokine (panel B) LINCOplex kit (BioRad, Hercules, CA) with an accuracy of 93%, inter-assay variation (% CV) of <20%, and intra-assay variation (%CV) of 1.4–7.9%.

Statistical data were analyzed using SPSS/+PC Windows version 20.0 statistical package (IBM Corp, Armonk, NY), for which all measurements are expressed as mean±standard error. To examine significant differences between the three groups, a two-way ANOVA (time (2) × group (3)) was used. In addition, if statistically significant differences were detected, post-hoc testing was performed using the Duncan's post-hoc test method. The statistically significant level of all data was defined as α=0.05.

RESULTS

Descriptive characteristics of the participants are provided in Table 1. At baseline body weight, BMI, and %fat were significantly higher in the OB and T2DM groups than in the CO group (p<0.05). These parameters were significantly decreased in the OB and T2DM groups following completion of the 12-week exercise program (p<0.05). VO_{2max} was significantly increased in the OB and T2DM groups following the exercise program (p<0.05). Furthermore, significant decreases were evident in the levels of TC, TG, and LDL-c in the OB and T2DM groups following completion of the exercise program (p<0.05). In contrast HDL-c levels were significantly increased after the exercise program in the two groups (p<0.05). However, both pre and post exercise TG and LDL-c levels were significantly higher in the T2DM group compared with the OB group (p<0.05) (Table 2).

Table 2. Blood lipid levels, before and after 12 weeks exercise program

Variable	CO		OB		T2DM	
	pre	post	pre	post	pre	post
TC (mg/dL)	184.27±9.50	179.71±6.57	219.39^{a}±10.13	191.86^{ab}±9.39	256.52^{a}±9.73	201.52^{ab}±9.74
TG (mg/dL)	94.50±7.10	92.93±3.21	131.41^{a}±4.96	109.68^{b}±4.14	147.62^{a}±8.38	123.57^{abc}±4.42
HDL-c (mg/dL)	48.88±1.38	48.19±1.35	50.49±2.50	53.39^{b}±1.71	39.76^{ac}±1.32	42.48^{bc}±1.15
LDL-c (mg/dL)	116.49±9.53	112.94±6.15	142.62^{a}±10.37	116.53^{b}±8.74	187.26^{ac}±9.27	134.33^{bc}±9.30

Values are mean ± SE; $^{a}p<0.05$ vs. CO, $^{b}p<0.05$ vs. pre, $^{c}p<0.05$ vs. OB
CO: control group; OB: obese group; T2DM: type 2 diabetes mellitus group; TC: total cholesterol; TG: triglycerol; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol

Table 3. Glycemic control before and after 12 weeks exercise program

Variable	CO		OB		T2DM	
	pre	post	pre	post	pre	post
Glucagon (pg/mL)	136.05±6.54	125.06±12.91	116.09^{a}±3.44	118.97±3.09	136.61±4.59	140.72±11.22
Insulin (uU/mL)	23.86±2.84	21.20±1.77	45.59^{a}±5.59	30.16^{ab}±2.71	35.29^{ac}±2.73	27.83^{ab}±2.46
Glucose (mg/dL)	73.09±1.42	75.36±0.89	139.50^{a}±8.87	96.36^{ab}±5.10	203.50^{abc}±14.34	140.42^{abc}±9.78
HOMA-IR	4.29±0.45	3.94±0.29	15.35^{a}±1.75	7.30^{ab}±0.81	17.83^{a}±1.86	9.60^{ab}±1.02
C-peptide (ng/dL)	3.18±0.36	2.58±0.21	4.18^{a}±0.56	2.98^{b}±0.41	5.05^{a}±0.36	2.53^{b}±0.17

Values are mean ± SE; $^{a}p<0.05$ vs. CO, $^{b}p<0.05$ vs. pre,$^{c}p<0.05$ vs. OB
CO: control group; OB: obese group; T2DM: type 2 diabetes mellitus group; HOMA-IR: homoeostasis model assessment-insulin resistance

Table 4. Changes of blood adipokines concentration

Variable	CO		OB		T2DM	
	pre	post	pre	post	pre	post
Leptin (ng/mL)	1.34±0.17	1.20±0.12	2.54^{a}±0.24	1.69^{b}±0.16	2.93^{a}±0.32	2.13^{ab}±0.24
Resistin (ng/mL)	6.73±0.49	6.67±0.70	8.07^{a}±0.47	6.11^{b}±0.36	8.40^{a}±0.63	7.39^{b}±0.61
Visfatin (pg/mL)	129.74±12.16	127.66±6.93	247.72^{a}±14.95	184.22^{ab}±7.75	268.39^{a}±9.62	192.88^{ab}±8.97
RBP4 (pg/mL)	483.40±4.01	479.02±5.79	631.53^{a}±17.39	595.36^{ab}±10.80	629.91^{a}±20.83	596.52^{ab}±14.92

Values are mean ± SE $^{a}p<0.05$ vs. CO, $^{b}p<0.05$ vs. pre
CO: control group; OB: obese group; T2DM: type 2 diabetes mellitus group

In addition insulin, glucose, HOMA-IR and C-peptide levels were decreased in the OB and T2DM groups following the exercise program ($p<0.05$) (Table 3). Glucose levels were significantly higher in the T2DM group than the OB group ($p<0.05$) (Table 3).

Leptin, resistin, visfatin, and RBP4 levels were significantly higher in the OB and T2DM groups compared with the CO group prior to the 12-week exercise program ($p<0.05$). All of these adipokines were significantly decreased in the OB and T2DM groups following the exercise program ($p<0.05$) (Table 4).

DISCUSSION

In this study, 12 weeks of exercise produced positive effects on body composition, serum lipid profiles, and adipokines in Korean children who were obese or who had T2DM. These results suggest that regular exercise plays a role in improving body composition control, cardiovascular disease risk factors and glycemic control in these groups.

Regular exercise and cardiovascular fitness have positive effects on insulin resistance and cardiovascular disease risk factors in children and adolescents[15, 16]. Cardiovascular fitness is the strongest predictor for cardiovascular disease[17]. Data from the US National Health and Nutrition Examination Survey NHANES have implicated VO_{2max} as a risk factor for T2DM and cardiovascular disease in adolescents[18]. Kim et al. reported that TC and TG levels were higher and HDL-c levels were lower among participants with low fitness levels than in those with high fitness levels[19]. These results suggest that improvements in fitness and reduction of obesity are important factors for the prevention of cardiovascular disease[19]. Our findings that regular exercise reduces cardiovascular disease risk factors, as well as improving body composition and glycemic control in Korean children who are obese or who have T2DM further strengthens the evidence for the benefits of exercise.

In South Korea, the average time spent by children physical activity is less than 40 minutes each a week. This is due to lack of impetus to improve health despite evidence that, exercise improve insulin sensitivity in children[20–22]. In a study by Nassis et al. overweight adolescent girls were assigned to a 12-week aerobic exercise program consisting of 40-minute exercise sessions three days per week[21]. Insulin levels were reduced significantly by the end of the study[21]. Reduction in insulin levels are not always accompanied by a reduction in %fat suggesting that physical activity has a positive effect on insulin sensitivity independent of body mass[23]. Interestingly, in the Diabetes Prevention Program, those who met the physical activity goal and not the weight loss goal had a 44% decrease in diabetes incidence[24], Furthermore, in the Finnish Diabetes Trial, achieving 4-hours of physical activity per week led to a reduction in diabetes risk in subjects who did not lose weight[25]. Aerobic and resistance exercises have important implications and provide therapeutic strategies for the treatment of childhood obesity and the reduction of insulin resistance[26]. Six months of lifestyle modification, through a combination of improved diet and physical exercise, significantly reduced body weight, adiposity, waist circumference, blood pressure, fasting glucose, and insulin, and improved insulin resistance and lipid profiles in obese children[27]. A recent meta-analysis reported that aerobic exercise performed for 60 minutes three times a week lowers LDL-c and TG levels in obese children, and combined exercise increases the level of HDL-c[28].

Resistin levels are comparatively high in obese individuals without or without metabolic syndrome[29]. Significantly higher visfatin levels have also been reported in obese individuals[30]. Reductions in adipokine levels and cardiometabolic risk factors have been associated with weight loss. Elevated circulating levels of adipokines are independently associated with a higher risk for cardiovascular disease[31]. However, Siegrist et al. showed that only baseline BMI was associated with higher TG, higher insulin levels, and reduced HDL-c levels. Especially, baseline leptin has been associated with higher levels of TG and insulin levels[11]. The benefits of regular exercise on adipokine levels are not permanent: discontinuation of exercise can lead to negative effects on lipid profiles and leptin levels in overweight children[32].

Increases in serum RBP4 concentration have been observed in obese adults with insulin-resistant T2DM, whereas reductions in circulating concentrations are associated with improved insulin action[33, 34]. In addition, increased RBP4 concentrations have been observed in lean individuals with insulin resistance[33, 35], and regulatory single nucleotide polymorphisms of the RBP4 gene have recently been described in patients with T2DM[36]. RBP4 levels could be linked to obesity and insulin resistance, although it must be emphasized that a positive association has not always been demonstrated[37]. Most studies report increased RBP4 levels with increasing levels of obesity, and high RBP4 levels have been demonstrated in obese children[10, 38–40]. Resistin is expressed in adipose tissue and has roles in glucose homeostasis, lipid metabolism and insulin action[41, 42]. It might be a weak biochemical marker of metabolic dysfunction, but it does not predict insulin resistance in Chinese children[43]. Robertes et al. showed that an intensive short-term diet and exercise intervention decreased resistin (control 40%, obese 35.1%) and leptin (control 69.3%, obese 44.1%) levels in children[6]. In the current study, baseline adipokines levels were higher in children who were obese or who had T2DM. However, adipokines levels were significantly decreased after regular exercise in these children. Thus regular exercise from childhood is believed to be necessary to control body weight and metabolic syndrome.

Regular aerobic exercise in Korean children with obesity or T2DM improved body composition and VO_{2max}, ameliorated lipid profiles and glycemic control, and decreased adipokines levels. These results suggest that weight loss associated with regular exercise reduces the risks associated with obesity and T2DM in children. Thus, regular exercise is beneficial for glycemic control in Korean children with obesity or T2DM.

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