Effects of regular exercise on obesity and type 2 diabetes 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 (VO₂max), 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 (This article was submitted Jan. 29, 2015, and was accepted Mar. 7, 2015)

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 countries1–3. 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 diabetes1. T2DM has, also been associated with the growing prevalence of childhood obesity4. In addition, increases in childhood obesity have been accompanied by an increased incidence of type 2 diabetes in youth4, 5. In Asia the prevalence of T2DM has increased rapidly in recent decades and is characterized by a younger age and lower body mass index (BMI) at onset compared with Western countries5.

Early treatment of T2DM in children is essential to slow or delay disease progression and prevent complications.

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
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 children in the T2DM group were D University Hospital inpatients with a normal 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. 9) was conducted for 40–60 minutes per session four times a week, for 12 weeks. Participants achieved 50% of their oxygen consumption through the VO2max 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 VO2max. Each session was preceded and followed by a 5-minute warm-up and cool-down6.

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 (Taech, Seoul, Korea) and a Quark b2 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 > 1.1514.

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 × group) 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). VO2max 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 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±2.66 | 69.16±2.64 | 63.98±4.43 | 62.93±4.19 |
| BMI (kg/m²)       | 21.18±0.72 | 21.13±0.70 | 26.56±0.58 | 24.65±0.62 | 24.28±1.27 | 23.88±1.20 |
| %fat (%)          | 16.77±2.19 | 16.85±2.17 | 30.54±1.11 | 26.96±0.87 | 28.97±1.90 | 27.94±1.69 |
| VO2max (mL/min/kg)| 33.17±1.41 | 33.98±1.04 | 28.05±1.12 | 31.16±1.36 | 30.12±1.61 | 33.57±1.31 |

Values are mean ± SE; *p<0.05 vs. CO, *p<0.05 vs. pre
CO: control group; B: obese group; T2DM: type 2 diabetes mellitus group; BMI: body mass index
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 VO2max 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 physically active is less than 40 minutes each a week. This is due to lack of impetus to improve health despite evidence that,

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

| Variable | CO pre | post | OB pre | post | T2DM pre | post |
|----------|--------|------|--------|------|----------|------|
| TC (mg/dL) | 184.27±9.50 | 179.71±6.57 | 219.39±10.13 | 191.86±9.39 | 256.52±9.73 | 201.52±9.74 |
| TG (mg/dL) | 94.50±7.10 | 92.93±3.21 | 131.41±4.96 | 109.68±4.14 | 147.62±8.38 | 123.57±4.42 |
| HDL-c (mg/dL) | 48.88±1.38 | 48.19±1.35 | 50.49±2.50 | 53.39±1.71 | 39.76±1.32 | 42.48±1.15 |
| LDL-c (mg/dL) | 116.49±9.53 | 112.94±6.15 | 142.62±10.37 | 116.53±8.74 | 187.26±9.27 | 134.33±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 pre | post | OB pre | post | T2DM pre | post |
|----------|--------|------|--------|------|----------|------|
| Glucagon (pg/mL) | 136.05±6.54 | 125.06±12.91 | 116.09±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±5.59 | 30.16±2.71 | 35.29±2.73 | 27.83±2.46 |
| Glucose (mg/dL) | 73.09±1.42 | 75.36±0.89 | 139.50±8.87 | 96.36±7.10 | 203.50±14.34 | 140.42±9.78 |
| HOMA-IR | 4.29±0.45 | 3.94±0.29 | 15.35±1.75 | 7.30±0.81 | 17.83±1.86 | 9.60±1.02 |
| C-peptide (ng/mL) | 3.18±0.36 | 2.58±0.21 | 4.18±0.56 | 2.98±0.41 | 5.05±0.36 | 2.53±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: homeostasis model assessment-insulin resistance

### Table 4. Changes of blood adipokines concentration

| Variable | CO pre | post | OB pre | post | T2DM pre | post |
|----------|--------|------|--------|------|----------|------|
| Leptin (ng/mL) | 1.34±0.17 | 1.20±0.12 | 2.54±0.24 | 1.69±0.16 | 2.93±0.32 | 2.13±0.24 |
| Resistin (ng/mL) | 6.73±0.49 | 6.67±0.70 | 8.07±0.47 | 6.11±0.36 | 8.40±0.63 | 7.39±0.61 |
| Visfatin (pg/mL) | 129.74±12.16 | 127.66±6.93 | 247.72±14.95 | 184.22±7.75 | 268.39±9.62 | 192.88±8.97 |
| RBP4 (pg/mL) | 483.40±4.01 | 479.02±5.79 | 631.53±17.39 | 595.36±10.80 | 629.91±20.83 | 596.52±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
exercise improve insulin sensitivity in children. 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. Insulin levels were reduced significantly by the end of the study. 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. 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. 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. Aerobic and resistance exercises have important implications and provide therapeutic strategies for the treatment of childhood obesity and the reduction of insulin resistance. 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. 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.

Resistin levels are comparatively high in obese individuals without or without metabolic syndrome. Significantly higher visfatin levels have also been reported in obese individuals. 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. However, Siegrist et al. showed that only baseline BMI was associated with higher TG, higher insulin levels, and reduced HDL-c levels. Especialy, baseline leptin has been associated with higher levels of TG and insulin levels. 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. 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. In addition, increased RBP4 concentrations have been observed in lean individuals with insulin resistance, and regulatory single nucleotide polymorphisms of the RBP4 gene have recently been described in patients with T2DM. RBP4 levels could be linked to obesity and insulin resistance, although it must be emphasized that a positive association has not always been demonstrated. Most studies report increased RBP4 levels with increasing levels of obesity, and high RBP4 levels have been demonstrated in obese children. Resistin is expressed in adipose tissue and has roles in glucose homeostasis, lipid metabolism and insulin action. It might be a weak biochemical marker of metabolic dysfunction, but it does not predict insulin resistance in Chinese children. 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. 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 VO2max, 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.

REFERENCES

1) American Diabetes Association: Type 2 diabetes in children and adolescents. Pediatrics, 2000, 105: 671–680. [Medline] [CrossRef]
2) Scott CR, Smith JM, Craddock MM, et al.: Characteristics of youth-onset non-insulin-dependent diabetes mellitus at diagnosis. Pediatrics, 1997, 100: 84–91. [Medline] [CrossRef]
3) Fagot-Campagna A, Petitt DJ, Engelgau MM, et al.: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr, 2000, 136: 664–672. [Medline] [CrossRef]
4) Pinhas-Hamiel O, Zeitzer P: The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr, 2005, 146: 693–700. [Medline] [CrossRef]
5) Chan JC, Malik V, Jia W, et al.: Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA, 2009, 301: 2129–2140. [Medline] [CrossRef]
6) Roberts CK, Izadpanah A, Angadi SS, et al.: Effects of an intensive short-term diet and exercise intervention: comparison between normal-weight and obese children. Am J Physiol Regul Integr Comp Physiol, 2013, 305: R552–R557. [Medline] [CrossRef]
7) Izadpanah A, Barnard RJ, Almeida AJ, et al.: A short-term diet and exercise intervention ameliorates inflammation and markers of metabolic health in overweight/obese children. Am J Physiol Endocrinol Metab, 2012, 303: E542–E550. [Medline] [CrossRef]
8) Jia W, Wu H, Bao Y, et al.: Association of serum retinol-binding protein 4 and visceral adiposity in Chinese subjects with and without type 2 diabetes. J Clin Endocrinol Metab, 2007, 92: 3224–3229. [Medline] [CrossRef]
9) Klöting N, Graham TE, Berndt J, et al.: Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. Cell Metab, 2007, 6: 79–87. [Medline] [CrossRef]
10) Mabrouk R, Ghaeeri H, Shehab A, et al.: Serum visfatin, resistin and IL-18 in a group of Egyptian obese diabetic and non diabetic individuals. Egypt J Immunol, 2013, 20: 1–11. [Medline]
11) Siegrist M, Rank M, Wolfarth B, et al.: Leptin, adiponectin, and short-term and long-term weight loss after a lifestyle intervention in obese children. Nutrition, 2013, 29: 851–857. [Medline] [CrossRef]
12) Steppan CM, Bailey ST, Bhat S, et al.: The hormone resistin links obesity to diabetes. Nature, 2001, 409: 307–312. [Medline] [CrossRef]
13) Boyraz M, Cekmez F, Karaoğlu A, et al.: Relationship of adipokines (adiponectin, resistin and RBP4) with metabolic syndrome components in pubertal obese children. Biomarkers Med, 2013, 7: 423–428. [Medline] [CrossRef]
14) American College of Sports Medicine: ACSM’s guidelines for exercise testing and prescription. Philadelphia: Lippincott, Williams & Wilkins. 2008.
15) Meyer AA, Kundt G, Steiner M, et al.: Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. Pediatrics, 2006, 117: 1560–1567. [Medline] [CrossRef]
16) Rauramaa R, Rankinen T, Tuomainen P, et al.: Inverse relationship between cardiorespiratory fitness and carotid atherosclerosis. Atherosclerosis, 1995, 112: 213–221. [Medline] [CrossRef]
17) Hurtig-Wennlöf A, Ruiz JR, Harro M, et al.: Cardiorespiratory fitness relates more strongly than physical activity to cardiovascular disease risk factors in healthy children and adolescents: the European Youth Heart Study. Eur J Cardiovasc Prev Rehabil, 2007, 14: 575–581. [Medline]
18) Carnethon MR, Gulati M, Greenland P: Prevalence and cardiovascular disease correlates of low cardiorespiratory fitness in adolescents and adults. JAMA, 2005, 294: 2981–2988. [Medline] [CrossRef]
19) Kim ES, Im JA, Kim KC, et al.: Improved insulin sensitivity and adiponectin level after exercise training in obese Korean youth. Obesity (Silver Spring), 2007, 15: 3023–3030. [Medline] [CrossRef]
20) Bell LM, Watts K, Siafarikas A, et al.: Exercise alone reduces insulin resistance in obese children independently of changes in body composition. J Clin Endocrinol Metab, 2007, 92: 4230–4235. [Medline] [CrossRef]
21) Nassis GP, Papantakou K, Skenderi K, et al.: Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. Metabolism, 2005, 54: 1472–1479. [Medline] [CrossRef]
22) Shaibi GQ, Cruz ML, Ball GD, et al.: Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. Med Sci Sports Exerc, 2006, 38: 1208–1215. [Medline] [CrossRef]
23) Guiliéry IK, Cullen KW, Thompson D, et al.: Physical activity in youth with well-controlled versus poorly controlled type 2 diabetes. Clin Pediatr (Philad), 2012, 51: 354–358. [Medline] [CrossRef]
24) Hamman RF, Wing RR, Edelstein SL, et al.: Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care, 2006, 29: 2102–2107. [Medline] [CrossRef]
25) Tuomilehto J, Lindström J, Eriksson JG, et al. Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med, 2001, 344: 1343–1350. [Medline] [CrossRef]
26) Lee DC, Lee JW, Im JA: Association of serum retinol binding protein 4 and insulin resistance in apparently healthy adolescents. Metabolism, 2007, 56: 327–331. [Medline] [CrossRef]
27) Garanty-Bogacka B, Syrenicz M, Goraj J, et al.: Changes in inflammatory biomarkers after successful lifestyle intervention in obese children. Endokrynol Pol, 2011, 62: 499–505. [Medline] [CrossRef]
28) Escalante Y, Saavedra JM, García-Hermoso A, et al.: Improvement of the lipid profile with exercise in obese children: a systematic review. Prev Med, 2012, 54: 293–301. [Medline] [CrossRef]
29) Makri E, Mosalla W, Benecedezline-Boussaid L, et al.: Correlation of resistin with inflammatory and cardiometabolic markers in obese adolescents with and without metabolic syndrome. Obes Facts, 2013, 6: 393–404. [Medline] [CrossRef]
30) Jaleel A, Aheed B, Jaleel S, et al.: Association of adipokines with obesity in children and adolescents. Biomarkers Med, 2013, 7: 731–735. [Medline] [CrossRef]
31) Koh KK, Park SM, Quon MF: Leptin and cardiovascular disease: response to therapeutic interventions. Circulation, 2008, 117: 3238–3249. [Medline] [CrossRef]
32) Woo J, Shin KO, Yoo JH, et al.: The effects of detraining on blood adipokines and antioxidant enzyme in Korean overweight children. Eur J Pediatr, 2012, 171: 235–243. [Medline] [CrossRef]
33) Graham TE, Yang Q, Blüher M, et al.: Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med, 2006, 354: 2552–2563. [Medline] [CrossRef]
34) Yang Q, Graham TE, Mody N, et al.: Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature, 2005, 436: 356–362. [Medline] [CrossRef]
35) Polonsky KS: Retinol-binding protein 4, insulin resistance, and type 2 diabetes. N Engl J Med, 2006, 354: 2596–2598. [Medline] [CrossRef]
36) Munkhtulga L, Nakayama K, Utsumi N, et al.: Identification of a regulatory SNP in the retinol binding protein 4 gene associated with type 2 diabetes in Mongolia. Hum Genet, 2007, 120: 879–888. [Medline] [CrossRef]
37) Kanaka-Gantenbein C, Margeli A, Pervanidou P, et al.: Retinol-binding protein 4 and lipoprotein-L2 in childhood and adolescent obesity: when children are not just “small adults”. Clin Chem, 2008, 54: 1176–1182. [Medline] [CrossRef]
38) Balagopal P, Graham TE, Kahn BB, et al.: Reduction of elevated serum retinol binding protein in obese children by lifestyle intervention: association with subclinical inflammation. J Clin Endocrinol Metab, 2007, 92: 1971–1974. [Medline] [CrossRef]
39) Lee S, Bacha F, Hannon T, et al.: Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. Diabetes, 2012, 61: 2787–2795. [Medline] [CrossRef]
40) Rhie YJ, Choi BM, Eun SH, et al.: Association of serum retinol binding protein 4 with adiposity and pubertal development in Korean children and adolescents. J Korean Med Sci, 2011, 26: 797–802. [Medline] [CrossRef]
41) Rajala MW, Obici S, Scherer PE, et al.: Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production. J Clin Invest, 2003, 111: 225–230. [Medline] [CrossRef]
42) Reilly MP, Lehrke M, Wolfe ML, et al.: Resistin is an inflammatory marker of atherosclerosis in humans. Circulation, 2005, 111: 932–939. [Medline] [CrossRef]
43) Li M, Fisette A, Zhao XY, et al.: Serum resistin correlates with central obesity but weakly with insulin resistance in Chinese children and adolescents. Int J Obes, 2009, 33: 424–439. [Medline] [CrossRef]