MUFAs and n-6 PUFAs and a decrease in n-3 PUFAs over a 3-year period. The difference between the first and second phases of the study might be explained, in part, by changes in dietary fatty acid composition; however, endogenous fatty acid metabolism, which is modulated by desaturase activities, might be an important determinant of the plasma fatty acid composition of plasma phospholipids[16]. Furthermore, our findings of the 3-year changes in D5D and D6D indices suggest that they might also be determined by body fatness and insulin resistance. Earlier, a longitudinal study of phospholipid fatty acid composition in German children demonstrated that n-3 and n-6 PUFAs were higher and the contents of saturated fat and MUFA were lower when they were 5 years old than when they were 2 years old, and the AA (20:4n-6)/LA (18:2n-6) ratio showed no change in 3 years, although the dietary intake of fatty acid composition changed. It was also suggested that the metabolism of individual endogenous fatty acids, rather than dietary fatty acid composition, determined the longitudinal changes in plasma fatty acid profile[16].

The SCD, D5D and D6D indices are regulated by diet and hormones, which affect insulin sensitivity[22]. In our longitudinal study, we found sexual dimorphism in the relationship between changes in the D6D and D5D indices and changes in body fatness. Increased D6D index and decreased D5D index were associated with increased RW only in boys, whereas sexual dimorphism was not detected in association with changes in WHtR. During puberty, the change in body composition is markedly different between boys and girls[23]. The fat percentage decreases in boys and increases in girls; thus, increasing RW in pubertal girls does not always indicate a trend toward obesity. On the other hand, the percentage of abdominal fat, both visceral and subcutaneous, does not change with age in either boys or girls[23]; therefore, an increase in WHtR suggests a trend toward obesity in both sexes. The sexual dimorphism of the association between changes in the D6D and D5D indices and changes in body fatness could be explained by sex-specific pubertal changes in body composition.

Another novel finding of this study was that changes in the D6D and D5D indices were associated with changes in HOMA-R in girls but not in boys. During puberty, children develop transient insulin resistance in response to physiological changes, resulting in a decrease in peripheral insulin sensitivity and a compensatory increase in insulin secretion[24]. The main determinants of insulin sensitivity during this period are total body fat and central body fat in girls and total body fat and lean mass in boys[25]. The association between changes in the D6D and D5D indices and changes in HOMA-R in our study might reflect the influence of physiological insulin resistance during this period.

SCD plays a crucial role in the development of obesity and insulin resistance in animal models[26]. In some human studies, an elevated SCD index in plasma[27] and adipose tissue[28] reflects higher levels of adiposity, TG levels and insulin resistance. In this study, however, changes in the SCD16 index were not associated with changes in RW, WHtR or HOMA-R in either sex, and the change in the SCD18 index in boys was negatively associated with changes in RW and WHtR. It was difficult to interpret these findings; however, Warensjö *et al.*[14] also found that the SCD18 index obtained from the fatty acid composition of plasma phospholipids was correlated negatively with body mass index, which was compatible with our findings in boys at baseline. This might well be because other lipid fractions are appropriate for estimation of the SCD index via product/precursor ratios[29].

The present study was not designed to evaluate dietary intake, hormonal changes or pubertal stages, which are key factors of changes in body fatness and insulin resistance during early puberty; therefore, the influence of pubertal change on fatty acid composition and desaturase indices could not be evaluated. However, our results demonstrated that the association between the D6D and D5D indices and body fatness might be modified by sex, suggesting that the determinants of longitudinal changes in D6D and D5D indices are different between boys and girls. Further studies are needed to investigate the interaction between the desaturase indices and the changes in growth and sex hormones.

In conclusion, the fatty acid composition of plasma phospholipids in obese children showed an increase in DGLA (20:3n-6), an increase in the D6D index and a decrease in the D5D index. This longitudinal study demonstrated that the D6D and D5D indices and DGLA (20:3n-6) tracked strongly, and the 3-year changes in both desaturase indices and DGLA (20:3n-6) were associated with the change in WHtR; therefore, obesity, especially abdominal adiposity, is a determinant of the fatty acid composition of plasma phospholipids and its longitudinal changes during puberty.

Conflict of Interest

None.

References

1) Flynn MA, McNeil DA, Maloff B, Mutasingwa D, Wu M, Ford C, Tough SC: Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with 'best practice' recommendations. Obes Rev, 2006; 7: 7-66
2) Han JC, Lawlor DA, Kimm SY: Childhood obesity. Lancet, 2010; 375: 1737-1748
3) Warensjö E, Sundström J, Lind L, Vessby B: Factor analysis of fatty acids in serum lipids as a measure of dietary fat quality in relation to the metabolic syndrome in men. Am J Clin Nutr, 2006; 84: 442-448
4) Risérus U: Fatty acids and insulin sensitivity. Curr Opin Clin Nutr Metab Care, 2008; 11: 100-105
5) Yanagisawa N, Shimada K, Miyazaki T, Kume A, Kitamura Y, Ichikawa R, Ohmura H, Kiyanagi T, Hiki M, Fukao K, Sumiyoshi K, Hirose K, Matsumori R, Takizawa H, Fujii K, Mokuno H, Inoue N, Daida H: Polyunsaturated fatty acid levels of serum and red blood cells in apparently healthy Japanese subjects living in an urban area. J Atheroscler Thromb, 2010; 17: 285-294
6) Decsi T, Molnár D, Koletzko B: Long-chain polyunsaturated fatty acids in plasma lipids of obese children. Lipids, 1996; 31: 305-311
7) Decsi T, Csábi G, Török K, Erhardt E, Minda H, Burus I, Molnár S, Molnár D: Polyunsaturated fatty acids in plasma lipids of obese children with and without metabolic cardiovascular syndrome. Lipids, 2000; 35: 1179-1184
8) Klein-Platat C, Drai J, Oujaa M, Schlienger JL, Simon C: Plasma fatty acid composition is associated with the metabolic syndrome and low-grade inflammation in overweight adolescents. Am J Clin Nutr, 2005; 82: 1178-1184
9) Karlsson M, Mårild S, Brandberg J, Lönn L, Friberg P, Strandvik B: Serum phospholipid fatty acids, adipose tissue, and metabolic markers in obese adolescents. Obesity (Silver Spring), 2006; 14: 1931-1939
10) Saito E, Okada T, Abe Y, Kuromori Y, Miyashita M, Iwata F, Hara M, Ayusawa M, Mugishima H, Kitamura Y: Docosahexaenoic acid content in plasma phospholipids and desaturase indices in obese children. J Atheroscler Thromb, 2011; 18: 345-350
11) Okada T, Furuhashi N, Kuromori Y, Miyashita M, Iwata F, Harada K: Plasma palmitoleic acid content and obesity in children. Am J Clin Nutr, 2005; 82: 747-750
12) Bolton-Smith C, Woodward M, Tavendale R: Evidence for age-related differences in the fatty acid composition of human adipose tissue, independent of diet. Eur J Clin Nutr, 1997; 51: 619-624
13) Maruyama C, Yoneyama M, Suyama N, Yoshimi K, Teramoto A, Sakaki Y, Suto Y, Takahashi K, Araki R, Ishizaka Y, Yamakado M, Teramoto T: Differences in serum phospholipid fatty acid compositions and estimated desaturase activities between Japanese men with and without metabolic syndrome. J Atheroscler Thromb, 2008; 15: 306-313
14) Warensjö E, Risérus U, Gustafsson IB, Mohsen R, Cederholm T, Vessby B: Effects of saturated and unsaturated fatty acids on estimated desaturase activities during a controlled dietary intervention. Nutr Metab Cardiovasc Dis, 2008; 18: 683-690
15) Moilanen T, Räsänen L, Viikari J, Akerblom HK, Nikkari T: Tracking of serum fatty acid composition: a 6-year follow-up study in Finnish youths. Am J Epidemiol, 1992; 136: 1487-1492
16) Guerra A, Demmelmair H, Toschke AM, Koletzko B: Three-year tracking of fatty acid composition of plasma phospholipids in healthy children. Ann Nutr Metab, 2007; 51: 433-438
17) Yamazaki K, Matsuoka H, Kawanobe S, Hujita Y, Murata M: Evaluation of standard body weight by sex, age and height- on the basis of 1990 school year data. J Jpn Ped Sci, 1994; 98: 96-102 (in Japanese with English abstract)
18) Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 1972; 18: 499-502
19) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985; 28: 412-419
20) Bligh EG, Dyer WJ: A rapid method of total lipid extraction and purification. Can J Biochem Physiol, 1959; 37: 911-917
21) Okada T, Murata M, Yamauchi K, Harada K: New criteria of normal serum lipid levels in Japanese children: the nationwide study. Pediatr Int, 2002; 44: 596-601
22) Nakamura MT, Nara TY: Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases. Annu Rev Nutr, 2004; 24: 345-376
23) Roemmich JN, Clark PA, Lusk M, Friel A, Weltman A, Epstein LH, Rogol AD: Pubertal alterations in growth and body composition. VI. Pubertal insulin resistance: relation to adiposity, body fat distribution and hormone release. Int J Obes Relat Metab Disord, 2002; 26: 701-709
24) Hannon TS, Janosky J, Arslanian SA: Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res, 2006; 60: 759-763
25) Brufani C, Tozzi A, Fintini D, Ciampalini P, Grossi A, Fiori R, Kiepe D, Manco M, Schiaffini R, Porzio O, Cappa M, Barbetti F: Sexual dimorphism of body composition and insulin sensitivity across pubertal development in obese Caucasian subjects. Eur J Endocrinol, 2009; 160: 769-775
26) Popeijus HE, Saris WH, Mensink RP: Role of stearoyl-CoA desaturases in obesity and the metabolic syndrome. Int J Obes (Lond), 2008; 32: 1076-1082
27) Zhou YE, Egeland GM, Meltzer SJ, Kubow S: The association of desaturase 9 and plasma fatty acid composition with insulin resistance-associated factors in female adolescents. Metabolism, 2009; 58: 158-166
28) Sjögren P, Sierra-Johnson J, Gertow K, Rosell M, Vessby B, de Faire U, Hamsten A, Hellenius ML, Fisher RM: Fatty acid desaturases in human adipose tissue: relationships between gene expression, desaturation indexes and insulin resistance. Diabetologia, 2008; 51: 328-335
29) Karpe F, Hodson L: Caution on the interpretation of plasma fatty acid composition as a proxy marker for SCD1 activity: Particular implications for using the 16:1/16:0 ratio in QTL studies involving hyperlipidemic patients. Arterioscler Thromb Vasc Biol, 2008; 28: e152

Significant associations between hemostatic/fibrinolytic systems and accumulation of cardiovascular risk factors in Japanese elementary schoolchildren

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The aim of this study was to establish the reference values of hemostatic/fibrinolytic markers and investigate their relationship with physical constitution and cardiovascular risk factors in a normal schoolchildren population. This study comprised 148 healthy Japanese children aged 9–10 years (males 73; females 75). We performed laboratory tests including blood levels of leptin, high-sensitive C-reactive protein (hs-CRP), hemostatic and fibrinolytic markers [plasminogen activator inhibitor 1 (PAI-1), coagulation factor VII (FVII), coagulation factor X (FX), fibrinogen (Fbg), protein C, protein S], as well as common biochemical markers in the morning after an overnight fast. We investigated the mean, 10th, 50th and 90th percentile values of these markers. All parameters were compared between two groups, that is those with body mass index (BMI) 90th percentile or higher and BMI less than 90th percentile, and between subgroups based on the number of cardiovascular risk factors. Multiple-linear regression was used to assess associations between these hematological parameters and the components related to metabolic syndrome (MetS). Alanine aminotransferase (ALT), uric acid, leptin, hs-CRP, and all hemostatic/fibrinolytic markers (PAI-1, FVII, FX, Fbg, protein C, protein S) tested were significantly higher in the group with BMI 90th percentile or higher, and increased with accumulation of cardiovascular risk factors. Multiple-linear regression analysis showed that these values were associated with one or more components related to MetS. Reference values of hemostatic/fibrinolytic markers in Japanese schoolchildren were obtained. Many hemostatic/fibrinolytic markers showed significant association with BMI and accumulation of cardiovascular risk factors in normal Japanese schoolchildren. *Blood Coagul Fibrinolysis* 26:75–80 © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Cardiovascular disease (CVD) is the main cause of death worldwide, and is known to have close relationships with metabolic syndrome (MetS), whose incidence is increasing following an increase in the obese population [1]. MetS is defined as a constellation of clinical features including central obesity, lipid abnormality, high blood pressure, and insulin resistance. Each component is considered to be an independent cardiovascular risk factor, and the sum of them increases the risk synergistically [2,3]. Though the mechanisms of the complex pathways that form MetS have not yet been completely elucidated, existence of these cardiovascular risk factors in childhood is believed to contribute to arteriosclerotic changes, leading to cardiovascular events in adulthood [4]. Besides the traditional risk factors noted above, a number of studies of adults have demonstrated that a hypercoagulate/hypofibrinolytic state, variation in adipokines, chronic inflammations, endothelial dysfunctio and hyperuricemia are also related to MetS or CVD. Laboratory markers that reflect these conditions may be sensitive indexes for detecting progression to MetS [5–8].

Recent studies in children demonstrated a close relationship between fibrinogen (Fbg), tissue-type plasminogen activator (tPA), plasminogen activator inhibitor 1 (PAI-1) and obesity [9,10]. These results suggest the presence of a prothrombotic state in obese children at an early age. Meanwhile, the relationship of hemostatic/fibrinolytic systems and cardiovascular risk factors in childhood and the underlying pathophysiological mechanism for the further CVD remain elusive [11].

Although various works have already been done with respect to hemostatic/fibrinolytic alterations in childhood, most of these studies focused on overweight children and their comparision with nonobese or normal control subjects. Few studies have been conducted with a normal pediatric population. Furthermore, there are few standard values of hemostatic/fibrinolytic markers obtained after strict overnight fasting from a normal child

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population. Our previous study provides standard values of hemostatic/fibrinolytic markers in Japanese preschool-children, and showed that hemostatic/fibrinolytic or adipose tissue-related variables are associated with the components of MetS from an early age [12].

In this study, we investigated the standard values of hemostatic/fibrinolytic markers, and their relationships with physical constitution and cardiovascular risk factors in healthy elementary schoolchildren in Japan.

Methods

Participants

The study comprised 148 children, (the fourth grade, aged 9–10 years; males 73, females 75), from a public elementary school in Joso city, Ibaraki prefecture, Japan. These subjects are recognized as representative of the general population of the fourth graders. Children with illness on examination including common cold or a history of significant disease were excluded from the study. The Ethics Committee of Human Research of the University of Tsukuba Hospital approved the study protocol in advance. In addition, before the commencement of the study, parents of the participants attended an instruction lecture about the importance of prevention of MetS from childhood. Written informed consent was subsequently obtained from each parent.

Table 1 Measured variables

	n	Mean ± SD	Min–Max	10th	50th	90th
Height (cm)	148	135.5 ± 6.0	117.0–149.0	127.4	136.0	142.8
Weight (kg)	148	33.45 ± 7.92	20.0–64.3	26.10	31.25	44.95
BMI (kg/m^2)	148	18.08 ± 3.33	13.81–31.89	14.70	17.28	22.70
SBP (mmHg)	148	104.8 ± 10.1	79–126	91.0	106.0	117.1
DBP (mmHg)	148	55.6 ± 6.8	31–70	47.0	56.0	65.0
Waist (cm)	148	62.8 ± 9.5	49.0–94.0	54.2	59.3	75.2
W/H	148	0.46 ± 0.06	0.38–0.68	0.40	0.44	0.54
Total cholesterol (mg/dl)	148	180.0 ± 27.1	119–282	146.9	178.0	216.2
HDL-C (mg/dl)	148	64.8 ± 13.1	35–105	49.0	62.0	84.0
LDL-C (mg/dl)	148	106.5 ± 24.9	67–201	79.9	101.0	140.0
Triglyceride (mg/dl)	147	66.8 ± 41.0	19–230	28.6	53.0	126.2
FPG (mg/dl)	148	93.9 ± 6.3	76–109	85.9	94.0	102.1
Insulin (μIU/ml)	144	7.81 ± 6.46	0.3–49.3	2.27	6.27	15.70
HOMA-IR	144	1.83 ± 1.51	0.06–11.44	0.51	1.40	3.86
ALT (IU/l)	148	17.9 ± 18.9	7–179	9.0	13.0	27.1
Uric acid (mg/dl)	148	4.44 ± 0.90	2.3–7.3	3.29	4.40	5.60
Ln hs-CRP	145	5.51 ± 1.38	3.91–10.06	3.91	5.31	7.62
Leptin (ng/ml)	146	6.04 ± 5.64	0.8–28.4	1.50	4.20	13.48
PAI-1 (ng/ml)	145	26.7 ± 16.5	10–97	11.0	22.0	46.4
Fbg (mg/dl)	145	236.9 ± 47.4	122–393	181.6	227.0	297.6
FVII (%)	145	93.6 ± 11.7	69–125	78.0	94.0	108.4
FX (%)	145	93.4 ± 11.9	60–127	76.6	94.0	108.4
Protein C (%)	145	94.6 ± 17.0	62–166	74.0	94.0	116.0
Protein S (%)	145	94.7 ± 14.0	67–137	75.0	95.0	113.4

ALT, alanine aminotransferase; Fbg, fibrinogen; FPG, fasting plasma glucose; FVII, factor VII; FX, factor X; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; ln, logarithms nature; PAI-1, plasminogen activator inhibitor 1; W/H, waist/height. Data are mean ± standard deviation (SD), minimum (Min), maximum (Max), 10th, 50th, 90th percentiles.

Anthropometric and biometric assessment

Height and weight were measured using standard methods (TTM-HV; Tsutsumi Co, Kyoto, and DC-320; Tanita Co, Tokyo, Japan), and the BMI was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured three times using an automated oscillatory system (TM-2571; A&D Co, Tokyo, Japan), after the participants had rested for at least 10 min in a seated position; the reported values represent the average of the second and third measurements.

Blood sampling and laboratory analyses

Blood samples were collected from the antecubital vein in the morning (between 0900 and 1030 h) after an overnight fast (except for water) and after a rest of at least 15 min immediately before sampling. Parents were required to restrict their children from taking meals or any sugar-containing liquids overnight. Children who consumed food before blood sampling were excluded from the study. The sample was drawn into three polypropylene tubes: one for serum collection to measure biochemical parameters and adipokines; one containing fluorescein Na, EDTA 2Na and heparin Na to measure fasting plasma glucose; one containing 1/10 volume of 3.13% sodium citrate to measure the hemostatic/fibrinolytic parameters. The parameters measured in this study are listed in Table 1. The latter two tubes were centrifuged, with the resultant plasma samples frozen immediately and then stored at −20°C until assayed. The homeostasis model assessment of insulin resistance (HOMA-IR) represented the product of fasting plasma glucose (FPG) (mg/dl) and insulin (μIU/ml) levels divided by a constant value of 405. Alanine aminotransferase (ALT), uric acid, triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Fbg, insulin, high-sensitivity C-reactive protein (hs-CRP) and FPG were measured by standard automated methods using the appropriate devices (JEOL, Sysmex, Mitsubishi Chemical Medience, Fujirebil, and Siemens Healthcare Diagnostics, Japan). Leptin was measured by radioimmunoassay (RIA; Aloka, Japan). Coagulation factor VII (FVII) and coagulation factor X (FX) were measured by clotting time methods. Protein C antigen, free protein S antigen and PAI-1 in a complex with tissue plasminogen activator 1 were assayed by latex photometric immunoassay (Mitsubishi Chemical Medience and JEOL).

Statistics

All continuous variables were expressed as mean ± standard deviation, with the 10th, 50th and 90th percentile values calculated for each parameter. Logarithms of the values were also calculated for hs-CRP (ln hs-CRP). The number of data differed slightly for parameters (maximum 148 and minimum 144; see Table 1) because the specimen volume was insufficient to allow all measurements in some children who needed to be resampled but refused. The study cohort was divided into two groups: those with 90th percentile or higher values of BMI, those with less than 90th percentile values of BMI. Each continuous variable was compared between the two groups using Student's t test. Participants were then assigned to subgroups based on the number of the following traditional cardiovascular risk factors: waist 75 cm or greater, and/or waist/height 0.5 cm or greater; triglyceride 120 mg/dl or higher and/or HDL-C 40 mg/dl or less; SBP 125 mmHg or higher and/or DBP 75 mmHg or higher; plasma glucose level 100 mg/dl or higher. These are used as the diagnostic criteria for pediatric MetS in Japan [13]. The number of each subgroup are described in the Results section and Tables 2 and 3. The hematological parameters, including ALT, uric acid, ln hs-CRP, leptin and hemostatic/fibrinolytic markers that were tested were compared between the subgroups using analysis of variance (ANOVA) followed by Bonferroni multiple comparisons. The relationships between the hematological parameters, including hemostatic/fibrinolytic systems and adipokines, and the components related to MetS were tested by the simple linear regression model, and significant variables were then subjected to stepwise linear regression analysis to identify independent predictors of MetS. A P value less than 0.05 was considered statistically significant.

Results

Every fourth grade child, except 20 children who did not approve participation in the study or the ones who fitted the exclusion criteria, was recruited. Table 1 details the anthropometric, biometric and hematological data for all participants. There were no sex differences in anthropometric and biometric data. Analysis of various parameters between children with BMI 90th percentile or higher ($n = 14$) and those with BMI less than 90th percentile ($n = 134$) was showed in Table 2. Children with BMI 90th percentile or higher demonstrated significantly higher levels of HDL-C, LDL-C, triglyceride, insulin, HOMA-IR, ALT, uric acid, ln hs-CRP, leptin, PAI-1, Fbg, FVII, FX, protein C and protein S compared with those with BMI less than 90th percentile.

Considering all participants, 0, 1, 2 and 3 traditional cardiovascular risk factor accumulations were observed in 86 (58.1%), 42 (28.4%), 18 (12.2%) and 2 (1.3%) cases, respectively. ALT, uric acid, ln hs-CRP, leptin, PAI-1, Fbg, FVII, FX, protein C and protein S were increased significantly with the number of cardiovascular risk factors accumulated (Fig. 1, Table 3). Stepwise regression analysis revealed that ALT, uric acid, ln hs-CRP, leptin, PAI-1, Fbg, FVII, FX, protein C and protein S were independently associated with one or more components related to MetS (Table 4).

Discussion

The physical measurement in this study group showed no significant difference from the national survey in Japan in 2008 [14], indicating that this study population was a standard one.

The hemostatic/fibrinolytic values that we obtained in this study showed some difference from previous studies [15,16]. Differences in the race of the subjects or laboratory procedures may provide the explanation for the different results. In addition, we conducted the investigation at a predetermined time with strict overnight fasting, in a population that has a normal distribution of physical constitution. Details of these conditions were not clearly mentioned in the previous works. Hemostatic/fibrinolytic variables are related to physical constitution [9,10], and fibrinolytic activity reduced in the morning because of the circadian alteration of PAI-1, a key

Table 2 Variables in children with BMI ≥90th percentile and those with BMI <90th percentile

	BMI <90th percentile ($n = 134$)	BMI ≥90th percentile ($n = 14$)	P value
SBP (mmHg)	104.3 ± 10.1	109.8 ± 9.4	0.051
DBP (mmHg)	55.4 ± 6.7	57.8 ± 7.7	0.204
Total cholesterol (mg/dl)	179.4 ± 27.3	185.6 ± 24.6	0.421
HDL-C (mg/dl)	65.9 ± 12.9	54.0 ± 9.8	0.001
LDL-C (mg/dl)	104.9 ± 23.8	122.0 ± 30.0	0.014
Triglyceride (mg/dl)	62.4 ± 36.1	108.9 ± 59.9	0.013
FPG (mg/dl)	93.8 ± 6.2	94.9 ± 8.0	0.570
Insulin (μIU/ml)	6.61 ± 4.07	18.95 ± 12.10	<0.001
HOMA-IR	1.55 ± 0.99	4.40 ± 2.75	0.002
ALT (IU/l)	14.8 ± 9.0	47.7 ± 46.4	0.020
Uric acid (mg/dl)	4.37 ± 0.86	5.12 ± 0.97	0.003
Ln hs-CRP	5.35 ± 1.30	7.06 ± 1.08	<0.001
Leptin (ng/ml)	4.73 ± 3.57	18.41 ± 6.68	<0.001
PAI-1 (ng/ml)	24.6 ± 14.1	46.3 ± 23.5	0.004
Fbg (mg/dl)	231.2 ± 43.4	280.6 ± 51.1	<0.001
FVII (%)	92.3 ± 11.1	105.6 ± 11.3	<0.001
FX (%)	92.0 ± 10.9	106.6 ± 12.6	<0.001
Protein C (%)	93.6 ± 17.1	103.5 ± 13.7	0.039
Protein S (%)	93.7 ± 13.3	103.5 ± 17.3	0.012

ALT, alanine aminotransferase; DBP, diastolic blood pressure; Fbg, fibrinogen; FPG, fasting plasma glucose; FVII, factor VII; FX, factor X; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; ln, logarithms nature; PAI-1, plasminogen activator inhibitor 1; SBP, systolic blood pressure. Data are mean ± standard deviation (SD).

Table 3 Various parameters among children classified on the basis of the number of cardiovascular risk factors (0, 1, ≥2)

	Number of cardiovascular risk factors		
	0 ($n=86$)	1 ($n=42$)	≥2 ($n=20$)
ALT (IU/l)	13.1 ± 4.0	19.5 ± 26.4	35.5 ± 27.3‡§
Uric acid (mg/dl)	4.33 ± 0.86	4.46 ± 0.91	4.92 ± 0.92*
Ln hs-CRP	5.17 ± 1.30	5.79 ± 1.43*	6.37 ± 1.06§
Leptin (ng/ml)	3.52 ± 2.32	7.74 ± 6.46‡	13.24 ± 6.50‡¶
PAI-1 (ng/ml)	21.3 ± 10.2	29.4 ± 17.0*	44.3 ± 22.9‡¶
Fbg (mg/dl)	226.4 ± 44.2	249.1 ± 44.3*	257.4 ± 55.6*
FVII (%)	89.2 ± 10.4	97.8 ± 10.0‡	104.1 ± 11.0‡
FX (%)	90.1 ± 11.1	95.1 ± 10.8	104.4 ± 9.7‡‖
Protein C (%)	90.3 ± 16.7	98.1 ± 15.8*	106.0 ± 14.4
Protein S (%)	91.9 ± 12.4	96.5 ± 14.5	103.0 ± 16.1

ALT, alanine aminotransferase; Fbg, fibrinogen; FVII, factor VII; FX, factor X; hs-CRP, high-sensitivity C-reactive protein; In, logarithms nature; PAI-1, plasminogen activator inhibitor 1. Data are mean ± standard deviation (SD). Parameters that showed statistically significant differences within the subgroup that have 0 cardiovascular risk factors are expressed as follows: *$P<0.05$, †$P<0.01$, ‡$P<0.001$. Parameters that showed statistically significant differences within the subgroup that have 1 CV risk factors are expressed as follows: §$P<0.05$, ‖$P<0.01$, ¶$P<0.001$.

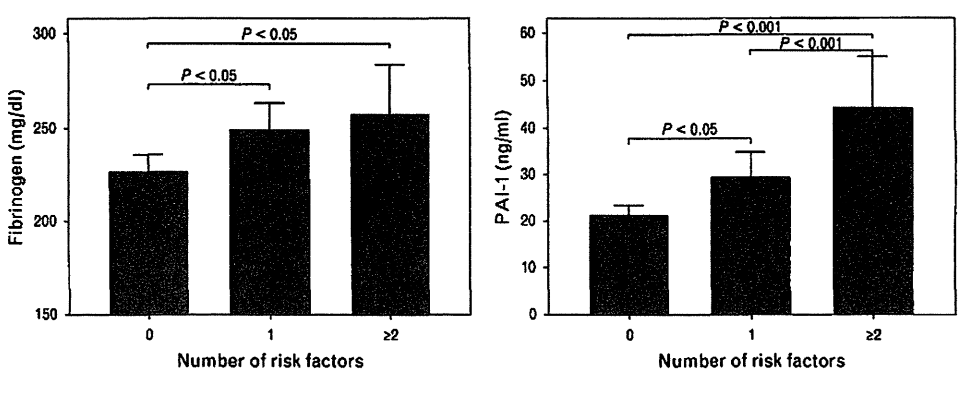
circulating prothrombotic factor [17]. Our data therefore should provide an accuate and valuable reference guide for hemostatic/fibrinolytic parameters in schoolchildren.

Hemostatic and fibrinolytic disturbances are considered to have close relationships with MetS, and are important risk factors for cardiovascular disease in adults [18,19]. Investigation in obese children also demonstrated hypercoagulabable and hypofibrinolytic status in pediatric obesity [20,21]. Meanwhile, the direct relationship between the hemostatic/fibrinolytic system and traditional cardiovascular risk factors besides obesity, or MetS in childhood is still controversial. Fritsch *et al.* [9] reported that parameters of the hemostatic system relate to the degree of overweight, but found no significant relationship with insulin resistance or occurrence of MetS in children. Physical activity-based interventions in obese children showed decrease in the levels of Fbg along with weight reduction and improvement of insulin resistance, but the effects on PAI-1 and the fibrinolytic system varied [10,22,23].

In this study, we demonstrated the association between hemostatic/fibrinolytic parameters and the components of MetS. Children with higher BMI and who had accumulated cardiovascular risk factors showed a tendency to hypercoagulability indicated by increased blood level of Fbg, FVII and FX, as well as a hypofibrinolytic state indicated by increased PAI-1 levels. Our results supported previous investigations substantially, and furthermore demonstrated that these unfavorable changes may exist even in a normal-child population.

Our study was a population-based study, unlike the various clinical-based observations that have been done previously in which the potential subject characteristics may be different. Recruiting subjects based only on their level of obesity may possibly lead to overestimation of the relationship between obesity and hemostatic/fibrinolytic status, downplaying the influence of other factors such as insulin resistance or dyslipidemia, which may complicate matters. In this study, we focused on the relationship between the levels of hemostatic/fibrinolytic parameters and accumulation of traditional cardiovascular risk factors. It is important because the sum of them increases the cardiovascular risk synergistically [2,3]. Our results showed that not only obesity, but also accumulation of

Fig. 1



Each bar shows the mean value and standard deviation (SD) of the mean. PAI-1, plasminogen activator inhibitor 1

Table 4 Association between the variables and the components related to MetS

Dependent variable	Independent variable	β (Standard error)	T	*P* value
ALT	BMI	2.388 (0.460)	5.188	<0.001
	Triglyceride	0.089 (0.037)	2.383	0.0185
Uric acid	BMI	0.088 (0.021)	4.176	<0.001
	DBP	0.022 (0.010)	2.169	0.0318
Ln hs-CRP	BMI	0.176 (0.031)	5.665	<0.001
Leptin	BMI	1.221 (0.088)	13.868	<0.001
	Insulin	0.198 (0.045)	4.357	<0.001
PAI-1	BMI	1.962 (0.379)	5.171	<0.001
	FPG	0.529 (0.180)	2.937	0.0039
	Triglyceride	0.070 (0.031)	2.276	0.0244
Fbg	BMI	5.110 (1.112)	4.597	<0.001
FVII	BMI	1.206 (0.289)	4.170	<0.001
	FPG	0.359 (0.137)	2.609	0.0101
	Triglyceride	0.048 (0.023)	2.041	0.0432
FX	BMI	1.481 (0.269)	5.515	<0.001
Protein C	Triglyceride	0.120 (0.033)	3.667	<0.001
Protein S	BMI	1.097 (0.339)	3.230	0.0015

ALT, alanine aminotransferase; DBP, diastolic blood pressure; Fbg, fibrinogen; FPG, fasting plasma glucose; FVII, factor VII; FX, factor X; hs-CRP, high-sensitivity C-reactive protein; ln, logarithms nature; MetS, metabolic syndrome; PAI-1, plasminogen activator inhibitor 1.

cardiovascular risk factors may significantly affect the levels of hemostatic/fibrinolytic parameters since childhood.

Elevated protein C and protein S levels in children with higher BMI and accumulated cardiovascular risk factors were also observed in this study, as in previous studies on obese adults [24]. Protein C is an anticoagulant enzyme activated by the thrombin-thrombomodulin complex on the surface of endothelial cells. It inactivates FV and FVIII when its cofactor, protein S, is present. The mechanism by which proteins C and S are elevated in obese subjects is not yet exactly clear. In obese subjects, enhanced hepatic protein synthesis [25], and a protective response toward increasing thrombin generation states [26], plus increased glucosylceramide, (a modulator of the anticoagulant protein C pathway) [27,28] may explain it. Our results showed that these interactions may already exist in childhood.

Imbalance of adipokines, hyperuricemia and chronic inflammation are believed to be deeply associated with obesity and the development of MetS [5,29–32]. In this study, increased levels of leptin, uric acid and hs-CRP in children with higher BMI and those with accumulated cardiovascular risk factors were observed, confirming that changes in adipokine levels, increased uric acid and the inflammatory process already start during childhood, in addition to the alteration of hemostatic/fibrinolytic status.

Compared with our previous investigation in normal preschoolchildren [9], more parameters increased with cardiovascular risk factor accumulation in elementary schoolchildren. Differences in the results from the two age groups may be because of difference in the duration that the children were exposed to abnormal adipose depots, difference in physical activities or diet pattern. Meyer *et al.* [33] reported impaired flow-mediated vasodilation and intima–media thickness of carotid arteries in obese children, and their association with increased levels of Fbg and C-reactive protein, suggesting the existence of endothelial dysfunction and arteriosclerotic changes in the early stages of life. Our results thus lend support to the notion that changes in hemostatic/fibrinolytic systems may be associated with the development of MetS and arteriosclerotic changes in childhood.

Study limitations

In this study, the number of participants analyzed was relatively small for providing normative values of hemostatic/fibrinolytic parameters, though the distribution of anthropometric measurements was considered similar to a standard one. As a large pediatric population-based study is not easy to conduct, our data should be useful.

Lifestyle factors such as dieting pattern or exercise behavior, which could have impacts on the hemostatic/fibrinolytic systems [22], were not measured in this study. Likewise, details of individual Tanner stage were not available in this study. However, the age of this study group is lower compared with the average age of puberty onset in Japanese boys and girls.

Finally, this cross-sectional study is not able to draw conclusions. Therefore, further longitudinal studies are needed to confirm how the alterations in those parameters that we have reported here could be implicated in later-life development of CVDs.

Conclusions

The present study established the reference values of hemastatic/fibrinolytic parameters for schoolchildren. Even in normal pediatric population, hemostatic/fibrinolytic parameters showed significant association with BMI and accumulation of cardiovascular risk factors. This study should provide useful data for further longitudinal observation or intervention studies to clarify the relationship between the alteration of hemostatic/fibrinolytic systems and later-life CVDs.

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Conflicts of interest

There are no conflicts of interest.

References

1 Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, *et al.* Metabolic syndrome risk of incident cardiovascular events and death. *J Am Coll Cardiol* 2007; **49**:403–414.

2 Koskinen J, Kähönen M, Viikari JS, Taittonen L, Laitinen T, Rönnemaa T, *et al.* Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in young Finns study. *Circulation* 2009; **120**:229–236.
3 Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham risk score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med* 2005; **165**:2644–2650.
4 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011; **128 (Suppl 5)**:S213–S256.
5 Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, *et al.* Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). *Circulation* 2001; **18**:3052–3056.
6 Feiq DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008; **359**:1811–1821.
7 Fibrinogen Studies CollaborationDanesh J, Lewington S, Thompson SG, Lowe GD, Collind R, Kostis JB, *et al.*. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 2005; **294**:1799–1809.
8 Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004; **110**:380–385.
9 Fritsch P, Kleber M, Rosenkranz A, Fritsch M, Muntean W, Mangge H, Reinehr T. Haemostatic alterations in overweight children: Associations between metabolic syndrome, thrombin generation, and fibrinogen levels. *Atherosclerosis* 2010; **212**:650–655.
10 Balagopal P, George D, Sweeten S, *et al.* Response of fractional synthesis rate (FSR) of fibrinogen, concentration of D-dimer and fibrinolytic balance to physical activity-based intervention in obese children. *J Thromb Haemost* 2008; **6**:1296–1303.
11 Balagopal PB, de Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL, *et al.* Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic research, and clinical considerations for youth: a scientific statement from the American Heart Association. *Circulation* 2011; **123**:2749–2769.
12 Horigome H, Katayama Y, Yoshinaga M, Kato Y, Takahachi H, Sumazaki R. Significant associations among hemostatic parameters, adipokines, and components of the metabolic syndrome in Japanese preschool children. *Clin Appl Thromb Hemost* 2012; **18**:189–194.
13 Ohzeki T, Nakagawa Y, Ochiai F. Epidemiology and diagnostic criteria for metabolic syndrome and obesity in Japanese children. *Nihon Rinsho* 2011; **69 (Suppl 1)**:745–751; (in Japanese).
14 Ministry of Education, Culture, Sports, Science and Technology. *Annual report of school health survey.* The Printing Office, Ministry of Finance. Tokyo (in Japanese), 2008.
15 Sosothikul D, Seksarn P, Lusher JM. Pediatric reference values for molecular markers in hemostasis. *J Pediatr Hematol Oncol* 2007; **29**:19–22.
16 Monagle P, Barnes C, Ignjatovic V, Furmedge J, Newall F, Chan A, *et al.* Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost* 2006; **95**:362–372.
17 Scheer FA, Shea SA. Human circadian system causes a morning peak in prothrombotic plasminogen activator inhibitor-1 (PAI-1) independent of the sleep/wake cycle. *Blood* 2014; **123**:590–593.
18 Mertens I, Van Gall LF. Obesity, haemostasis and the fibrinolytic system. *Obes Rev* 2002; **3**:85–101.
19 Singh A, Foster GD, Gunawardana J, McCoy TA, Nguyen T, Vander Veur S, *et al.* Elevated circulating tissue factor procoagulant activity, factor VII, and plasminogen activator inhibitor-1 in childhood obesity: evidence of a procoagulant state. *Br J Haematol* 2012; **158**:523–527.
20 Semeraro F, Giordano P, Faienza MF, Cavallo L, Semeraro N, Colucci M. Evidence that fibrinolytic changes in paediatric obesity translate into a hypofibrinolytic state. *Thromb Haemost* 2012; **108**:311–317.
21 Siklar Z, Ocal G, Berberoqiu M, Hachiamdioglu B, SavasErdeve S, Egin Y, *et al.* Evaluation of hypercoagulability in obese children with thrombin generation test and microparticle release: effect of metabolic parameters. *Clin Appl Thromb Hemost* 2001; **17**:585–589.
22 Ferguson MA, Gutin B, Owens S, Barbeau P, Tracy RP, Litaker M. Effects of physical training and its cessation on the hemostatic system of obese children. *Am J Clin Nutr* 1999; **69**:1130–1134.
23 Balagopal P, George D, Patton N, Yarandi H, Roberts WL, Bayne E, *et al.* Lifestyle-only intervention attenuates the inflammatory state associated with obesity: a randomized controlled study in adolescents. *J Pediatr* 2005; **146**:342–348.
24 Solá E, Navarro S, Medina P, Vayá A, Estellés A, Hernández-Mijares A, *et al.* Activated protein C levels in obesity and weight loss influence. *Thromb Res* 2009; **123**:697–700.
25 Cucuianu M, Brudasca I, Trif I, Stancu A. Clinical studies on plasma protein C. Correlation with serum cholinesterase. *Nouv Rev Fr Hematol* 1993; **35**:481–486.
26 De Pergola G, Pannacciulli N. Coagulation and fibrinolysis abnormalities in obesity. *J Endocrinol Invest* 2002; **25**:899–904.
27 Kohyama-Koganeya A, Nabetani T, Miura M, Hirabayashi Y. Glucosylceramide synthase in the fat body controls energy metabolism in Drosophila. *J Lipid Res* 2011; **52**:1392–1399.
28 Deguchi H, Fernández JA, Pabinger I, Heit JA, Griffin JH. Plasma glucosylceramide deficiency as potential risk factor for venous thrombosis and modulator of anticoagulant protein C pathway. *Blood* 2001; **97**:1907–1914.
29 Vendrell J, Broch M, Vilarrasa N, Molina A, Gómez JM, Gutiérrez C, *et al.* Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: Relationships in obesity. *Obes Res* 2004; **12**:962–1971.
30 Ford ES, Ajani UA, Mokdad AH, National Health and Nutrition Examination. The metabolic syndrome and concentrations of C-reactive protein among U.S. youth. *Diabetes Care* 2005; **28**:878–881.
31 Yoshinaga M, Sameshima K, Tanaka Y, Wada A, Hashiguchi J, Tahara H, *et al.* Adipokines and the prediction of the accumulation of cardiovascular risk factors or the presence of metabolic syndrome in elementary school children. *Circ J* 2008; **72**:1874–1878.
32 Wang JY, Chen YL, Hsu CH, Tang SH, Wu CZ, Pei D. Predictive value of serum uric acid levels for the diagnosis of metabolic syndrome in adolescents. *J Pediatr* 2012; **161**:753–756.
33 Meyer AA, Kundt G, Steiner M, Schuff-Werner P, Kienast W. 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.

Ⅱ 基礎

小児の肥満・メタボリックシンドロームの現状と対策

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Key words:
obesity, metabolic syndrome, insulin resistance, adipokines

Current Status and Strategies for Obesity and Metabolic Syndrome in Children and Adolescents

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A new concept and definition for metabolic syndrome pronounced in 2005 in Japan elucidated the importance of abdominal obesity and insulin resistance. Until then, treatment and research for obesity might be a minor and an unsolved field in both internal medicine and pediatrics. Especially in pediatrics, we were educated and we also sent messages based on personal experience and/or information because of the paucity of evidence. Are the following messages true for recent Japanese children and adolescents?

1. Childhood and adolescent obesity has been increasing.
2. Childhood obesity will disappear after entering school.
3. Do not worry about mild obesity.
4. Childhood obesity is mainly associated with maternal obesity.
5. There is no concern about metabolic syndrome in pediatrics.
6. It is difficult to treat obesity in both the adult and pediatric population.

The author presents the current status and strategies for obesity and metabolic syndrome based on the recently obtained evidences in pediatric population.

要　旨

2005 年に日本においてメタボリックシンドロームという新しい概念と診断基準が発表され，内臓肥満とインスリン抵抗性の重要性が俄かにクローズアップされた．それまで肥満を治療・研究することは，内科においても小児科においても循環器医療の中では minor な，放置してよいカテゴリーであったと思っている．特に小児科領域ではデータが少なく，私たちはデータに基づかない個人的な経験，情報で教育され，また伝達していたように思う．私が長い間教えられてきた次の命題は現在の日本人小児にあてはまるのだろうか．

1. 小児期の肥満は増え続けている
2. 小学校に行けば肥満はなくなる
3. 軽度肥満なら心配することはない
4. 子どもの肥満は母親との関係が強い
5. 子どものメタボは気にするほどではない
6. 成人だけでなく小児期・思春期の肥満の治療は難しい

最近発表されたエビデンスに基づいて小児の肥満，メタボリックシンドロームの現状と対策を考えてみたい．

はじめに

文部科学省は学校保健統計調査報告書の中で児童生徒の身長・体重相関表を 1948 年から公表している．鹿児島市では 1992 年より肥満度 40%以上（1998 年からは 35%以上）の小学生に対して無料の小児生活習慣病予防検診と事後処置としての相談室を続けてきた．私の病院では 2005 年より肥満治療を開始した．これらのデータから日本人小児の肥満・メタボリックシンドロームの現状と対策を考えてみたい．

1．小児期の肥満は増え続けている？

小児期で肥満になる時期は，全世界で胎児期，幼児期後半(4～6 歳)，思春期の 3 時期と報告されてきた[1]．日本でもこの事実があてはまるか，学校保健統計調査報告書をもとに 5～17 歳の 1980～2010 年の肥満頻度の変化を検討した[2,3]．

肥満の程度の判定には肥満度を用いた．6，9，12，15 歳の肥満頻度の横断的変化をみると，男女のどの年齢でも 2000 年前後に肥満頻度のピークを迎え，その後漸減している(Fig. 1)．6 歳と 9 歳の肥満頻度の差は極めて大きいことがわかる．

Fig. 2 に出生年ごと(5 年ごと)のコホートの縦断的変化を示した．1990 年生まれのコホートは，9 歳から 17 歳まで一番高い肥満頻度で成長していたことがわかる．1990 年は日本のバブル期(1986 年 11 月～1991 年 2 月)にあたる．バブル期以降はより低い肥満頻度で成長している．日本では小児の肥満頻度は減少傾向に向かっている．

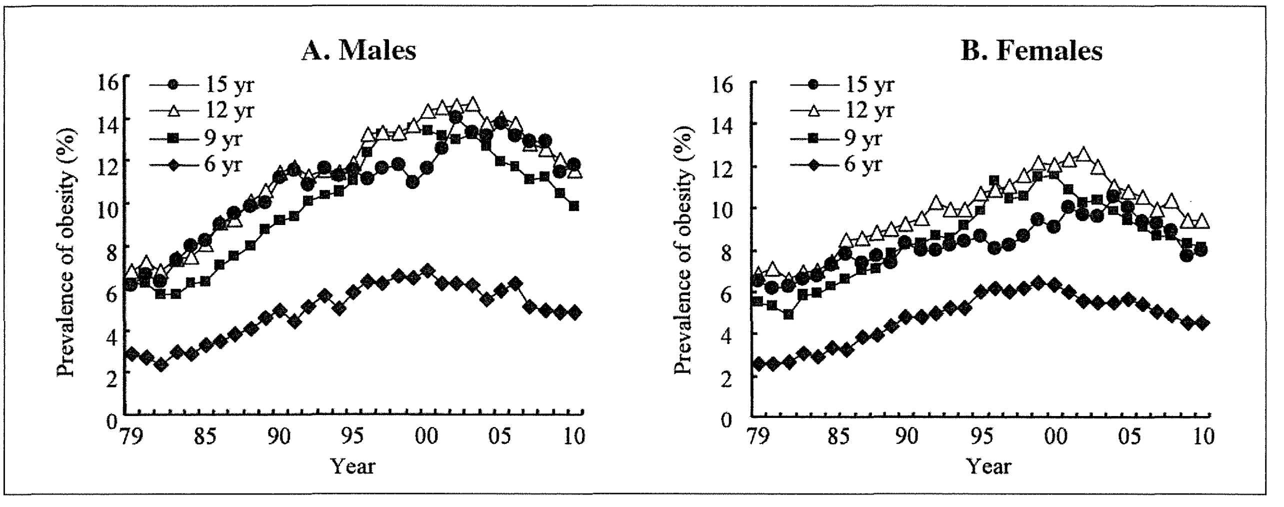

Fig. 1 Cross-sectional changes in the prevalence of obesity.
(Figure 1 in this review was rearranged from the figure in the paper now in submission[3]. Then, originality is present in the paper in submission[3])
The prevalence of obesity was highest in the late 1990s and early 2000s in both males (A) and females (B).

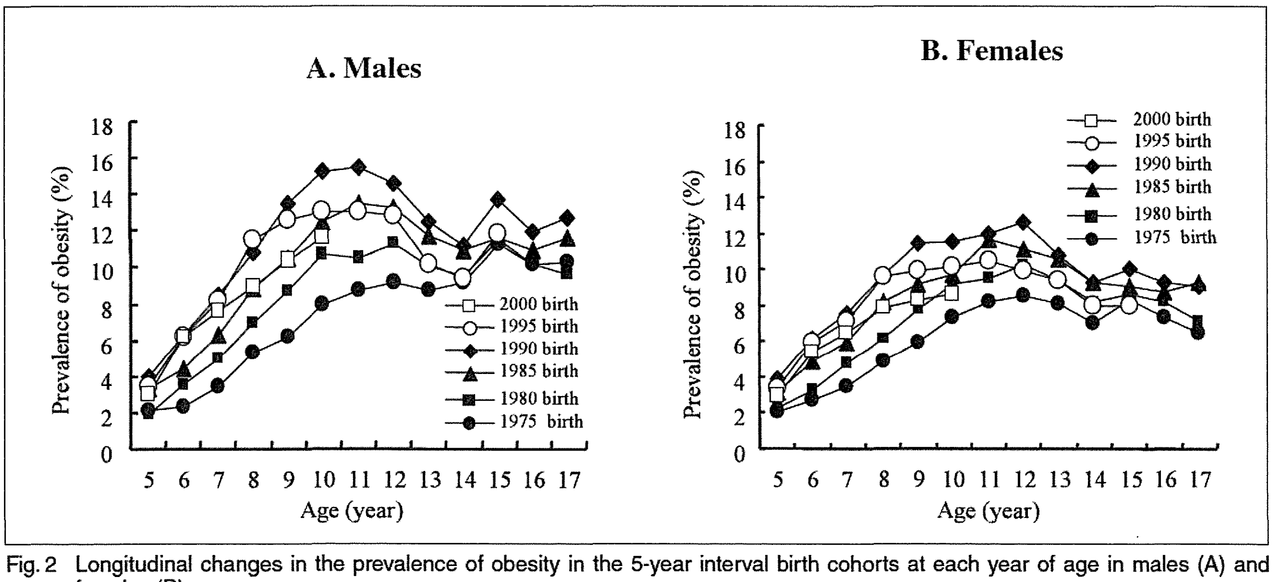

Fig. 2 Longitudinal changes in the prevalence of obesity in the 5-year interval birth cohorts at each year of age in males (A) and females (B).
(Figure 2 in this review was rearranged from the figure in the paper now in submission[3]. Then, originality is present in the paper in submission[3])
The 1990 birth cohort had the highest prevalence of obesity between ages of 9 and 17 years.

2. 小学校にいけば肥満はなくなる？

Fig. 2は別の問題も示している．小学校入学時(5～6歳になる時)男女とも頻度が急上昇し，小学校低学年の間は頻度が急上昇を続けることである．

2010年の5～17歳の肥満頻度を横断的にみると，肥満度は小学生の間は増え続け，中学校で一時減少するものの，高校生でまた増加する(Fig. 3)．16歳男子だけで全国に12万人の高度肥満が存在する．

日本での小児期・思春期の肥満予防対策の対象は小学校と高校と考えられる．特に小学校入学時から数年間の肥満の出現防止ができれば，高校卒業時の肥満頻度は10%近く減少できる．その中でも男子に対する対策は緊急課題である．

【用語の解説】

メタボリックシンドロームの源は内臓肥満とインスリン抵抗性といわれている．インスリン抵抗性を含め，いくつかの用語を解説したい．

(1)インスリン抵抗性[4)]

標的細胞または標的臓器のインスリンに対する反応性が減少した状態，臨床的には高インスリン血症の状態をいう．インスリン抵抗性の存在は前糖尿病状態といえる．

(2)Homeostasis model assessment of insulin resistance(HOMA-IR)[5)]

インスリン抵抗性の指標の1つである．(空腹時血糖)×(空腹時インスリン)／405で計算する．

(3)アディポネクチン[6)]

脂肪細胞に特異的に発現している．抗糖尿病作用，抗動脈硬化作用，抗炎症作用を持つ．一方でTNF-αはアディポネクチンの遺伝子発現を転写レベルで抑制する．酸化ストレス，アンジオテンシンII，テストステロンなどにより抑制される．最近，心筋細胞に対する抗線維化作用も有していることが示された．肥満では，絶対的に脂肪細胞が増加しているにもかかわらずアディポネクチンの血中レベルが低下する機序については十分解明されていない．

(4)レプチン[7)]

主に脂肪細胞から分泌され，脂肪細胞の肥大化によって分泌量が増加する．レプチンの作用点は視床下部に発現している受容体であり，食欲の抑制，交感神経活動を介した熱産生，褐色脂肪組織や骨格筋での糖利用促進作用を持つ．肥満状態ではレプチンの作用不全が生じ，血中濃度が上昇するにもかかわらず，濃度に見合ったレプチン作用が発揮されない(レプチン抵抗性)．

(5)肥満度

肥満度(%){(現在の体重÷標準体重)－1}×100の算出に用いられる標準体重計算式は学校保健統計調査報告書をもとに10年ごとに改訂され，現在は1990年と2000年の報告書から作られた計算式が使われている．本報告では1990年版を用いた．

(6)心血管危険因子 cardiovascular risk factors

成人領域における心筋梗塞，糖尿病，脳卒中を引き起こす因子を指す．多くはメタボリックシンドローム

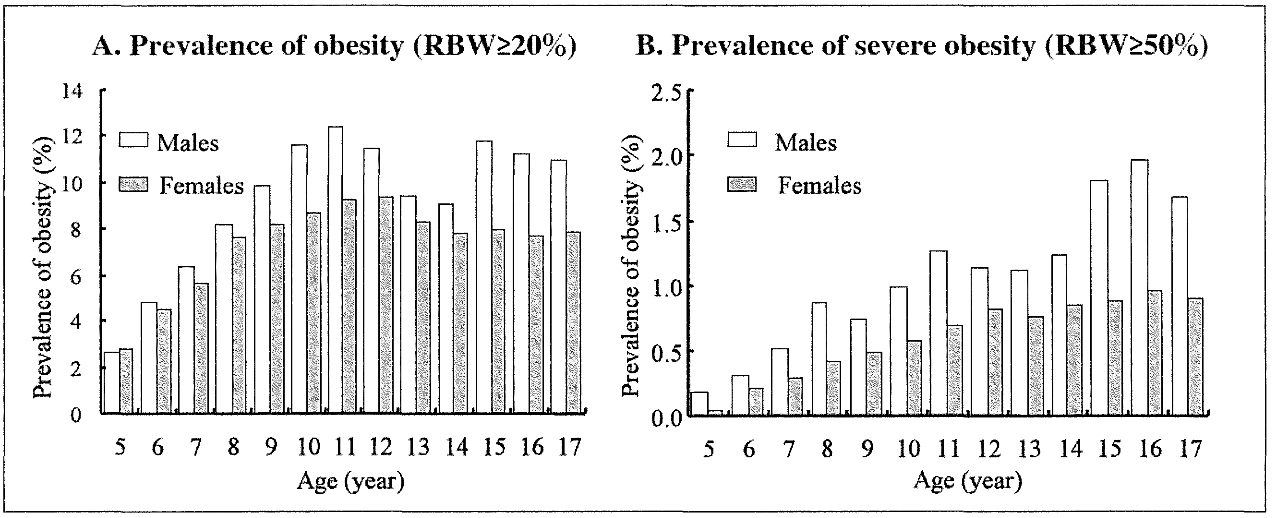

Fig. 3 Prevalence of obesity {relative body weight (RBW) ≥20%)} (A) and that of severe obesity (RBW ≥50%) (B) in males and females.
(Figure 3 in this review was rearranged from the figure in the paper now in submission[3)]. Then, originality is present in the paper in submission[3)])

の診断基準である内臓肥満，高血圧，高中性脂肪血症，低HDLコレステロール血症，空腹時高血糖が使用される．尿酸，ALTが採用される時もある．肥満時のALT高値に対して"脂肪肝"が使用されるが，医学論文的にはNonalcoholic Steatohepatitis (NASH)，非アルコール性脂肪性肝炎が用いられる．

3. 軽度肥満なら心配することはない？

軽度肥満は心配することはない，と教えられてきた．高コレステロール血症や高中性脂血症がなければ"単純性肥満"と診断し"合併症はないけどやせたほうがいいですよ"と指導していた．これでは心配して来た母親の減量に対するmotivationはなくなる．子どものインスリン抵抗性を成人と比較検討した[8]．

男児では健常群から軽度肥満になる時と高度肥満になる時，急にHOMA-IR値が悪化する(Fig. 4A)．日本人成人の肥満は日本の肥満基準(BMIで25以上)と欧米の基準(30以上)に二分した[9]．軽度肥満男子のインスリン抵抗性は日本の肥満基準を満たす成人とほぼ同じ値である(Fig. 4B)．論文ではこの群のBMIの平均値は26.6になっている．身長が165 cmなら72.4 kg, 175 cmなら81.5 kgである．

女児では肥満度が10%増すごとにインスリン抵抗性が悪化する(Fig. 4C)．軽度肥満女児のインスリン抵抗性が日本の肥満基準を満たす成人と同じ値なのは男児と同様である．中等度肥満群の女児は欧米での肥満基準を満たす成人女性と同じである(Fig. 4D)．この群のBMIの平均値は34.4となっている．身長が155 cmなら体重82.6 kg，165 cmなら93.7 kgである．

血管の病気は20～30年で形成されると考えられる．平均9歳の軽度肥満の小学生は，日本の肥満基準を満

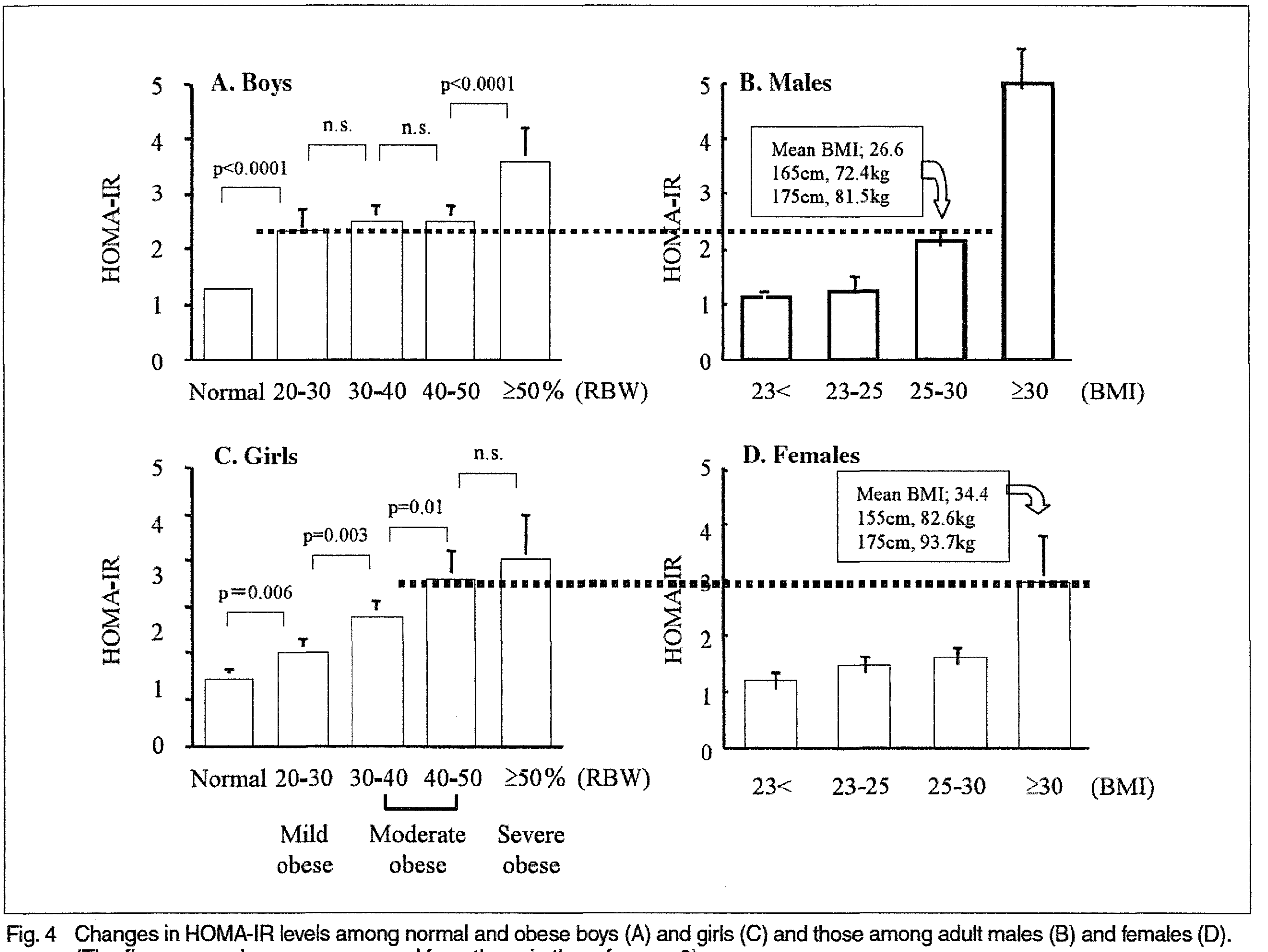

Fig. 4 Changes in HOMA-IR levels among normal and obese boys (A) and girls (C) and those among adult males (B) and females (D). (The figures a and c were rearranged from those in the reference 8)
The HOMA-IR levels in mild obese boys and girls (RBW; 20-30%) (between 6 and 12 years of age) correspond to those of obese Japanese adults (BMI; 25-30) (between 30 and 60 years of age). Importantly, the HOMA-IR levels in moderate obese girls (RBW; 40% to 50%) correspond to those of obese Japanese adults (BMI ≥30) who fulfilled the international criteria of obesity.

Table 1　Risk of presence of adolescent obesity associated with parental obesity.

	Males		Females	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Paternal obesity	2.47 (1.28, 4.77)	0.007	1.09 (0.44, 2.70)	0.86
Maternal obesity	1.74 (0.71, 4.26)	0.23	3.00 (1.13, 8.00)	0.03
Combined parental obesity	6.36 (1.86, 21.8)	0.003	2.72 (0.56, 13.2)	0.21

Parental obesity was defined as a BMI ≥25kg/m², based on the recommendation by The Examination Committee of Criteria for Obesity Disease for the Japanese adult population[11]. Therefore, adolescent obesity in the present study was defined using age- and sex-specific International Obesity Task Force standard corresponding to BMI cutoffs of 25 kg/m² at age 18 years[12].
Abbreviation; CI: confidence interval, OR: odds ratio.

たす成人のインスリン抵抗性と同じレベルで生活している．彼らは29～39歳の時に糖尿病，心筋梗塞，脳血管障害を発症することになる．中等度肥満の女児は欧米の基準を満たす成人と同じ値である．この値なら血管病を発症するのに10～20年で十分であろう．

平成20年度から40歳以上の特定健診・特定保健指導が始まった．さらに若い年齢への対応が望まれていたが，リーマンショックや今年の東北大震災・原発事故後の経済状態は悪化し続けている，私たち小児科医，小児循環器医が患児・家族・地域社会と一緒になり，限りを尽くさなければ小児期への対策は始まらないと思う．

4．子どもの肥満は母親との関係が強い？

平成18～20年度の厚生労働科学研究費で高校生ボランティアの生活習慣病検診を行い，1,358名に参加してもらった．うち，アンケートにすべて答えてもらった755名について両親のBMIと高校生のBMIとの関係を調査した[10]．Table 1の通り，男子の肥満は父の肥満と，女子の肥満は母の肥満と関係していた．母親だけでなく，父親へのアプローチも重要である．高校生において心血管危険因子出現予防の最も大きな因子は体育系部活への参加であった[10]．

5．子どものメタボは気にするほどではない？

前述した高校生ボランティアのデータで検討してみた[13]．心血管危険因子値の高校生用の基準値としては，ボランティア高校生の90パーセンタイル値を用いた．腹囲(男子≥80 cm，女子≥79 cm)，収縮期血圧(男子≥129 mmHg，女子≥119 mmHg)，拡張期血圧(男子≥75 mmHg，女子≥73 mmHg)，中性脂肪(男子≥106 mg/dl，女子≥95 mg/dl)，空腹時血糖(男子≥96 mg/dl，女子≥93 mg/dl)，HDL-cholesterol(男子＜46 mg/dl，女子＜50 mg/dl)とした．参加した健康ボランティア高校生であっても，心血管危険因子が1個増えるごとにすべての心血管危険因子値および，アディポサイトカイン値が悪化していた．代表として，収縮期血圧，中性脂肪，レプチン，アディポネクチンの値をFig. 5に示した．それぞれの心血管危険因子値に強い性差があることがわかる．心血管危険因子数と各因子値の変化，性差については小学生でも検討したが，同様であった[14]．

6．成人だけでなく小児期・思春期の肥満の治療は難しい？

肥満治療は最初の動機づけがうまくいけばそれほど困難なことではないのではないか，と考えてきた．肥満外来時，噛むことにより摂取量制限なしに減量できる，歩くことは脂肪を減少させる最良の方法である，治療初期に減量できれば，治療を継続できる，ことを理解してもらい，下記のような約束事を決め，“約束事の実行表”に○，×を記載してもらった．

1回口に入れたら20回以上噛む，休日は1万歩以上歩く，野菜をたくさん食べる，砂糖の入った飲料は飲まない．

受診回数4回以上および3カ月以上経過観察できた58名中，肥満度がわずかでも減少した人は56名(97%)，10%以上減少した人は45名(78%)，20%以上減少した人が22名(38%)である[15]．肥満治療に成功する予測因子は初回から2回目受診間での大きな肥満度減少であった．成人では5%の体重減少を成功基準としている．小児期での肥満治療は本人が治療初期に強いmotivationを持てば成功すると思う．

小児期・思春期の肥満・メタボリックシンドロームに関するデータが不足している．データに基づいた小児期・思春期肥満に対する一次・二次予防ガイドライン作成が必要である．

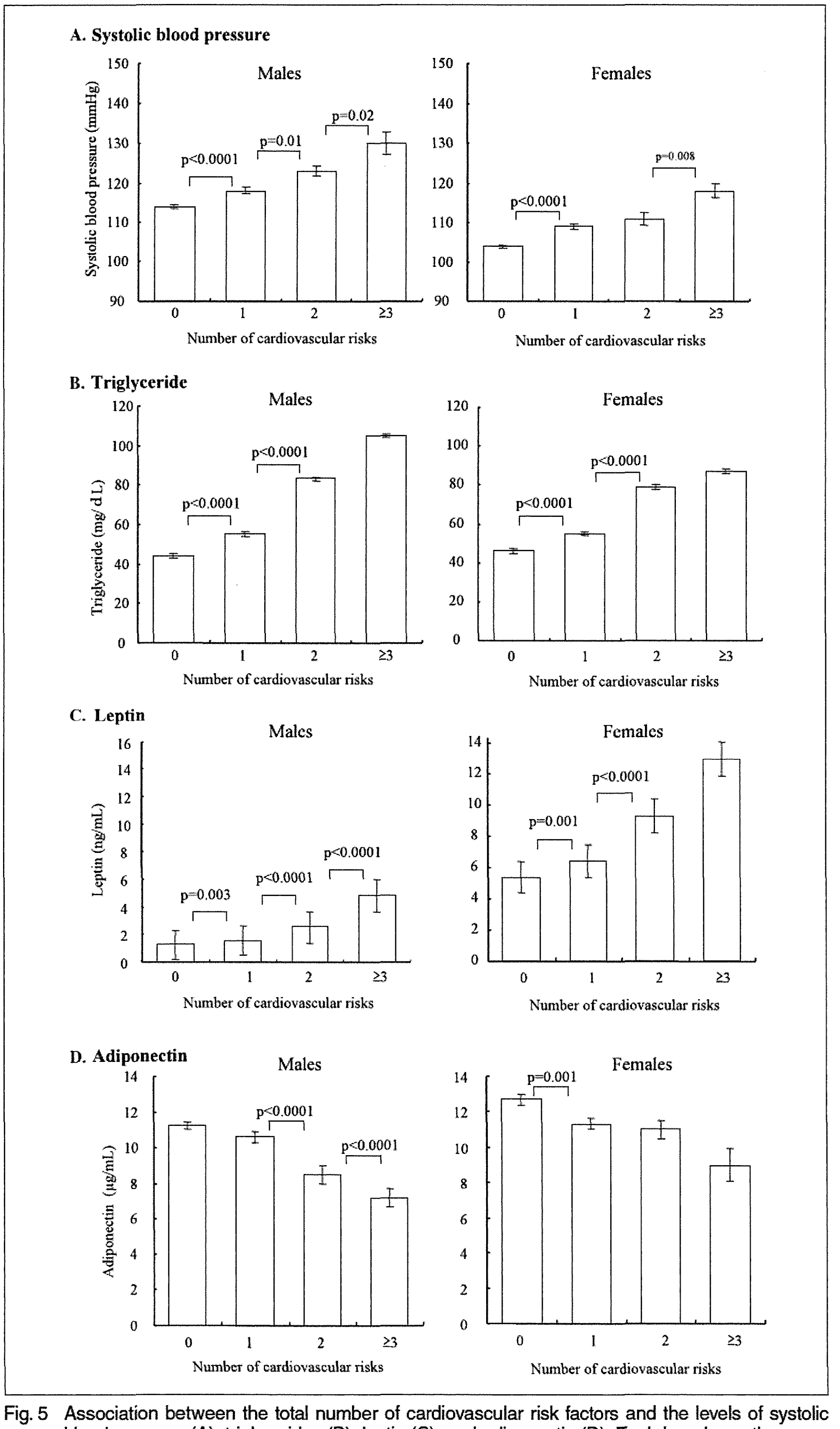

Fig. 5 Association between the total number of cardiovascular risk factors and the levels of systolic blood pressure (A), triglycerides (B), leptin (C), and adiponectin (D). Each bar shows the mean and the standard error of the mean. Statistical analysis was carried out by Tukey's multiple comparison, and *p* values were shown when the value was significant between any two successive groups.

【参考文献】

1) Dietz WH: Critical periods in childhood for the development of obesity. Am J Clin Nutr 1994; **59(5)**: 955-959

2) Yoshinaga M, Ichiki T, Tanaka Y, et al: Prevalence of childhood obesity from 1978 to 2007 in Japan. Pediatr Int 2010; **52(2)**: 213-217

3) 崎向幸恵，吉永正夫：日本人小児期・思春期の肥満頻度変化の横断的・縦断的研究．(投稿中)

4) Shanik MH, Xu Y, Skrha J, et al: Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? Diabetes Care 2008; Suppl 2: S262-268

5) Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; **28(7)**: 412-419

6) 前田法一：アディポネクチンとアポアクリンの病態的意義の解明．肥満研究 2010; **16**: 155-162

7) 益崎裕章，田中智洋，海老原健，他：レプチンとアディポステロイド：肥満症における臨床的意義．肥満研究 2010; **15**: 250-259

8) Yoshinaga M, Sameshima K, Jougasaki M, et al: Emergence of cardiovascular risk factors from mild obesity in Japanese elementary school children. Diabetes Care 2006; **29**: 1408-1410

9) Shiwaku K, Anuurad E, Enkhmaa B, et al: Overweight Japanese with body mass indexes of 23.0-24.9 have higher risks for obesity-associated disorders: a comparison of Japanese and Mongolians. Int J Obes Relat Metab Disord 2004; **28**: 152-158

10) Yoshinaga M, Hatake S, Tachikawa T, et al: Impact of lifestyles of adolescents and their parents on cardiovascular risk factors in the adolescents. J Atheroscler Thromb 2011; **18**: 981-990

11) Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity: New criteria for 'obesity disease' in Japan. Circ J 2002; **66**: 987-992

12) Cole TJ, Bellizzi MC, Flegal KM, et al: Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000; **320**(7244): 1240-1243

13) Yoshinaga M, Takahashi H, Shinomiya M, et al: Impact of having one cardiovascular risk factor on other cardiovascular risk factor levels in adolescents. J Atheroscler Thromb 2010; **17**: 1167-1175

14) Yoshinaga M, Sameshima K, Tanaka Y, et al: Adipokines and the prediction of the accumulation of cardiovascular risk factors or the presence of metabolic syndrome in elementary school children. Circ J 2008; **72**: 1874-1878

15) Yoshinaga M, Hatake S, Tachikawa T, et al: Impact of lifestyles of adolescents and their parents on cardiovascular risk factors in adolescents. J Atheroscler Thromb 2011; **18**: 981-990

原　著

小児における食後トリグリセリドおよびLDLコレステロール測定の意義

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Key words:
children, non-fasting triglyceride, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, metabolic syndrome

Evaluation of Non-fasting Serum Triglyceride and Low-density Lipoprotein Cholesterol Levels in Children

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Background: Recently, hypertriglyceridemia, especially in the non-fasting state, has been recognized as one of the most important atherosclerotic risk factors, in addition to hypercholesterolemia, in adults. The purpose of this study was to evaluate the usefulness of measuring non-fasting triglyceride levels and low-density lipoprotein cholesterol levels in schoolchildren.

Subjects and Methods: The subjects were 2,961 fouth and seventh grade schoolchildren in Takaoka City. They received the screening for preventing life-style related disease in 2010. Along with anthropometric measurements, blood samples obtained immediately after the school lunch were tested for total cholesterol, high-density lipoprotein cholesterol (HDLC), triglyceride (TG), and low-density lipoprotein cholesterol (LDLC) levels. Some children were re-examined later during fasting, and their data were compared to those in the non-fasting state.

Results: There were no differences in the mean values of non-fasting TG between children in either grade or between the different sexes. The 50th percentile levels were 86 to 90 mg/dl, which are 20 to 30 mg/dl higher than the fasting levels in the nationwide reports. Non-fasting TG correlated with the values of body mass index, percentage overweight, atherosclerotic index, non-HDLC (TC-HDLC), and LDLC positively and with HDLC negatively. However, the subjects with high levels of non-fasting TG did not always have high levels of fasting TG. Directly measured LDLC highly correlated with non-HDLC ($r = 0.98$, $p < 0.001$).

Conclusions: Non-fasting TG levels are considered useful predictors of metabolic syndrome in schoolchildren. LDLC levels can be estimated from non-HDLC levels instead of measuring directly.

要　旨

背景：近年成人では，高コレステロール血症に加え高トリグリセリド血症(特に食後)が重要な動脈硬化危険因子として注目されている．よって本研究では，小児における食後のトリグリセリド(TG)，およびLDLコレステロール(LDLC)を測定し，その有用性を検討した．

対象と方法：対象は，平成22年度に小児生活習慣病予防健診を受診した高岡市内の小学4年生，中学1年生2,961名である．身体計測に加え，給食後1～2時間の採血で，総コレステロール(TC)，HDLコレステロール(HDLC)，TG，およびLDLCを測定し，種々の検討を施行した．さらに二次検診で空腹値が得られた対象に関して，食後値との比較を行った．

結果：児童生徒の食後TG平均値は学年差，性差を認めず，50パーセンタイル値は86～90 mg/dlで，全国集計の空腹値より20～30 mg/dl高値であった．また食後TGはBMI，肥満度，動脈硬化指数，non-HDLC(TC-HDLC)，LDLCと正相関，HDLCと逆相関を認めたが，食後高値例は必ずしも空腹時高値ではなかった．LDLCはnon-HDLCときわめて良好な相関を認めた($r = 0.98$，$p < 0.001$)．

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結論：食後TGは小児生活習慣病健診でのメタボリックシンドロームのスクリーニング指標として有用である．LDLCはnon-HDLCより推定可能であり，直接測定の必要性は低い．

はじめに

成人の循環器疾患では，動脈硬化がその要因としてきわめて重要であるが，動脈硬化性の変化がすでに10代に端を発していることは，周知の事実となっている[1]．しかし動脈硬化が小児期に直接疾患の原因になることはきわめて稀であり，必ずしも小児循環器医の中で比重が大きい分野ではない．

小児の肥満児は，1980年代からのバブル期，すなわち飽食，電子機器発達などの時代の波に乗るように急増し，「小児成人病」という言葉が登場するに至った[2]．バブル崩壊を経て，2000年頃からその割合は頭打ちにはなったものの，いまだ高い水準にある[3,4]．これらの肥満児は内臓脂肪増加から小児メタボリックシンドロームの状況に陥りやすいことが判明してきており[5]，小児期からの動脈硬化促進が懸念されている．また，小児循環器疾患の中で重要な位置にある川崎病は，発見から50年以上を経過してその長期予後が解明される中で，急性期に心合併がなかった例でも将来的に動脈硬化性の変化が進みやすいとの報告もみられるようになっている[6,7]．このような背景の下，小児循環器医にとっても動脈硬化に関する認識をより高める必要性が増している．

小児の動脈硬化の実態を把握するには，スクリーニングの場としての学校健診が貴重となる．現在全国的に自治体で実施されている小児生活習慣病健診は，1980年代後半から始まった「小児成人病健診」の流れをくむ[8]．われわれの市においても，1994年に小児生活習慣病予防健診を開始して以来，主に肥満や高脂血症の児童生徒ピックアップを目的に継続されてきた．しかし小児メタボリックシンドロームの診断基準が確立された現在[9]，その概念を取り入れた新たな内容への改変が課題となっている．

当市の健診は給食後採血であるため，当初より総コレステロール，HDLコレステロール測定のみを行い，メタボリックシンドロームの指標として重要なトリグリセリド測定は行ってこなかった．高トリグリセリド血症は従来動脈硬化との関連が明確でなかったが，近年は動脈硬化危険因子としての認識が定着してきており，特に食後高値の危険性が注目されている[9-13]．よって昨年度の健診では，試みに食後トリグリセリドを測定し，さらにLDLコレステロール直接測定も施行して，それらの健診における意義，有用性を検討した．

対象・方法

対象は，平成22年度に高岡市の小児生活習慣病予防健診を受診した，市内すべての小学校(27校)の4年生1,515名(男792名・女723名)，および中学校(11校)の1年生1,446名(男744名・女702名)，計2,961名の児童生徒である．受診率は小中学校おのおの96.4%，91.9%であった．当健診は毎年9～10月に実施され，各学校における身長，体重，血圧測定，および給食後の採血検査結果から肥満や脂質異常者を二次検診に抽出している．採血は学校医および高岡市医師会検査センター職員が各学校に出向し，おおよそ給食後1～2時間で実施，同検査センターで一括して測定を行っている．検査項目は平成21年度までは総コレステロール，HDLコレステロール2項目であったが，平成22年度は試行的にトリグリセリド，LDLコレステロールの2項目を加えた．LDLコレステロール測定には，デタミナーL LDL-C(協和メデックス)を使用した．なお，当健診受診は保護者の申込書提出が前提であり，その際に今回の健診項目追加およびデータ集計結果の公表につき，書面で同意を得ている．

当健診における二次検診抽出基準は，肥満度30%以上，もしくは総コレステロール220 mg/dl以上であり，該当者には医療機関受診による精査を勧奨している．平成22年度は平成22年11月～23年1月の間に152名が二次検診を受診した．そのうち空腹時(前日夕食後は食事未摂取)と申告のあった92名(肥満64名，高コレステロール血症28名)につき，当健診でのトリグリセリド食後値と二次検診空腹値との比較を行った．

統計学的には，各学年別男女別の比較にはTukey法を，トリグリセリドと各計測値との比較にはPearsonの相関係数検定を施行し，$p < 0.05$を有意とした．また，トリグリセリド食後値と空腹値との比較やLDLコレステロール直接測定値と計算値(Friedewald式：総コレステロール－HDLコレステロール－トリグリセリド／5)およびnon-HDLコレステロール(総コレステロール－HDLコレステロール)との相関に関しては，単回帰分析にて検討した．これらの解析には，SPSS ver.11を使用した．

結　果

健診受診者のプロフィールおよび食後脂質値の測定結果をTable 1に示す．総コレステロール，HDLコレステロール，LDLコレステロール，およびnon-HDLコレステロールはいずれも中1男で有意に低値を示した．トリグリセリドには有意差を認めず，いずれも平均100 mg/dl前後となったが，標準偏差が大であった．各脂質をパーセンタイル値で表し(Table 2)，Okadaらの全国データによる報告[14]の10歳，13歳と比較すると，総コレステロールは近似した値であったが，HDLコレステロールは高値傾向を示し，異常値基準の5

Table 1　Characteristics and non-fasting serum lipid levels of the subjects

	4th grade		7th grade		m vs f#		4th vs 7th#	
	males	females	males	females	4th	7th	m	f
n	792	723	744	702				
Height (cm)	136.5 ± 5.8	136.4 ± 6.4	156.4 ± 7.6	153.7 ± 5.8		***	***	***
Weight (kg)	32.4 ± 7.3	31.3 ± 6.3	45.7 ± 9.1	44.2 ± 7.9	**	**	***	***
BMI (kg/m^2)	17.3 ± 2.9	16.7 ± 2.4	18.6 ± 2.9	18.7 ± 2.8	***		***	***
POW (%)	0.6 ± 15.7	-0.5 ± 13.9	-0.7 ± 14.9	-4.9 ± 14.2		***		***
SBP (mmHg)	102 ± 11	102 ± 12	110 ± 13	106 ± 12		***	***	***
DBP (mmHg)	61 ± 9	61 ± 9	60 ± 9	62 ± 9		**		
TC (mg/dl)	171 ± 26	172 ± 24	159 ± 24	168 ± 25		***	***	*
HDLC (mg/dl)	67 ± 13	65 ± 13	63 ± 12	65 ± 12		**	***	
non-HDLC (mg/dl)	104 ± 25	107 ± 22	97 ± 22	103 ± 23		***	***	*
AI	1.6 ± 0.6	1.7 ± 0.5	1.6 ± 0.5	1.7 ± 0.5	***			
TG (mg/dl)	100 ± 50	101 ± 48	98 ± 50	97 ± 44				
LDLC (mg/dl)	89 ± 22	91 ± 20	83 ± 20	90 ± 22	*	***	***	
LDL/HDL	1.4 ± 0.5	1.5 ± 0.4	1.4 ± 0.5	1.4 ± 0.5				

Values were presented as mean ± standard deviation.
#Differences between children in different sexes or in either grade were evaluated using Tukey's test.
(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$)
BMI: body mass index (weight / height^2), POW: percentage overweight, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, HDLC: high-density lipoprotein cholesterol, non-HDLC: non-high-density lipoprotein cholesterol (TC-HDLC), AI: atherosclerotic index [(TC-HDLC) / HDLC], TG: triglyceride, LDLC: low-density lipoprotein cholesterol, LDL/HDL: low-density lipoprotein/high-density lipoprotein choresterol

Table 2　Percentile values of serum lipid levels in the subjects

	percentile	males				females			
		50th	75th (25th)	90th (10th)	95th (5th)	50th	75th (25th)	90th (10th)	95th (5th)
TC (mg/dl)	4th grade	168	187	203	214	170	187	202	216
	7th grade	157	175	190	199	167	183	200	210
HDLC (mg/dl)	4th grade	66	(57)	(50)	(47)	64	(56)	(50)	(46)
	7th grade	62	(54)	(48)	(44)	64	(57)	(50)	(47)
non-HDLC (mg/dl)	4th grade	101	119	135	148	105	120	135	147
	7th grade	95	110	125	133	100	117	135	144
TG (mg/dl)	4th grade	89	121	170	196	90	119	158	197
	7th grade	87	116	157	181	86	113	149	171
LDLC (mg/dl)	4th grade	86	103	116	127	90	103	118	127
	7th grade	82	90	110	116	86	100	118	127

TC: total cholesterol, HDLC: high-density lipoprotein cholesterol, non-HDLC: non-high-density lipoprotein cholesterol (TC-HDLC), TG: triglyceride, LDLC: low-density lipoprotein cholesterol

パーセンタイル値はOkadaらの提唱する40 mg/dlより高い45 mg/dl程度となった．LDLコレステロールは同報告の計算値と単純比較はできないものの低値傾向を示し，95パーセンタイル値は同報告140 mg/dlに比べ125 mg/dl程度とかなり低いレベルとなった．また当健診の食後トリグリセリドは，小4男女，中1男女50パーセンタイル値がおのおの89，90，87，86 mg/dlであり，全国データ空腹時おのおの61，65，61，68 mg/dlと約20～30 mg/dlの差を認めた．なお当健診食後90パーセンタイル値は170，157，158，149 mg/dl，95パーセンタイル値は196，197，181，171 mg/dlであり，ばらつきの大きさを考慮すると，食後値による二次検診抽出基準としては，150～180 mg/dl程度が適当と判断された．

食後トリグリセリドに関し，肥満度20%未満の非肥満児2,702名と20%以上の肥満児259名とに分けてヒストグラムを作成すると(Fig. 1)，非肥満児に比べ肥満児は明らかに高値側に偏った分布となった．さらに，食後トリグリセリドと各測定値との相関を検討したところ，BMI，肥満度，総コレステロール，non-HDLコレステロール，LDLコレステロール，動脈硬化指数，LDL/HDLと正相関，HDLコレステロールと

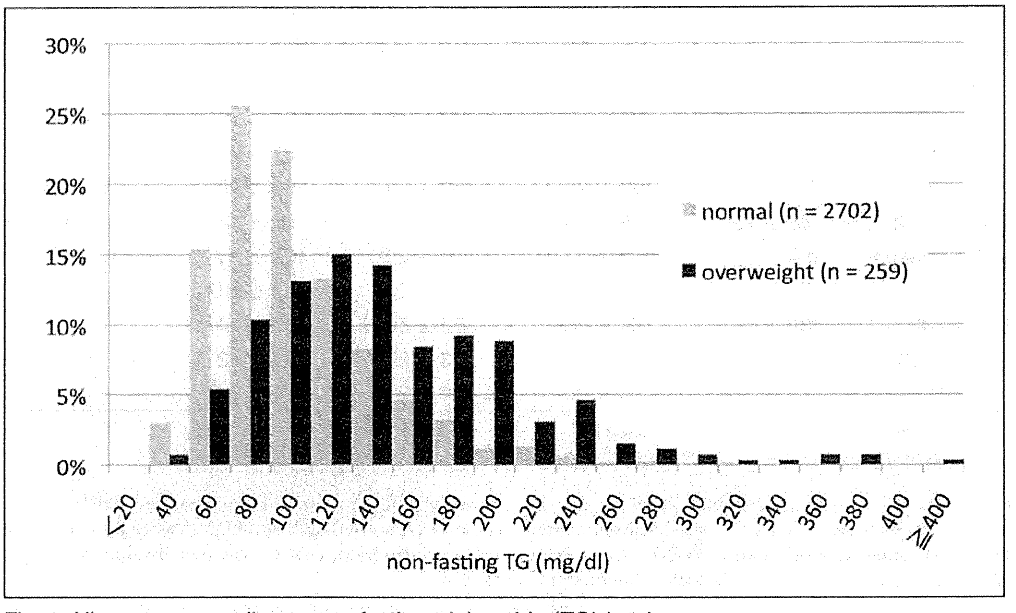

Fig. 1 Histogram according to non-fasting triglyceride (TG) levels

Table 3 Relationship between non-fasting triglyceride levels and other variables

	4th grade		7th grade	
	males	females	males	females
BMI	0.41**	0.25**	0.28**	0.26**
POW	0.39**	0.24**	0.30**	0.26**
SBP	0.14**	n.s.	0.08*	n.s.
DBP	n.s.	n.s.	n.s.	n.s.
TC	0.22**	0.09*	0.16**	0.20**
HDLC	- 0.34**	- 0.35**	- 0.31**	- 0.29**
non-HDLC	0.41**	0.30**	0.35**	0.36**
AI	0.51**	0.48**	0.49**	0.47**
LDLC	0.28**	0.14**	0.20**	0.24**
LDL/HDL	0.42**	0.37**	0.38**	0.39**

Abbreviations are listed in Table 1.
Each relationship was examined by Pearson's correlation coefficient test.
(*$p < 0.05$, **$p < 0.001$, n.s.: not significant)

逆相関を認めた(Table 3).

二次検診で空腹時採血を行った92名において当健診でのトリグリセリド食後値と二次検診空腹値との関係をみると，$r = 0.427$($p < 0.001$)と正相関を認めた(Fig. 2). しかしばらつきが大きく，食後高値であっても空腹時正常例が多数存在し，逆に食後正常でも空腹時高値となる例も少数ながらみられた.

なお，LDLコレステロール直接測定値と食後脂質値を用いた計算値に関し，食後トリグリセリド正常群(150 mg/dl 未満)と高値傾向群(150 mg/dl 以上)とに分けて比較を試みたところ，正常群では測定値と計算値が良好に相関して値もほぼ同水準になったが，高値傾向群では測定値に比べ計算値が20 mg/dl 前後過小評価となることがわかった(Fig. 3A). さらにLDLコレステロール直接測定値とnon-HDLコレステロールとの相関を検討したところ，$r = 0.982$($p < 0.001$)と，non-HDLコレステロールがやや高い値となるものの，きわめて良好な正相関を認めた(Fig. 3B).

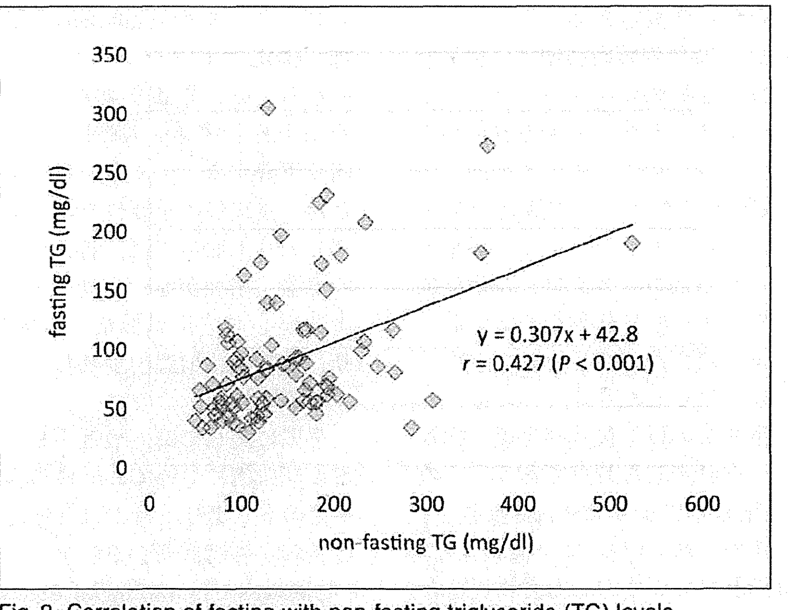

Fig. 2 Correlation of fasting with non-fasting triglyceride (TG) levels

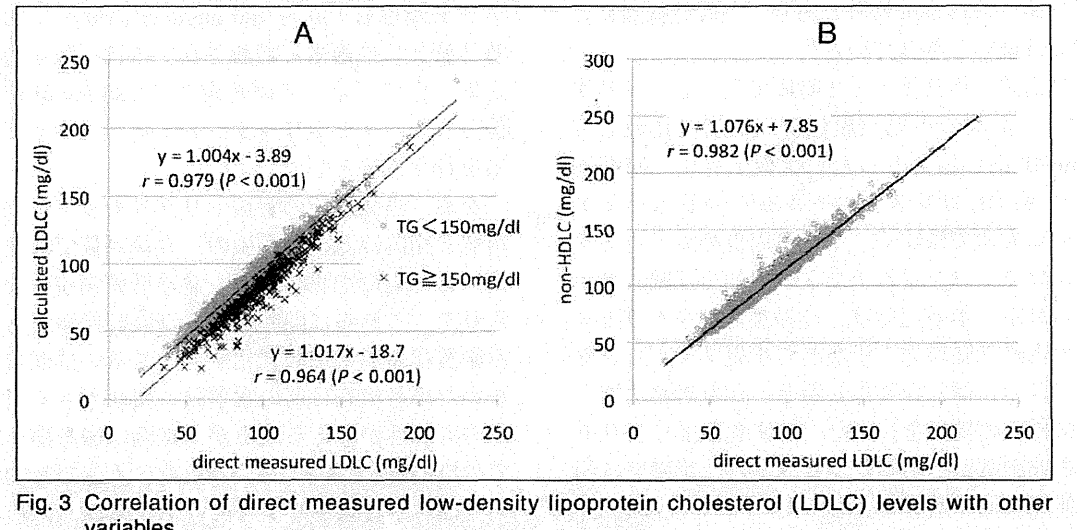

Fig. 3 Correlation of direct measured low-density lipoprotein cholesterol (LDLC) levels with other variables
A: vs. calculated low-density lipoprotein cholesterol levels
B: vs. non-high-density lipoprotein cholesterol levels