Recent Trends of Hyperuricemia and Obesity in Japanese Male Adolescents, 1991 Through 2002

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The aim of the present study was to determine the change of serum uric acid (UA) levels in male adolescents and to characterize the relationship between UA levels and obesity or its related factors. This study was conducted in 17,155 students at enrollment in Okayama University from 1991 through 2002, in which the mean serum UA level as a whole was 5.64 ± 0.009 mg/dL (mean ± SEM) and the incidence of hyperuricemia (≥7.6 mg/dL) was 4.13%. Serum UA levels were correlated with obesity-related indicators, including body mass index (BMI; $r = 0.282$, $P < .0001$) and skin-fold thickness ($r = 0.286$, $P < .0001$). The incidence of hyperuricemia was increased in parallel with BMI. In the last 4 years (1999 through 2002) of the study period, serum UA levels (5.76 mg/dL) and the incidence of hyperuricemia (4.5%) were significantly increased compared with those in the earlier period (1991 through 1994: 5.50 mg/dL and 3.5%, respectively). However, BMI has been rather gradually decreased throughout 12-year observation in all the subjects. Hyperuricemia was related to the presence of other risk factors, including hypercholesterolemia, liver function abnormality, and hypertension. The frequencies of such abnormalities were higher than euuricemic subjects and this trend was notable in the most recent students enrolled from 1999 through 2002. Hyperuricemia was even found in the group of non-obese male adolescents. Taking into consideration that hyperuricemia is associated with a high prevalence of lifestyle-related diseases in adults, it is of great importance to prevent hyperuricemia at the early stage in Japanese adolescents.

HYPERURICEMIA is commonly detected in subjects with abnormal purine metabolism, including overproduction of uric acid (UA) and insufficient UA excretion from the kidney.[1] Prolonged hyperuricemia is a causal factor to develop damages in joints, connective tissues, and the kidney. Disorders of UA metabolism are often seen in conjunction with various genetic conditions, as well as factors associated with lifestyles such as unbalanced diet abundant in purine, obesity, and alcohol consumption.[1,2] Recent studies has reported that high UA levels were often found in sera of patients who had suffered cardiovascular diseases with coexisting cluster of metabolic abnormalities, including obesity, glucose intolerance, hypertension (HT), and hyperlipidemia.[3-5] Thus, hyperuricemia is considered to be a critical health problem, as well as a common lifestyle disorder similar to hyperlipidemia, diabetes mellitus, and HT. However, it remains uncertain whether a high UA level is an independent risk factor regarding the progress of common lifestyle-related diseases.[6]

In the present study, we investigated the trend of serum UA level and incidence of hyperuricemia in 17,155 male university students enrolled from 1991 through 2002. To elucidate the relationships between hyperuricemia and major lifestyle-related diseases, we evaluated obesity, UA levels and several key factors associated with obesity. Namely, we analyzed the correlations between body mass index (BMI) and serum UA, total cholesterol (TC), alanine aminotransferase (ALT), and HT. Our study provides assessment of lifestyle-related diseases in male adolescents. Understanding of recent trends of hyperuricemia and obesity is important in order to provide appropriate guidance for improvement of Japanese lifestyle, which should lead to prevention of potential lifestyle-related diseases in adults.

MATERIALS AND METHODS

Subjects

A total of 17,155 male subjects ranging in age from 18 to 19 years were selected from 18,020 male students who enrolled in Okayama University from 1991 through 2002. The inclusion criterion was the availability of medical data at the entrance health examination. All data had been stored in the Health and Medical Center of Okayama University. Thus the inclusion rate of this study was 95.4% among the total subjects.

Methods

Data of height, body weight, BMI, thickness of skin-fold (TSF), blood pressure (BP), and serum concentrations of UA, TC, and ALT were collected on the matriculation health examination. Determination of serum concentrations of these variables had been performed in the same university laboratory for 12 years. The original laboratory data produced by the assays, which are different from the currently used system, were mathematically converted using formulas established based on the linear regression analysis (regression coefficiency > 0.98) obtained from more than 800 control samples. TSF represented the total amount of triceps and subscapular skin-fold evaluated by subcutaneous measuring calipers (Eiken type, Meiko Co, Tokyo, Japan). Upper normal ranges of serum UA, TC, and ALT were 7.6 mg/dL, 220 mg/dL, and 40 IU/L, respectively. Hypouricemia was defined as serum UA concentration below 2.0 mg/dL. Urine samples were also examined to detect occult blood, glucose, and protein using testing strips. Only when an apparent abnormality was found even after the repeated examinations, we further evaluated levels of serum urea nitrogen and creatinine. BP was automatically measured in the same condition using oscillometric method (Nihon-Colin Co, Aichi, Japan) throughout the study period. The definition of HT was based on the World Health Organization (WHO) classification of systolic (SBP) or diastolic blood pressure (DBP) exceeding 140 mm Hg and/or 90 mm Hg, respectively.

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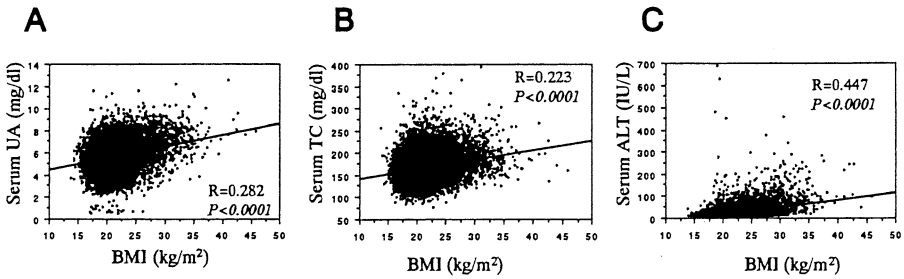

Fig 1. Correlation between body mass index (BMI) and (A) serum uric acid (UA), (B) total cholesterol (TC), and (C) alanine aminotransferase (ALT) using data of all subjects (n = 17,155).

All of the enrolled students were asked about habitual intake of alcohol by public health nurses using a questionnaire. We set the standard BMI level at 21 kg/m^2 based on our previous survey.[7] Subjects were then divided into 6 groups according to BMI: B1, $<$ 17 kg/m^2; B2, $\geq$ 17 and $<$ 19; B3, $\geq$ 19 and $<$ 21; B4, $\geq$ 21 and $<$ 23; B5, $\geq$ 23 and $<$ 25; and B6, $\geq$ 25 kg/m^2. Thus the B3 and B4 groups included subjects with normal BMI. For statistical comparison, we also divided the subjects into 3 groups according to their entrance year: 1991 through 1994, 1995 through 1998, and 1999 through 2002.

Statistical Analysis

Data were expressed as mean ± SEM. Differences between groups were analyzed for statistical significance using the 1-way analysis of variance (ANOVA) followed by post-hoc Fisher test, or ANOVA when appropriate (StatView, version 4.5, Abacus Concept, Inc, Berkeley, CA). A P value less than .05 denoted the presence of a statistically significant difference.

RESULTS

The mean height tended to be stable throughout the 12-year period, while BMI and TSF tended to be decreased during the same period. Figure 1 shows the correlations between BMI and various parameters using all of the data from17,155 subjects. There were weak but positive correlations between BMI and serum UA, TC, and ALT, showing the highest correlation with serum ALT (r = 0.447, P < .0001). These relationships were confirmed after subdividing the subjects according to BMI. Namely, both the levels of UA, TC and ALT (Fig 2A through C) and the incidence of HT (Fig 2D) were increased in accordance with the BMI levels. Furthermore, the percentage of subjects with one or more complication factors, including high UA, TC, ALT, and BP, was clearly dependent on the BMI level (Fig 2E) and the number of complicating factors per subject was also increased together with the BMI level (Fig 2F). Although urine abnormalities, including chance hematuria, glucosuria, and proteinuria, were detected in 2% to 3% of all the enrolled subjects at our annual check-up for the freshman students, none of the students had renal dysfunctions by further examinations.

Figure 3A shows the mean values of BMI and TSF, and the incidence of HT, while Figure 3B shows parameters of blood examinations for each year from 1991 through 2002. The mean serum concentrations of UA and TC and the incidence of HT were gradually increased during the 12-year observation period, although the serum ALT level showed no remarkable change. During the same 12-year period, 708 (4.13%), 694 (4.05%), 1,438 (8.38%), and 1,863 (10.9%) subjects had high serum UA, TC, ALT, and BP, respectively, among 17,155 subjects. The population of habitual alcohol intake was very small in our freshman subjects, which was not differed between hyper- and normouricemic groups in this study (data not shown).

To consider the generation differences among the subjects, we re-evaluated all of the factors in 3 groups divided according to the year of entrance (Table 1). The mean height was increased from 1991-1994 to 1995-1998 or 1999-2002 and the

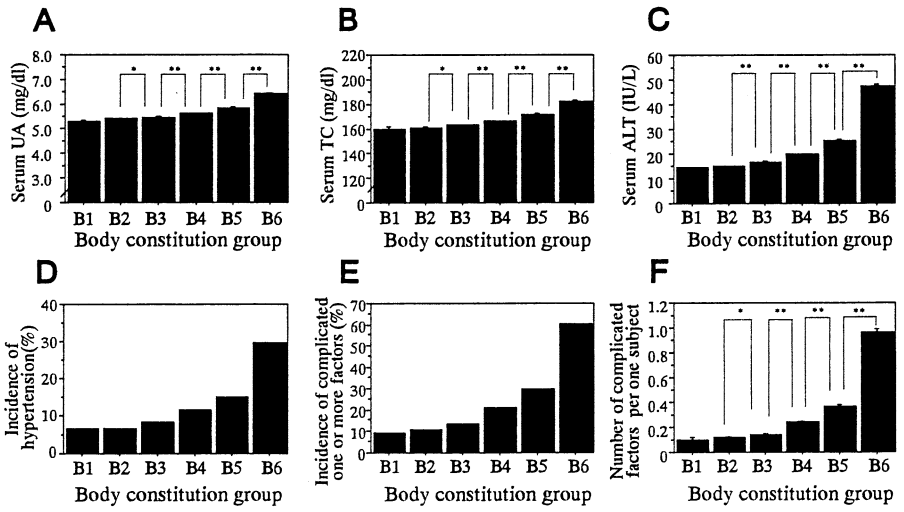

Fig 2. Serum concentrations of (A) serum UA, (B) TC, and (C) ALT; and (D) prevalence of HT, (E) presence of one or more complicating factors, and (F) number of complicating factors per subject, stratified according to BMI in the total population (n = 17,155). Data are mean ± SEM. *P < .05 and **P < .0001. "Factors" refers to subjects with 4 abnormal laboratory tests of hyperuricemia, hypercholesterolemia, high ALT, and HT.

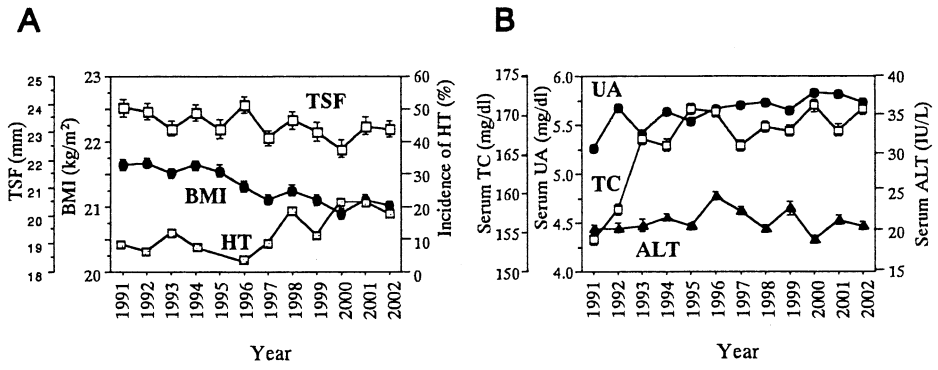

Fig 3. Trends of (A) TSF and BMI, and incidence of HT, and (B) changes in serum UA, TC, and ALT in all students enrolled in our university from 1991 through 2002. Data are mean ± SEM.

mean BMI was decreased. Figure 4 shows the population of BMI-graded subjects among the 3 period-related groups. The population of lean subjects (B1 + B2) was gradually increased from 1991-1994 to 1999-2003, whereas the obese population (B5 + B6) was decreased. However, the mean levels of serum UA, TC, SBP, and DBP from 1999 to 2003 were higher than those in 1991 to 1994 and the incidence of hyperuricemia, hypercholesterolemia, and HT was also increased from 1991-1994 to 1999-2002 (Table 1).

To clarify the cause of the recent increase in serum UA concentration, we estimated the changes in serum UA level and the incidence of hyperuricemia among the lean (B1 + B2), normal (B3 + B4), and overweight (B5 + B6) groups in each period-related group (Fig 5). Serum UA levels and the incidence of hyperuricemia were not changed from 1995-1998 to 1999-2002 in the overweight group; however, these were gradually increased from 1991-1994 to 1999-2002 in normal and lean groups.

Among the factors that relate to hyperuricemia, the incidence of hypercholesterolemia (Fig 6A), increased ALT level (Fig 6B), and HT (Fig 6C) were markedly higher in the subjects with hyperuricemia than in eu-uricemic and hypouricemic subjects. Furthermore, the levels of serum TC and ALT, and SBP and DBP of hyperuricemic subjects were also higher than those without hyperuricemia (Table 2). The proportion of hyperuricemic subjects with one or more abnormalities among the aforementioned medical parameters was higher in 1999 through 2002 than that in 1991 through 1994 (Fig 6D). The number of complicated factors found per one subject from 1999 through 2002 was more than that from 1991 through 1994 (Fig 6E). This trend was further enhanced in the non-obese subjects (Fig 6F).

In addition, we identified 24 (of 17,155, 0.14%) subjects with hypouricemia (2.00 ± 0.44 cases per year during 1991 through 2002), who showed extremely low levels of serum UA (Table 2). The body constitution, serum biochemistry, and BP of hypouricemic subjects were not different from those of eu-uricemic subjects.

DISCUSSION

On the basis of our study of 17,155 male students over a period of 12 years, the major findings were as follows: (1) Serum UA levels were tightly related to BMI levels. (2) BMI levels and the population of obesity were unexpectedly decreased during the 12-year period, whereas UA level and the incidence of hyperuricemia were increased during the same period. (3) The increase in serum UA levels was notable in non-obese subjects. (4) The number of the subjects who showed hyperuricemia associated with other metabolic dis-

Table 1. Comparison of Body Constitution, Blood Examinations, and BP Among the Three Period Groups

	1999-1994 (n = 5,945)	1995-1998 (n = 5,872)	1999-2002 (n = 5,338)
Height (cm)	171.0 ± 0.07	171.3 ± 0.07†	171.4 ± 0.08†
Body weight (kg)	63.2 ± 0.12	62.6 ± 0.12†	61.8 ± 0.13†§
BMI (kg/m^2)	21.6 ± 0.04	21.3 ± 0.04†	21.0 ± 0.04†§
TSF (mm)	23.6 ± 0.15	23.4 ± 0.15	22.9 ± 0.15*
UA (mg/dL)	5.50 ± 0.014	5.66 ± 0.015†	5.76 ± 0.015†§
Hyperuricemia (%)	3.5	4.4	4.5
TC (mg/dL)	161.4 ± 0.36	169.0 ± 0.37†	169.6 ± 0.38†
Hypercholesterolemia (%)	3.1	4.6	4.5
ALT (IU/L)	20.9 ± 0.3	22.1 ± 0.3*	21.1 ± 0.3‡
High ALT (%)	8.3	8.5	8.3
SBP (mm Hg)	120.6 ± 0.17	124.6 ± 0.19†	127.8 ± 0.19†§
DBP (mm Hg)	68.7 ± 0.14	71.7 ± 0.13†	74.2 ± 0.12†§
HT (%)	8.1	10.2	17.4

NOTE. Data expressed as mean ± SEM. The ages of subjects were not different in each period group.

*$P < .05$ and †$P < .001$ *v* 1999-1994.

‡$P < .05$ and §$P < .001$ *v* 1995-1998.

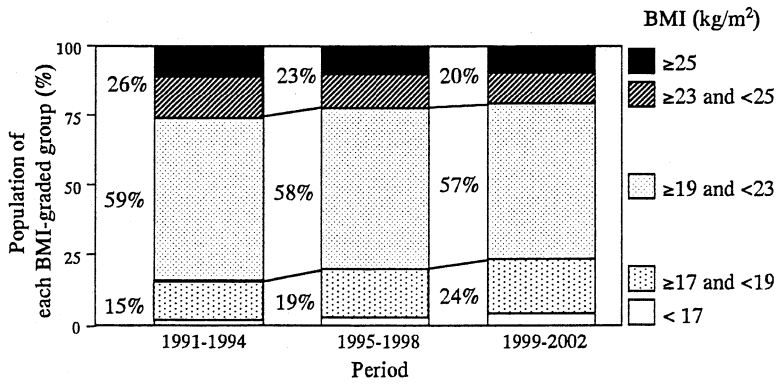

Fig 4. Changes in the percentages of each BMI group (B1, <17: B2, ≥17 and <19; B3 + B4, ≥19 and <23; B5, ≥23 and <25; B6, ≥25; numbers expressed as BMI [kg/m²]) in 3 period groups (1991-1994, 1995-1998, 1999-2002).

eases, including hypercholesterolemia, fatty liver, and HT, was markedly increased in the 4-year period of 1999 through 2002.

In this study, we assessed UA levels only in male subjects, since only a few female adolescents were found to have hyperuricemia. Unlike male subjects, the correlation between BMI and incidence of metabolic disorders was not significant in our preliminary study of female subjects.[8] The increase in UA levels of obese subjects is likely attributed to the impairment of UA excretion from the renal distal tubules[9,10] following UA absorption at the proximal tubular region,[11] rather than being due to excessive UA synthesis. In addition, habitual intake of alcohol that affects serum UA level was not found in our university freshmen (aged 18 to 19 years). Hence a relatively large proportion of adolescent males (4.13%) was found to have hyperuricemia.

As for obesity in Japanese, the population of morbidly obese is much smaller than among Europeans and Americans. Japanese males with BMI ≥25 or ≥30 kg/m² constituted only 17.1% and 1.6%, respectively, of university graduates examined in our previous study.[7] However, the proportion of subjects with lifestyle-related diseases was rather high among subjects with high BMI.[7] In this regard, our earlier questionnaire analysis of the influence of BMI changes on morbidity among 3,625 university graduates aged 26 to 62 years showed that increment of BMI inversely influences prospective morbidity in subjects with currently normal BMI.[7] This suggests that Japanese individuals with normal BMI may be susceptible to lifestyle-related diseases as a consequence of accumulation of visceral fat, associated with a high and/or rapid rise in BMI.[7] We therefore proposed the existence of preclinical obesity termed "masked obesity" in Japanese adolescents.[7]

We also reported a trend of gradual and significant increases in serum TC levels in the students (both males and females) who were newly enrolled in our university between 1989 and 1998.[8] The present study added a new finding that both the BMI level and proportion of male obese subjects were steadily decreased, which was further coupled with an increase in the proportion of lean subjects during the 12-year period. Importantly, our results showed an increase in the proportion of young adult males with hyperuricemia and other metabolic disorders in recent years who were otherwise of normal BMI. Although the exact cause of this phenomenon is poorly understood, the rapid increase in body fat mass due to a change in lifestyle in the young generation can be associated with increase in serum TC level.[12]

There is little information regarding the incidence of masked obesity in Japanese. We previously attempted to find a suitable marker for this obesity[12,13] and found a close relationship between the levels of leptin and UA in young adolescents. Our study demonstrated that a standardized parameter of endogenous leptin level, leptin/BMI ratio, correlated positively with serum UA level and that serum UA was an independent vari-

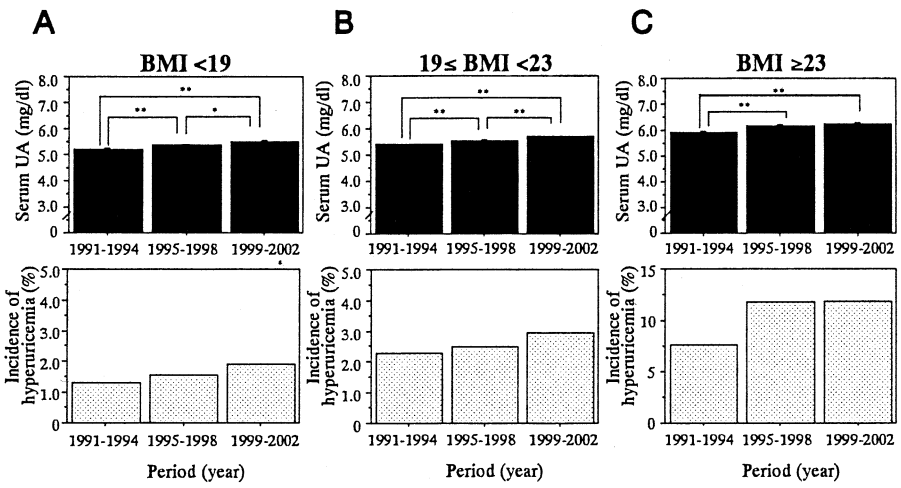

Fig 5. Changes in serum UA level (upper) and the incidence of hyperuricemia (lower) in the 3 period groups (1991-1994, 1995-1998, 1999-2002). (A) BMI < 19; (B) 19 ≤ BMI < 23; (C) BMI ≥ 23 (kg/m²). Data are mean ± SEM. *$P < .05$ and **$P < .0001$.

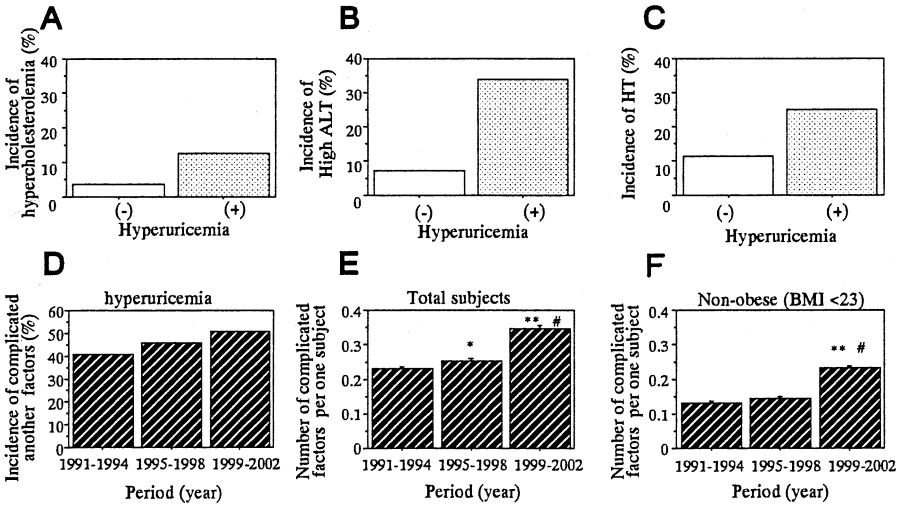

Fig 6. Incidence of complications (abnormal laboratory tests) of (A) hypercholesterolemia; (B) high ALT; (C) HT in subjects with or without hyperuricemia. Proportion of subjects with hyperuricemia (D) associated with one or more abnormal laboratory tests, and the number of associated factors/one person in (E) all and (F) non-obese subjects in the 3 period groups. *$P < .05$ and **$P < .0001$ *v* the 1991-1994 group. #$P < .0001$ *v* the 1995-1998 group.

able that influenced the leptin/BMI ratio as demonstrated by stepwise regression analysis.[13] Based on these findings, we proposed a close inter-relationship between UA synthesis and leptin production in male adolescents. Although other groups have also examined this relationship,[14,15] the physiological relevance of this relationship remains uncertain. Recently, Beltowski et al[16] reported that the effect of leptin administration on natriuresis and suppression of Na^+,K^+-adenosine triphosphatase (ATPase) activity in renal medulla is blunted in obese rats. Leptin also has a diuretic/natriuretic effects on the kidney without changing renal blood flow or glomerular filtration rate at physiological doses.[17] The high UA level induced partly by impaired UA excretion in obese subjects may be related to this direct action by leptin in the kidney, possibly at the same sites where either UA absorption or excretion occurs. Further investigation is necessary to elucidate this mechanism.

Our analysis also identified 24 subjects with hypouricemia. Recently, Enomoto et al[18] indicated that extremely low serum UA levels were caused by the mutation of urate-anion exchanger. Other studies reported that hypouricemic patients could potentially develop renal failure on strenuous exercise[19,20] because of excessive UA excretion through the distal tubules in the kidney. Although no specific abnormalities were reported on our 24 students with hypouricemia to date, it is important to provide appropriate medical advice for such subjects in order to prevent the serious complication.

In a series of this study, we can see the increased incidence of HT particularly in the male subjects. This could be related to the increased population of "masked obesity" in male adolescents since the body weight increase is closely related to the occurrence of HT even in adolescents.[21] Rapid increase in body weight, even when BMI level is within normal range, can deteriorate into the lifestyle-related disorders that induce hyperuricemia, hypercholesterolemia, or HT.[12] In our study, this was likely due to the decreased opportunity for exercise and increased habituation of food ingestion during the subjects' preparation for their entrance examinations. In addition, an occasional increase of BP, namely, "white-coat hypertension," may also be involved in this group of Japanese freshman students. Further study is necessary to confirm this issue.

In conclusion, we demonstrated in the present study that serum UA levels in male adolescents have been increasing during the last 12 years, especially in non-obese subjects. Our findings suggest that the lifestyle-related disorders may affect even the young generation irrespective of increase in obesity. Based on our present findings, we must make efforts to improve lifestyles in adolescents to prevent the prevalence of lifestyle-related diseases.

Table 2. Background of Subjects With Hypouricemia, Eu-uricemia and Hyperuricemia

	Hypouricemia (n = 24)	Normal serum UA (n = 16,423)	Hyperuricemia (n = 708)
Body weight (kg)	59.7 ± 1.46	62.1 ± 0.07	72.7 ± 0.56*‡
BMI (kg/m^2)	20.6 ± 0.49	21.2 ± 0.02	24.6 ± 0.18*‡
TSF (mm)	22.1 ± 1.45	22.8 ± 0.09	35.7 ± 0.69*‡
Serum UA (mg/dL)	0.92 ± 0.07*	5.53 ± 0.01	8.26 ± 0.03*‡
Serum TC (mg/dL)	166.6 ± 5.3	165.9 ± 0.2	181.5 ± 1.3*†
Serum ALT (IU/L)	20.3 ± 3.9	20.4 ± 0.2	44.2 ± 1.8*‡
SBP (mm Hg)	122.5 ± 2.4	123.9 ± 0.1	129.8 ± 0.6*†
DBP (mm Hg)	70.7 ± 1.7	71.4 ± 0.1	75.4 ± 0.4*†

NOTE. Data expressed as mean ± SEM. The ages of subjects were not different in each group.

*$P < .0001$ *v* normal serum UA.

†$P < .05$ and ‡$P < .0001$ *v* hypouricemia.

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