# Prevalence of Fatty Liver in Non-obese Japanese Children with Atopic Dermatitis

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*Fatty liver in non-obese Japanese children was observed in 3.2% of non-atopic children and in 17.6% of patients with atopic dermatitis in 2000. The prevalence of fatty liver in non-obese children aged 0-12 years was studied from 2001 to 2003. Subjects were either non-atopic children, or suffering from bronchial asthma, allergic rhinitis, or atopic dermatitis. Fatty liver was studied by abdominal ultrasound scans. The prevalence of fatty liver was increasing annually, and it reached to 12.5% in non-atopic children, 13.1% in patients with bronchial asthma, 13.7% in patients with allergic rhinitis, or 33.9% in patients with atopic dermatitis, in 2003. Since fatty liver in childhood may be a risk factor for lifestyle-related diseases in future, care should be taken to prevent it.*

**Key words:** *Atopic dermatitis,Fatty liver, Ciliary neurotrophic factor, Non-obese children.*

THE prevalence of non-alcoholic fatty liver in obese adults is increasing(1). Similarly, the prevalence of fatty liver in obese children is increasing, and many studies were reported(2-4). In contrast, the prevalence of fatty liver in non-obese children was not previously reported. It was reported that prevalence of atopic dermatitis (AD) was associated with intake of dietary factors, such as trans fatty acid or increased consumption of calories(5,6). During the study of AD, we found that not only obese children but also non-obese children with AD had fatty liver. Subsequently, we reported that the prevalence of fatty liver in non-obese Japanese children was 3.2% in non-atopic children, 5.0% in patients with bronchial asthma (BA), 3.7% in patients with allergic rhinitis (AR), and 17.6% in patients with AD in 2000(7). It should be noticed that the prevalence of fatty liver was significantly high in patients with AD, although the prevalence of other allergic diseases (BA and AR) was also associated with increased intake of fatty acid(6). It has been reported that fatty acid may be markedly absorbed by the increased permeability of the small intestine, and fatty acid dysregulation may be involved in the pathogenesis of AD, while such dysfunction is not observed in BA or AR(8,9). It would be tempting to speculate that fatty acid is abnormally absorbed, which in turn may cause fatty liver. Therefore, the prevalence of fatty liver from following years was studied in non-obese non-atopic children, or non-obese patients with AD, BA, or AR along with certain biochemical markers; including serum levels of GOT, GPT, total cholesterol (T-Chol), LDL-cholesterol (LDL-Chol), or triglycerides (TG). Moreover, since it was reported that ciliary neurotrophic factor (CNTF) reduced body fat and improved hepatic steatosis(10,11), plasma levels of

CNTF was also measured.

## Subjects and methods

After obtaining informed consent from parents, non-obese children aged 0-12 years were studied from 2001 to 2003. Non-atopic children who visited hospital for medical examination, mild BA patients, mild AR patients, or mild AD patients were included (*Table I*). Subjects who had endocrinological, renal, or hepatic diseases, or any acute diseases, were excluded. None of the subjects were undernourished, or took any oral medication at the time of study. All of the subjects were non-obese as assessed by BMI (less than 20). AD was defined according to the criteria of Hanifin and Rajka, including pruritus, facial and extensor involvement of eczema, personal or family history of atopy(12). BA was defined as chronic obstructive inflammation with wheezing, dyspnea, and cough, but symptoms were improved spontaneously or by treatment. AR was defined as allergic responses of the nose including sneeze, nasal discharge, and swelling of the nasal mucosa, and with positive serum allergen-specific IgE. Non-atopic children had no allergic diseases, while

**TABLE I**–*Prevalence of fatty liver in non-atopic children or patients with atopic dermatitis*

| | Year | | | | | |
|---|---|---|---|---|---|---|
| | Non-atopic children | | | Patients with atopic dermatitis | | |
| | 2001 | 2002 | 2003 | 2001 | 2002 | 2003 |
| Total number | 278 | 293 | 312 | 368 | 423 | 531 |
| Sex (F/M) | 145/133 | 150/143 | 158/154 | 190/178 | 213/210 | 276/255 |
| Age (years) | 6.7 ± 3.2 | 6.9 ± 3.4 | 6.3 ± 3.1 | 6.0 ± 3.2 | 6.5 ± 3.5 | 6.8 ± 3.3 |
| BMI | 15.0 ± 5.3 | 15.1 ± 4.9 | 15.5 ± 5.8 | 15.6 ± 5.5 | 15.1 ± 5.2 | 15.9 ± 6.4 |
| Fatty liver | | | | | | |
| Mild | 13 (4.7%) | 18 (6.1%) | 31 (9.9%) | 53 (14.4%) | 81 (19.1%) | 142 (26.7%) |
| Moderate | 2 (0.7%) | 4 (1.4%) | 8 (2.6%) | 15 (4.1%) | 21 (5.0%) | 38 (7.2%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Total | 15 (5.4%) | 22 (7.5%) | 39 (12.5%) | 68 (18.5%) | 102 (24.1%) | 180 (33.9%) |
| Serum | | | | | | |
| GOT | 28 ± 17 | 32 ± 19 | 29 ±16 | 30 ± 18 | 34 ± 20 | 31 ± 17 |
| GPT | 21 ± 14 | 20 ± 13 | 22 ± 15 | 20 ± 14 | 23 ± 15 | 25 ± 16 |
| T-Chol | 164 ± 22 | 179 ± 25* | 190 ± 27$^{+}$ | 169 ± 24 | 182 ± 27* | 194 ± 29$^{+}$ |
| LDL-Chol | 85 ± 17 | 93 ± 20* | 101 ± 23$^{+}$ | 83 ± 16 | 92 ± 22* | 107 ± 25$^{+}$ |
| TG | 71 ± 20 | 74 ± 22 | 79 ± 25 | 75 ± 22 | 79 ± 25 | 83 ± 27 |
| CNTF | < 8.0 | < 8.0 | 8.4 ± 3.8$^{+}$ | 9.2 ± 3.9 | 12.4 ± 4.2* | 16.7 ± 4.9$^{+}$ |

Values without SD are numbers of subjects or (%) of subjects with fatty liver.
Values with SD are mean ± SD of ages, body mass index (BMI), or serum levels of GOT (IU/mL), GPT (IU/mL), Total cholesterol (T-Chol) (mg/dL), LDL-cholesterol (LDL-Chol) (mg/dL), triglyceride (TG) (mg/mL), or ciliary neurotrophic factor (CNTF) (pg/mL).
* P value <0.05 compared to 2001 and $^{+}$ P value <0.05 compared to 2002 in each group.

BA patients had only BA, but not AR or AD. Similarly, AR patients had only AR, but not BA or AD, while AD patients had only AD, but not BA or AR. Fatty liver was studied by abdominal ultrasound scans and graded as mild, moderate or severe(2,7). Serum levels of GOT, GPT, T-Chol, LDL-Chol or TG were measured. CNTF was measured by ELISA (R & D Systems, Minneapolis, USA). The sensitivity of the assay was 8 pg/mL(13). This study was approved by the Ethical Committee of Ujitakeda Hospital. Statistical analysis were performed with ANOVA.

**Results**

As shown in *Table I,* all of the subjects were non-obese as indicated by BMI (<20). BMI value was not increased from 2001 to 2003 in each group. However, the prevalence of fatty liver was increasing annually, and it reached to 12.5% in 2003 in non-atopic children. Although most of the fatty liver was mild, the prevalence of moderate fatty liver was increasing gradually. In contrast, in AD patients, the prevalence of fatty liver was already high in 2001 as previously reported(7), and it reached to 33.9% in 2003. It should be noted that among them, 7.2% was moderate fatty liver.

To assess whether non-atopic children and AD patients were not obese or overweight differed from each other in frequency of fatty liver, BMI was calculated and compared as median (95% CI). In non-atopic children, median BMI (85% CI) were 15.2 (15.0-15.4), 14.9 (14.7-15.1) and 15.2 (14.9-15.5) in 2001, 2002, and 2003, respectively. In AD patients, median BMI (85% CI) were 15.3 (15.1-15.5), 15.0 (14.8-15.2) and 15.4 (15.1-15.7) in 2001, 2002, and 2003, respectively. There were no significant difference between non-atopic children and AD patients in any year, and there was no increase in BMI values over the years.

Serum levels of GOT or GPT were not increasing annually in non-atopic children or in AD patients. In contrast, serum levels of T-Chol and LDL-Chol, but not TG, were significantly increasing annually in both groups. On the other hand, plasma CNTF levels were undetectable in 2001 or 2002, but they were increased to be detectable in 2003 in non-atopic children. In contrast, CNTF levels were detectable in 2001, and the levels were increasing annually in AD patients. In our hospital, ranges of normal levels of serum GOT, GPT, T-Chol, LDL-Chol and TG in children were 10-40 IU/mL, 5-45 IU/mL, 130-200 mg/dL, 65-119 mg/dL, and 35-149 mg/dL, respectively. In non-atopic children, raised serum levels of GOT/GPT/T-Chol/LDL-Chol/TG were found in 3/4/36/48/5, 7/9/49/58/8, and 9/12/58/72/11 subjects in 2001, 2002 and 2003, respectively. On the other hand, in AD patients, raised serum levels of GOT/GPT/T-Chol/LDL-Chol/TG were found in 10/16/68/91/18, 19/21/72/95/25, and 28/32/98/107/52 patients in 2001, 2002 and 2003, respectively. To study whether there is statistical difference between non-atopic children and AD patients, each parameter is compared between two groups. Except the prevalence of fatty liver and serum CNTF levels, there was no statistical difference between two groups in each year. The P values of the prevalence of fatty liver and serum CNTF levels between non-atopic children and AD patients in 2001, 2002, and 2003 were <0.05 and <0.001, <0.05 and <0.01, and <0.001 and <0.001 respectively.

To address whether high prevalence of fatty liver may be due to allergic diseases, the prevalence of fatty liver in BA patients or AR patients was studied. As shown in *Table II*, the prevalence of fatty liver in BA patients or AR patients were similar to non-atopic children. They were increasing annually and reached to

**TABLE II–***Prevalence of fatty liver in patients with bronchial asthma or allergic rhinitis.*

| | Year | | | | | |
|---|---|---|---|---|---|---|
| | Patients with bronchial asthma | | | Patients with allergic rhinitis | | |
| | 2001 | 2002 | 2003 | 2001 | 2002 | 2003 |
| Total number | 265 | 272 | 298 | 233 | 241 | 256 |
| Sex (F/M) | 131/134 | 128/144 | 146/154 | 118/125 | 111/130 | 127/129 |
| Age (years) | 6.3 ± 3.0 | 6.6 ± 3.2 | 6.7 ± 3.3 | 6.2 ± 3.1 | 6.6 ± 3.3 | 6.5 ± 3.4 |
| BMI | 14.8 ± 5.0 | 14.9 ± 4.7 | 15.3 ± 5.2 | 15.2 ± 4.9 | 15.3 ± 5.1 | 15.7 ± 5.8 |
| Fatty liver | | | | | | |
| Mild | 12 (4.5%) | 19 (7.0%) | 30 (10.1%) | 11 (4.7%) | 21 (8.7%) | 30 (11.7%) |
| Moderate | 2 (0.8%) | 5 (1.8%) | 10 (3.4%) | 2 (0.9%) | 4 (1.7%) | 5 (1.9%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Total | 14 (5.3%) | 24 (8.8%) | 40 (13.1%) | 13 (5.6%) | 25 (10.4%) | 35 (13.7%) |
| Serum | | | | | | |
| GOT | 29 ± 19 | 33 ± 19 | 30 ±17 | 32 ± 19 | 31 ± 18 | 33 ± 20 |
| GPT | 20 ± 13 | 19 ± 18 | 23 ± 16 | 22 ± 16 | 25 ± 17 | 26 ± 17 |
| T-Chol | 160 ± 21 | 178 ± 23* | 193 ± 28$^{+}$ | 171 ± 25 | 184 ± 28* | 199 ± 30$^{+}$ |
| LDL-Chol | 86 ± 15 | 94 ± 19* | 103 ± 25$^{+}$ | 85 ± 15 | 94 ± 24* | 107 ± 26$^{+}$ |
| TG | 70 ± 18 | 73 ± 23 | 78 ± 24 | 73 ± 24 | 81 ± 26 | 84 ± 29 |
| CNTF | < 8.0 | < 8.0 | 9.7 ± 4.4$^{+}$ | <8.0 | <8.0 | 10.2 ± 4.6$^{+}$ |

Values without SD are numbers of subjects or (%) of subjects with fatty liver.
Values with SD are mean ± SD of ages, body mass index (BMI), or serum levels of GOT (IU/mL), GPT (IU/mL), Total cholesterol (T-Chol) (mg/dL), LDL-cholesterol (LDL-Chol) (mg/dL), triglyceride (TG) (mg/mL), or ciliary neurotrophic factor (CNTF) (pg/mL).
* P value <0.05 compared to 2001 and $^{+}$ P value <0.05 compared to 2002 in each group.

13.1% in BA patients and 13.7% in AR patients in 2003. Serum levels of GOT, GPT or TG were not increased, while serum levels of T-Chol and LDL-Chol were significantly increasing annually. In BA patients, raised serum levels of GOT/GPT/T-Chol/LDL-Chol/TG were found in 4/5/39/48/8, 8/7/40/52/9, and 7/14/59/61/11 patients in 2001, 2002 and 2003, respectively. On the other hand, in AR patients, raised serum levels of GOT/GPT/T-Chol/LDL-Chol/TG were found in 4/7/41/48/6, 6/9/50/51/10, and 10/15/62/82/25 patients in 2001, 2002 and 2003, respectively. On the other hand, plasma CNTF levels were undetectable in both groups of patients in 2001 or 2002, but serum CNTF levels were increased to be detectable in both groups in 2003.

## Discussion

These results indicated that the prevalence of fatty liver in non-obese Japanese children is increasing. The high prevalence of fatty liver may be due to increased intake of meat or fat in Japan(14). In fact, the prevalence of obesity in elementary school children is increasing from

**Key Messages**

- The prevalence of fatty liver in Japanese non-obese children, especially patients with atopic dermatitis, is increasing.
- Fatty liver in childhood may be a risk factor for lifestyle-related diseases in future, and care should be taken to prevent it.

2000 to 2002(15). Moreover, the prevalence of non-alcoholic fatty liver in Japanese adults is increasing(16). We have previously reported that the prevalence of fatty liver in non-atopic children and children with AD in 2000 was 3.2% and 17.6%, respectively(7). The inclusion and exclusion criteria for subjects were same for these groups in 2000 to 2003, and they were a comparable group to subjects in future years. Here, we have demonstrated that the prevalence of fatty liver in non-atopic children and children with AD in 2003 is 5.4% and 26.7%, respectively. These results indicate that the prevalence of fatty liver in non-obese children is increasing in non-atopic children and particularly in children with AD. This may be due to increased intake of meat or fat in Japan(15). Indeed, our preliminary study revealed that avoidance of fast food and high-caloric confectionary for 2 months without special exercise improved mild fatty liver in 42 out of 50 AD patients (manuscript in preparation).

The reason of high prevalence of fatty liver in AD patients remains to be elucidated. There were no significant differences between non-atopic children and AD patients in any year. In addition, there was no increase in BMI values over the years. Therefore, the increase in frequency over the years was not due to a greater number of obese/overweight children. On the other hand, this was not due to allergic symptoms since the prevalence of fatty liver in BA patients or AR patients was similar to non-atopic children. However, fatty acid may be markedly absorbed by the increased permeability of the small intestine, while fatty acid dysregulation may be involved in the pathogenesis of AD(8,9). It was reported that increased intestinal permeation caused fatty liver(17). On the other hand, high levels of serum lipids were correlated with AD(18). Moreover, changes of polysaturated fatty acids in maternal breast milk have been shown in patients with AD(19). Collectively, it would be tempting to speculate that fatty acid is abnormally taken and absorbed, which in turn may cause fatty liver in AD. In addition, AD patients may exercise less than non-atopic children(20).

The biological mechanisms of fatty liver in AD remains to be elucidated. However, allergic responses in AD patients were enhanced if they had fatty liver Moreover, cholesterol increases allergen-specific IgE production *in vitro* (Kimata H. *Cholesterol selectively enhances in vitro latex-specific IgE production in atopic dermatitis patients with latex allergy*. In press). It is postulated that cholesterol in tissues may augment allergic responses by these mechanisms, which in turn may aggravate AD.

This study has also demonstrated that plasma CNTF were detectable in non-atopic children, BA patients or AR patients in 2003, but not in 2001 or 2002, while it was detectable in 2001 in AD patients and CNTF

levels were increasing annually in 2002 and 2003, when the prevalence of fatty liver was also increasing. The mechanisms of involvement of CNTF in fatty liver remain to be elucidated. However, CNTF reduced body fat and improved hepatic steatosis(10,11). We are currently studying the relationship of plasma CNTF levels and fatty liver.

On the other hand, peripheral blood B cells from AD patients spontaneously produced CNTF upon in vitro culture, while peripheral blood B cells from non-atopic subjects produced no CNTF (<8 pg/mL)(13). It is possible that CNTF may be involved in the pathogenesis of AD. This possibility is currently under investigation.

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*Competing interests:* None stated.

**REFERENCES**

1. Zafrani ES. Non-alcoholic fatty liver disease: an emerging pathological spectrum. Virchows Arc 2004; 444: 3-12.
2. Schwimmer JB, Deutsch R, Rauch JB, Behling C, Neewbury R, Lavine JE. Obesity, insulin resistance, and other clnicopathological correlates of pediatric nonalcoholic fatty liver disease. J Pediatr 2003; 143: 500-505.
3. Fishbein MH, Miner M, Mogren C, Cghalekoson J. The spectrum of fatty liver in obese children and the relationship of serum aminotransferases to severity od steatosis. J Pediatr Gastroenterol Nutr 2003, 36: 54-61.
4. Roberts EA. Nonalcoholic steatohepatitis in children. Curr Gastroenterol Rep 2003, 5: 253-259.
5. Weiland SK, von Mutius E, Hushing A, Asher MI. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. ISAAC Steering Committee. Lancet 1999, 353: 2040-2041.
6. Ellwood P, Asher MI, Bjorksten B, Burt M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an economic analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISSAC Phase One Study Group. Eur Respir J 2001, 17: 436-443.
7. Kimata H. Fatty liver in atopic dermatitis. Allergy 2001; 56: 460.
8. Ukabam SO, Mann RJ, Cooper BT. Small intestinal permeability to sugars in patients with atopic eczema. Br J Dermatol 1984; 110: 649-652.
9. Lindskov R, Holmer G. Polyunsaturated fatty acids in plasma, red blood cells and mononuclear cell phospholipids of patients with atopic dermatitis. Allergy 1992; 47: 517-521.
10. Lambert PD, Anderson KD, Sleeman MW, Wong V, Tan J, Hijarunguru A, *et al*. Ciliary neurotrophic factor activates leptin-like pathways and reduces body fat, without cachexia or rebound weight gain, even in leptin-resistance obesity. Proc Natl Acad Sci USA 2001, 98: 4652-4657.
11. Sleeman MW, Garcia K, Liu R, Murray JD, Malinova L, Moncrieffe M, *et al*. Ciliary neurotrophic factor imprves diabetic parameters and hepatic steatosis and increases basal metabolic rate in db/db mice. Proc Natl Acad Sci USA 2003, 100: 14297-14302.
12. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980; Suppl 92: 44-47.
13. Kimata H. Ciliary neurotrophic factor preferentially enhances spontaneous IgE production by B cells from atopic patients. Neuropeptides 2004; 38: 92-97.
14. Ganmaa D, XM Li, Qin LQ, Wang PY, Takeda M, Sato A. The experience of Japan as a clue to the etiology of testicular and prostatic cancers. Med Hypotheses 2003; 60: 724-730.
15. Yoshinaga M, Shimago A, Koriyama C, Nomura Y, Miyata K, Hashiguhci J, *et al*. Rapid increase in the prevalence of obesity in elementary school children. Int J Obes Relat Metab Disord 2004; 28: 494-499.
16. Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty

liver in Japan over the past 12 years: analysis of clinical background. J Gastroenterol 2003; 38: 954-961.

17. DeMeo MT, Mutlu EA, Keshavarziqan A, Tobin MC. Intestinal permeation and gastrointestinal disease. J Clin Gastroenterol 2002; 34: 385-396.

18. Niwa Y, Iizawa O. Abnormalities in serum lipids and leukocyte superoxide dismutase and associated cataract formation in patients with atopic dermatitis. Arch Dermatol 1994; 130: 1387-1392.

19. Hamosh M, Bitman J. Human milk in disease: lipid composition. Lipids 1992; 27: 848-857.

20. Kibert G, Scorensen SV, Revicki D, Fagan SC, Doyke JJ, Cohen J, *et al.* Atopic dermatitis is associated with a decrement in health-related quality of life. Int J Dermatol 2002; 41: 151-158.

# Prevalence of Anemia Among School Going Adolescents of Chandigarh

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*This study was conducted to assess the prevalence of anemia and determine serum ferritin status among 1120 apparently healthy adolescents (12 to 18 years) sampled from 11 city and 2 rural schools in Chandigarh. All the boys and the girls were subjected to anthropometric examination and hemoglobin estimation. The estimation of hemoglobin was done by cyanmethemoglobin method. Serum ferritin was estimated by ELISA (UB1 Magiwel enzyme immuno assay) method in 183 students. The overall prevalence of anemia calculated as per WHO Guidelines was significantly higher among girls (23.9%) as compared to boys (odds ratio –3.75, 95% CI –2.59 to 5.43, P <0.01). Anemia was observed more in rural (25.4%) as compared to urban (14.2%) adolescents (OR - 0.49, 95% CI - 0.34 to 0.70, P < 0.01). Iron stores estimated by serum ferritin in 183 subjects were deficient in 81.7% and 41.6%of the adolescent girls and boys, respectively.*

**Key words :** *Adolescents, Anemia, Prevalence, Serum ferritin.*

**NUTRITIONAL** anemia is prevalent all over the world, with an estimated one billion people being iron deficient (1). Recent data from the District Nutrition Project (Indian Council of Medical Research) in 16 districts of 11 states, on prevalence of anemia in non pregnant adolescent girls (11-18 years) showed rates as high as 90.1% with severe anemia (Hb <7 g/dL) in 7.1%(2). In a study by Kapoor and Aneja(3) from public and government schools in Delhi, anemia among adolescent girls was as high as 50.8%. Compared to the vast amount of work done in pregnant mothers and young children, there are relatively few published studies on the prevalence of anemia in adolescents and