Reference Interval for the Apolipoprotein B-48 Concentration in Healthy Japanese Individuals

Daisaku Masuda¹, Makoto Nishida¹, ², Toshihiko Arai³, Hiroyuki Hanada⁴, Hiroshi Yoshida³, ⁵, Keiko Yamauchi-Takahara², Toshiaki Moriyama², Norio Tada³, ⁵ and Shizuya Yamashita¹, ⁶

¹Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
²Health Care Center, Osaka University, Osaka, Japan
³St. Marguerite Hospital, Chiba, Japan
⁴Division of Laboratory for Clinical Investigation, Department of Medical Technology, Osaka University Hospital, Osaka, Japan
⁵Division of General Medicine, Department of Internal Medicine, Kashiwa Hospital, The Jikei University School of Medicine, Chiba, Japan
⁶Department of Community Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Aim: Small intestine-derived chylomicrons and chylomicron remnants, which are predominant in patients with postprandial hypertriglyceridemia, chylomicron syndrome and/or familial dyslipidemia, carry one molecule of apolipoprotein B-48 (apo B-48) per lipoprotein particle. We investigated the reference interval for the apo B-48 concentration.

Methods: We studied 516 individuals who provided written informed consent and confirmed that they were not taking any medications. BMI, waist circumference, blood pressure and the fasting serum concentrations of LDL-C, triglyceride (TG), HDL-C and apo B-48 were measured. The Apo B-48 concentrations were compared according to sex, a pre- or postmenopausal status, dyslipidemia (LDL-C ≥ 140 mg/dL, TG ≥ 150 mg/dL, HDL-C < 40 mg/dL), metabolic syndrome (MetS) and the number of risk factors.

Results: The fasting apo B-48 concentrations (mean ± SD) were significantly higher in men than in women (3.8 ± 3.3 μg/mL vs 2.4 ± 1.9 μg/mL, p < 0.001), subjects with a BMI of ≥ 25 kg/m² versus a BMI of < 25 kg/m² (4.4 ± 3.7 μg/mL vs 2.8 ± 2.4 μg/mL, p < 0.001) and those with versus without MetS (6.5 ± 4.3 μg/mL vs 3.0 ± 2.6 μg/mL, p < 0.001). High apo B-48 concentrations were also observed in correlation with the number of risk factors for the MetS. The upper reference limit of apo B-48 was estimated to be 5.7 μg/mL among the 332 patients with normolipidemia, excluding those exhibiting a mean value above ± 2.58 standard deviations (SDs), as the mean and range of mean ± 1.96 SD were calculated to be 2.04 μg/mL (reference value) and 0.74 to 5.65 μg/mL (reference interval), respectively.

Conclusions: Based on our study of normolipidemic patients, the upper reference limit for the fasting apo B-48 concentration is estimated to be 5.7 μg/mL.

Key words: Apolipoprotein B-48 (apo B-48), Chylomicrons, Chylomicron remnants, Reference interval

(apo) B, apo B-100 derived from the liver and apo B-48 derived from the small intestine\(^9\).

Chylomicrons (CMs) are synthesized from apo B-48, TG and cholesterol ester in small intestinal cells following the ingestion of lipid-rich foods. After being released into the peripheral blood, CMs are metabolized into smaller remnant particles, CM-remnants, by lipoprotein lipase (LPL) attached to the peripheral vascular wall and taken up by the liver. Apo B-100, a major component of very-low-density lipoprotein (VLDL) is produced in the liver. VLDL is also reduced to smaller VLDL-remnants (or intermediate-density lipoprotein, IDL) by the actions of LPL in the peripheral blood. These remnant particles (CM-remnants and VLDL-remnants) directly infiltrate the vascular wall, subsequently triggering the development of atherosclerotic disease via accelerated macrophage foam cell formation, platelet coagulation and small dense LDL accumulation, as well as the induction of a low concentration of high-density lipoprotein (HDL) cholesterol (HDL-C)\(^5\).

A number of remnant cholesterol assays have been developed and are currently being used to evaluate the risks of atherosclerotic diseases, such as cardiovascular disease (CAD)\(^6-8\). However, these methods cannot be used to accurately discriminate small intestine-derived CM-remnants from liver-derived VLDL-remnants; therefore, the development of a new assay system is required in order to quantitatively measure the CM-remnant concentration independently. Since one CM-remnant particle contains one apo B-48 molecule and the concentration of apo B-48 is equivalent to that of CM-remnants, we developed a new assay system for measuring the apo B-48 concentration. First, we prepared an enzyme-linked immunosorbent assay (ELISA)\(^9\) for use on a fully automated analyzer system based on the chemiluminescent enzyme immunoassay (CLEIA)\(^10\). Remnants are usually metabolized immediately; however, the apo B-48 concentration remains elevated due to increased food-derived lipid intake, accelerated TRL synthesis and/or delayed TRL catabolism.

The half-life of the CM particles produced following the ingestion of fat is approximately 30 minutes in the peripheral blood, although the measurable concentration of apo B-48 proteins remains under a fasting condition due to the large amount of lipid absorption and CM production in the small intestine. Therefore, the fasting apoB-48 concentration is correlated with an increase in the TG level following the consumption of a high-fat meal, implying that the fasting apo B-48 concentration is a marker of postprandial hyperlipidemia\(^11\). High apo B-48 concentrations are usually observed in patients with type III hyperlipidemia\(^9\), metabolic syndrome (MetS)\(^12\), type IIb hyperlipidemia\(^13\) or CD36 deficiency\(^14\). However, the reference interval for the apo B-48 concentration in healthy fasting individuals has not yet been established.

**Aim**

In this study, we attempted to establish the upper reference limit and reference interval for the fasting apo B-48 concentration in individuals with normolipidemia.

**Subjects and Methods**

**Subjects**

The subjects of this study included 516 individuals who received their annual health checkup and were not taking any medications. The study was carried out under the approval of the Osaka University Health Care Center and Saint (St.) Marguerite Hospital, and all participants provided their written informed consent. The institutional ethics committees of both facilities approved the research protocol. After confirming the lack of a significant adverse medical history known to affect lipoprotein or carbohydrate metabolism, various anthropometric parameters, including height, body weight and waist circumference were obtained and the body mass index (BMI, body weight [kg]/height [m]\(^2\)) was calculated. Blood samples were collected in the morning after overnight fasting. The serum samples were then separated via low-speed centrifugation and stocked at \(-80^\circ\text{C}\) until the analyses. All specimens were handled according to the protocols of the Helsinki Declaration.

**Measurements**

Blood pressure (BP) was measured in the sitting position. Hypertension was diagnosed based on a systolic BP of \(\geq 140\) mmHg and/or a diastolic BP of \(\geq 90\) mmHg. A high BP status was determined based on a systolic BP of \(\geq 130\) mmHg and/or a diastolic BP of \(\geq 85\) mmHg (according to the guidelines for the management of hypertension issued by the Japanese Society of Hypertension). The serum TG concentration was measured according to an enzymatic method, and the LDL-cholesterol (LDL-C) and HDL-C levels were measured using direct methods. We identified cases of dyslipidemia and normolipidemia based on the diagnostic criteria for dyslipidemia of the Japan Atherosclerosis Society: (a) an LDL-C level of \(\geq 140\) mg/dL, (b) a TG level of \(\geq 150\) mg/dL, (c) an HDL-C level of
<40 mg/dL (according to the guidelines for the diagnosis and prevention of atherosclerotic cardiovascular disease for the Japanese)\(^{15}\). Abnormal factors were summarized in the patients with dyslipidemia. The fasting plasma glucose (FPG) concentration was measured according to the hexokinase UV method, and the hemoglobin A1c (HbA1c) (JDS) level was measured according to the latex agglutination method. A high fasting glucose level was defined as an FPG of ≥110 mg/dL, according to the criteria of the Japan Diabetes Society. MetS was diagnosed based on the criteria of the Japanese Society of Internal Medicine\(^ {16}\), namely, a waist circumference of ≥85 cm in men and ≥90 cm in women combined with at least two of the following factors: (a) a high BP status and hypertension (a systolic BP of ≥130 mmHg and/or a diastolic BP of ≥85 mmHg), (b) abnormal lipid metabolism (a TG level of ≥150 mg/dL and/or an HDL-C level of <40 mg/dL), (c) high fasting glucose (an FPG level of ≥110 mg/dL). Cardiac risk factors were summarized in cases of MetS.

The serum apo B-48 concentration was determined using the CLEIA system (Fujirebio, Inc., Tokyo, Japan)\(^ {10}\). Briefly, serum samples were incubated with treatment buffer solution supplemented with surfactant in order to separate apo B-48 from CMs and CM-remnants. The pre-treated samples were incubated with ferrite particles coupled with murine monoclonal antibodies against apo B-48 in the solid phase. After washing, further incubation was carried out with alkaline phosphatase-conjugated anti-apo B monoclonal antibodies as a second antibody. After further washing, a chemiluminescent substrate was added to the test cartridge, after which the relative chemiluminescent intensity was measured and the serum apo B-48 concentration was calculated according to a standard curve.

### Statistical Analysis

The statistical analysis was performed using the non-parametric Mann-Whitney \(U\) test according to F-study with the Stat Flex software program (ver. 6, Artec Inc., Osaka, Japan) after confirming the distribution. The level of significance was assumed to be 95%. The upper reference limit and reference interval for the apo B-48 concentration were estimated according to the methods recommended by CLSI (Clinical and Laboratory Standards Institute). Briefly, after normalizing all data using logarithm conversion, the mean and standard deviation (SD) were calculated and patients exhibiting a mean value above \(\pm 2.58\) SD were eliminated. This process was repeated until no exception data were calculated. Subsequently, the value was returned to the integer, and the upper reference limit and reference interval were defined.

### Results

#### Background Characteristics of the Subjects

The total number of registered subjects was 516 (284 men and 232 women: 183 premenopausal patients, 48 postmenopausal patients and one unknown patient) at two hospitals. The assay data and classification of the subjects are summarized in Table

<table>
<thead>
<tr>
<th>Men/Women</th>
<th>284/232</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>42 ± 10/42 ± 11</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>48/232</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22.4 ± 3.3</td>
</tr>
<tr>
<td>Waist circ. (cm)</td>
<td>91.1 ± 5.6</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>115.9 ± 14.6</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>73.2 ± 11.3</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>199 ± 31</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>94 ± 69</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>65 ± 15</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>121 ± 29</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>87 ± 13</td>
</tr>
<tr>
<td>HbA1c (JDS) (%)</td>
<td>5.0 ± 0.5</td>
</tr>
</tbody>
</table>

The abbreviations used in this Table are as follows. dBP: diastolic blood pressure, sBP: systolic blood pressure, BMI: body mass index, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides.

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<sup>6</sup> Masuda et al.  
<sup>14</sup> CLSI (Clinical and Laboratory Standards Institute).  
<sup>15</sup> The guidelines for the diagnosis and prevention of atherosclerotic cardiovascular disease for the Japanese.  
<sup>16</sup> The criteria of the Japanese Society of Internal Medicine.
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A total of 111 patients had a BMI of ≥25 kg/m², while a waist circumference beyond the standard range (indicating abdominal obesity) was observed in 114 cases (one-fifth of all cases). Regarding abnormal factors related to dyslipidemia (a high LDL-C concentration, high TG concentration or low HDL-C concentration), two-thirds of the subjects (337 patients, 161 men and 176 women: 152 premenopausal patients and 24 postmenopausal patients) were classified as having no abnormal factors for dyslipidemia; these patients were classified into the normolipidemic group. One-third of the patients exhibited more than one abnormal factor for dyslipidemia. Twenty-four patients, or one-fifth of those with a high BMI (≥25 kg/m²), were diagnosed with MetS, as their waist circumference was beyond the standard range and they exhibited two of three risk factors, including BP, FPG and abnormal lipid metabolism. Most of the patients exhibited either no risk factors (58.7%, 303 patients) or one risk factor (26.2%, 135 patients) for MetS, including hypertension (or a high BP status), hypertriglyceridemia, low HDL-cholesterolemia and a high FPG level.

**Apo B-48 Concentrations and their Distribution in Several Classifications**

We examined the fasting apo B-48 concentrations after classifying the patients into various groups. First, a sex difference was observed, namely, the mean apo B-48 concentration in men (284 patients) was higher than that observed in women (232 patients)

![Fig. 1A](image-url)  
**Comparison of the apolipoprotein B-48 concentrations in all cases.**  
The apolipoprotein B-48 concentrations in 284 men and 232 women (183 premenopausal patients, 48 postmenopausal patients and one unknown patient) were compared. The values indicate the mean ± standard deviation as follows: **women** = 2.4 ± 1.9 μg/mL, **premenopausal women** = 2.2 ± 1.8 μg/mL, **menopausal women** = 3.2 ± 2.0 μg/mL, **men** = 3.8 ± 3.3 μg/mL. Statistical significance was assessed using the Mann-Whitney U test. *p < 0.001 against women, §p < 0.001 against premenopausal women.

![Fig. 1B](image-url)  
**Comparison of the apolipoprotein B-48 concentrations in the subjects with a BMI of <25 kg/m² and those with a BMI of ≥25 kg/m².**  
The values indicate the mean ± standard deviation, as follows: BMI < 25 kg/m² = 2.8 ± 2.4 μg/mL (n=405), BMI ≥ 25 kg/m² = 4.4 ± 3.7 μg/mL (n=111). The number of subjects is shown in brackets. Statistical significance was assessed using the Mann-Whitney U test. *p < 0.001

(3.8 ± 3.3 μg/mL vs 2.4 ± 1.9 μg/mL, p < 0.001, Mann-Whitney U test) (Fig. 1A). A significant difference was also observed between the pre- and postmenopausal
women: the apo B-48 concentrations of the 48 postmenopausal patients were higher than those of the 183 premenopausal patients, while the mean value of the postmenopausal patients was increased, drawing near the average observed in men (3.2 ± 2.0 μg/mL vs 2.2 ± 1.8 μg/mL, p < 0.001). When all subjects were classified according to BMI, 111 patients with a BMI of ≥ 25 kg/m² were found to exhibit a statistically significantly high apo B-48 concentration in comparison with that observed in the 405 patients with a BMI of < 25 kg/m² (4.4 ± 3.7 μg/mL vs 2.8 ± 2.4 μg/mL, p < 0.001, Mann-Whitney U test) (Fig. 2). The number of abnormal factors for dyslipidemia (a high LDL-C concentration [LDL-C ≥ 140 mg/dL], high TG concentration [TG ≥ 150 mg/dL] or low HDL-C concentration [HDL-C < 40 mg/dL]) was counted in all patients. The apo B-48 concentrations were compared between four groups: patients with no abnormal factors (n = 337) and those with one (n = 138), two (n = 37) and three abnormal factors (n = 4). The values indicate the mean ± standard deviation, as follows: no abnormal factors = 2.4 ± 1.5 μg/mL, one abnormal factor = 3.8 ± 2.9 μg/mL, two abnormal factors = 7.1 ± 6.0 μg/mL, three abnormal factors = 7.3 ± 2.7 μg/mL. Statistical significance was assessed using the Mann-Whitney U test. *p < 0.01, **p < 0.001 against patients with no abnormal factors, §p < 0.05, §§p < 0.001 against patients with one abnormal factor.

The subjects were divided into two groups, MetS (n = 24) and non-MetS (n = 492), according to the criteria of the Japanese Society of Internal Medicine. The values indicate the mean ± standard deviation, as follows: non-MetS = 3.0 ± 2.6 μg/mL and MetS = 6.5 ± 4.3 μg/mL. Statistical significance was assessed using the Mann-Whitney U test. *p < 0.001
The occurrence of a high TG concentration after a meal, or postprandial hypertriglyceridemia, is a risk factor for atherosclerosis. Meal-derived TG elevation results from the assembly of CMs, which contain a large quantity of TG in each particle in comparison with VLDL. CMs are immediately hydrolyzed to CM-remnants in patients with normolipidemia, whereas an abnormally high concentration of CM-remnants is observed six hours after meal intake in those with postprandial hypertriglyceridemia. Therefore, the accumulation of CM-remnants due to postprandial hypertriglyceridemia is one of the most serious risk factors for the development of arteriosclerosis-related diseases. Several CM-remnant assay methods have been reported, including the retinyl palmitate method, the combination method employing SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) and Western blotting and the remnant-like particle-cholesterol assay method. However, these methods have limitations, such as the requirement for specialized equipment and the difficulty in standardization. In the present study, we investigated the concentration and the number of risk factors for the components of MetS (hypertension, including a high BP status, hypertriglyceridemia, low HDL-cholesterolemia and a high fasting glucose level) (Fig. 3B).

Calculation of the Upper Reference Limit for the Apo B-48 Concentration in the Patients with Normolipidemia

The upper reference limit and reference interval for the apo B-48 concentration were calculated in 337 patients without parameters of abnormal lipid metabolism, as no differences in data were observed between the 152 pre- and 24 postmenopausal normolipidemic patients, as shown in Fig. 4; namely, the mean value among the postmenopausal patients increased (2.1 ± 1.2 μg/mL vs 2.6 ± 1.8 μg/mL, not statistically significant) approaching the average observed in the 161 men (2.7 ± 1.7 μg/mL vs 2.6 ± 1.8 μg/mL, not statistically significant). We estimated the upper reference limit for the apo B-48 concentration in 332 normolipidemic patients, excluding those with a mean value of ±2.58 SD. The calculated mean value and range of mean ±1.96 SD were 2.04 μg/mL (reference value) and 0.74 to 5.65 μg/mL (reference interval), respectively. Based on these results, we consider 5.7 μg/mL to be the optimum apo B-48 upper reference limit (Fig. 5). The reference interval and upper reference limit for the apo B-48 concentration were determined according to the results obtained with the CLEIA system (Fujirebio, Inc., Tokyo, Japan).

Discussion

The occurrence of a high TG concentration after a meal, or postprandial hypertriglyceridemia, is a risk factor for atherosclerosis. Meal-derived TG elevation results from the assembly of CMs, which contain a large quantity of TG in each particle in comparison with VLDL. CMs are immediately hydrolyzed to CM-remnants in patients with normolipidemia, whereas an abnormally high concentration of CM-remnants is observed six hours after meal intake in those with postprandial hypertriglyceridemia. Therefore, the accumulation of CM-remnants due to postprandial hypertriglyceridemia is one of the most serious risk factors for the development of arteriosclerosis-related diseases. Several CM-remnant assay methods have been reported, including the retinyl palmitate method, the combination method employing SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) and Western blotting and the remnant-like particle-cholesterol assay method. However, these
for the apoB-48 concentration using serum samples obtained from healthy individuals with normolipidemia. Namely, normolipidemic patients were selected by applying the diagnostic criteria for dyslipidemia of the Japan Atherosclerosis Society: (a) an LDL-C level of ≥ 140 mg/dL, (b) a TG level of ≥ 150 mg/dL and (c) an HDL-C level of < 40 mg/dL. (Guidelines for the diagnosis and prevention of atherosclerotic cardiovascular disease for the Japanese)\textsuperscript{15)}.

We then used the CLSI recommended method to calculate the reference level. Briefly, we estimated the upper reference limit and reference interval for the apo B-48 concentration in 332 normolipidemic patients, excluding those with a mean value above ±2.58 SD. We thus determined the reference level for the apo B-48 concentration to be 2.04 μg/mL, the reference interval to range from 0.74 to 5.64 μg/mL and the upper reference limit to be 5.7 μg/mL. Incidentally, a different apo B-48 measuring kit (Human apo B-48 ELISA, Shibayagi, Gunma, Japan) is currently available in Japan. Therefore, the upper reference limit and reference interval for the apo B-48 concentration determined in this study should be restricted to the results obtained using the CLEIA system (Fujirebio, Inc., Tokyo, Japan).

We then attempted to determine whether abnormal CM-remnant metabolism was present in the normolipidemia group. When the apo B-48 concentrations of all health checkup patients were measured, a high apo B-48 concentration was observed in the following order: men, postmenopausal women and premenopausal women. The apo B-48 concentrations also differed according to the presence or absence of obesity or MetS. The TG and LDL-C concentrations, which are affected by the apo B-48 concentrations, also differed between men and women and between pre- and postmenopausal women. The upper reference limit and reference interval for the apo B-48 concentration were estimated in patients with normolipidemia; this group also contained patients with hypertension, obesity and hyperglycemia, all of which may affect lipoprotein metabolism. In this study, we examined patients who received their annual health checkup; it was not assumed that these patients had severe metabolic disorders. Therefore, it is necessary to conduct separate studies of different patient groups, including those with relatively severe metabolic disorders.

Recent reports have highlighted the clinical usefulness of the apo B-48 concentration as a screening marker of type III hyperlipidemia in patients with accumulated CM-remnants\textsuperscript{9, 24}) and parameter of the CM-remnants status in those with diabetes mellitus (DM) exhibiting carotid artery plaque\textsuperscript{25}). Additionally, correlations have been reported between the apo B-48
concentration and the carotid intima-media thickness in normotriglyceridemic (100<TG<150 mg/dL) subjects26) as well as the status of kidney dysfunction in DM patients27) and the incidence of CAD in ischemic heart disease patients in comparison with other risk factors, such as hypertriglyceridemia, low HDL-cholesterolemia, hypertension and/or hypoadiponec-tinemia28). Furthermore, an elevated incidence of CAD is observed in patients with a high apo B-48 concentration and the risk factors described above. Ultimately, this apo B-48 assay may have numerous applications in future studies.

**Conclusion**

Based on the results of this multicenter study of Japanese normolipidemic patients not taking any medications, the upper reference limit for the apo B-48 concentration in a fasting state is 5.7 μg/mL, as the mean value was found to be 2.04 μg/mL (reference value) and the mean ± 1.96 SD ranged from 0.74 to 5.65 μg/mL (reference interval).

**Study Limitations**

The limited number of subjects treated at two clinical facilities likely affected the results of this study.

**Acknowledgements**

We gratefully acknowledge the superior office work and technical assistance of Ms. Kyoko Ozawa and Ms. Risa Wada. We also appreciatively acknowledge Fujirebio, Inc. for measuring the samples using high quality standards.

**Conflicts of Interest**

Fujirebio, Inc. shared the costs of apo B-48 measurement. All authors have no other conflicts of interest to disclose.

**Funding**

This work was supported by the Japan Heart Foundation and an Astellas/Pfizer Grant for Research on Atherosclerosis Update (to D. Masuda) and by the Health and Labour Sciences Research Grants for Research on rare and intractable disease (to S. Yamashita).
**Author Contributions**


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