Evaluation of Hypertriglyceridemia using Non-fasting Health Checkup Data in a Japanese Population

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Aim: Some employees have difficulty undergoing health checkups in the workplace in a fasting state. However, hypertriglyceridemia is usually diagnosed based on fasting triglyceride (TG) measurements. The current study investigated the performance of non-fasting health checkup data for predicting hypertriglyceridemia in a Japanese population.

Methods: We recruited a total of 1,959 Japanese employees who had their fasting TG levels reexamined after undergoing initial health checkups under either a fasting (the fasting population; \( n = 856 \)) or non-fasting state (the non-fasting population; \( n = 1103 \)). Hypertriglyceridemia was defined as a fasting TG level of \( \geq 1.7 \) mmol/l.

Results: The area under the receiver operating characteristic (ROC) curve of the initial TG measurements for reexamination-detected hypertriglyceridemia was 0.85 in the fasting population and 0.83 in the non-fasting population. The area under the ROC curve of the initial TG measurements in the non-fasting population was not inferior to that of the multivariate model where other non-fasting health checkup data were added. The optimal non-fasting TG cutoff point was 2.0 mmol/l. The cutoff point was further lowered when the population was limited to patients undergoing health checkups four or more hours after their last meal and when the prevalence of hypertriglyceridemia in the population was simulated to be reduced.

Conclusions: The non-fasting workplace TG measurements by themselves exhibited a tolerable performance for predicting hypertriglyceridemia. The optimal cutoff point in Japanese employees appears to be lower than 2.3 mmol/l, the recently proposed Western cutoff point.


Key words: Non-fasting state, Hypertriglyceridemia, Health checkup

Introduction

Non-communicable diseases, or lifestyle-related diseases, including cardiovascular and metabolic syndrome, are now increasingly prevalent among middle-aged individuals worldwide. Asia is no exception. As is often discussed⁶, workplaces are considered to be one of the best places to screen people at risk for lifestyle-related diseases. However, health checkups conducted in the workplace are often accompanied by one challenging limitation. Some workers have difficulty undergoing health checkups in a fasting state and prefer to participate in a non-fasting state, although some laboratory examinations, such as tests of the serum triglyceride (TG) levels, require overnight fasting for proper assessment.

Hypertriglyceridemia, a known component of metabolic syndrome, is typically diagnosed when the fasting serum TG level is 1.7 mmol/l (150 mg/dl) or higher², ³. The presence of hypertriglyceridemia is now
well recognized to be a cardiovascular risk factor\textsuperscript{4,7}, and it is of health care importance to detect sustained hypertriglyceridemia as well as other metabolic abnormalities. Recently, the American Heart Association (AHA) scientific statement proposed 2.3 mmol/l (200 mg/dl) as a non-fasting cutoff point for screening\textsuperscript{8}. However, it remains unknown whether this cutoff point can be appropriately used in Japanese employees. The Japanese tend to have a different lifestyle than Westerners and prefer Japanese foods containing low amounts of fat. Japanese employees may attend health checkups after consuming lower amounts of fat than Westerners. It would not be surprising if a different TG cutoff point is appropriate for non-fasting Japanese employees.

Aim

The aim of our current study was to investigate how efficiently non-fasting examinations can screen Japanese employees for sustained hypertriglyceridemia, defined as a fasting TG level of $\geq 1.7$ mmol/l, in health care practice.

Methods

Study Population and Definitions

We used data obtained from the Amagasaki Visceral Fat Study, registered as UMIN000002391. The study was a cohort study approved by the human ethics committee of Osaka University in which recruitment was started in 2004. Written informed consent was obtained from every participant. In the current study, we recruited a total of 1,959 Japanese employees of the city office of Amagasaki, Hyogo who had their fasting serum TG levels reexamined following an initial health checkup at the office. The participants attended the initial health checkup in either a fasting or non-fasting state and reported the time from their last meal. Eight hundred and fifty six of the participants underwent the initial health checkup in a fasting state ($\geq 8$ hours) (the fasting population), with the remaining participants ($n=1,103$) undergoing the initial health checkup in a non-fasting state (the non-fasting population). The reexaminations were performed under a fasting state. The initial health checkups were performed in the period from June to July, and the reexaminations were performed four months after the initial health checkups. The exclusion criteria in the current study were as follows: a serum transaminase level $\geq 100$ IU/l, a serum creatinine level $\geq 177$ $\mu$mol/l, under treatment for hepatic or renal disease or having malignant neoplasms. We did not exclude subjects who received medication for dyslipidemia.

At the initial health checkups, anthropometric measurement, sphygmomanometry and laboratory examinations, including assessments of the medical history, were performed. The laboratory examinations included measurement of the levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, TG, glucose and hemoglobin A1c. In the subsequent fasting reexaminations of the serum TG levels, the subjects were diagnosed with hypertriglyceridemia when their reexamined fasting TG levels were equal to or exceeded 1.7 mmol/l.

Statistical Analysis

Since intraindividual variation in the serum TG levels was expected, we first assessed the concordance of the fasting TG measurements between the initial health checkups and the subsequent reexaminations in the fasting population. The area under the receiver operating characteristic (ROC) curve of the initial fasting TG measurements for predicting subsequent hypertriglyceridemia on reexamination was also evaluated.

We then assessed the non-fasting population. Given the considerable variation in the non-fasting TG measurements due to the variety of preceding foods, we speculated that additional consideration of other clinical factors, such as other lipid profiles and comorbidities\textsuperscript{4,5,6}, might improve the predictive capability for hypertriglyceridemia in this population. We therefore developed multivariate logistic regression models. The dependent variable was hypertriglyceridemia determined based on the subsequent fasting reexaminations, whereas the explanatory variables were the laboratory and non-laboratory data obtained from the initial health checkups. The predictive capabilities of the multivariate models and the non-fasting TG levels alone were evaluated using the area under the ROC curve as well as the sensitivity and specificity values given by arbitrary cutoff points.

The data are presented as the mean and standard deviation (SD) for continuous variables and the percentage for dichotomous variables, if not otherwise mentioned. The serum TG levels were log-transformed. A $p$ value of less than 0.05 was considered to be significant, and 95% confidence intervals (CIs) were provided when required. The statistical analyses were performed using the IBM SPSS Statistics Version 19 software program (SPSS Inc.).

Results

The recruited subjects were $52 \pm 9$ years of age, and 1,696 (87%) were men. The characteristics of the
Study population are shown in Table 1. The prevalence of hypertriglyceridemia detected on subsequent reexamination was 34% (n = 375) in the non-fasting population and 36% (n = 305) in the fasting population; no significant differences were observed between the two populations (p = 0.473). A total of 27 subjects (3%) received medication for dyslipidemia in the fasting population, whereas 37 subjects (3%) received such medication in the non-fasting population.

Predictive Performance with Respect to Hypertriglyceridemia in the Fasting Population

Fig. 1A shows the association between the fasting serum TG levels determined at the initial health checkups and those determined at the subsequent reexaminations. The measurements were 1.4 (1.0: 1.9)
mmol/l and 1.4 (1.0: 2.0) mmol/l (medians and quartiles), respectively, with no significant differences ($p=0.130$) and with a significant correlation ($r=0.73$, $p<0.001$). The concordance rate given by the cutoff point of 1.7 mmol/l in both measurements was 79% (95% CI 76-82%). The prevalence of a fasting TG level of $\geq 1.7$ mmol/l at the initial health checkups was similar to that observed at the subsequent reexaminations (35% vs. 36%: $p=0.608$). The area under the ROC curve of the initial TG levels for predicting reexamination-detected hypertriglyceridemia was 0.85 (95% CI 0.82-0.87).

**Associations between Hypertriglyceridemia and the Non-Fasting Health Checkup Data**

The serum TG levels at the initial non-fasting health checkups and the subsequent fasting reexaminations were 1.7 (1.2: 2.6) mmol/l and 1.4 (0.9: 2.0) mmol/l (medians and quartiles), respectively. There was a significant difference between the two measurements ($p<0.001$). Although the two measurements were significantly correlated ($r=0.65$, $p<0.001$) (Fig. 1B), their correlation coefficient was smaller than that obtained in the fasting population (i.e., $r=0.73$).

Table 2 shows the association between the initial health checkup data and the presence of reexamination-detected hypertriglyceridemia. The non-fasting TG levels at the initial checkups were significantly associated with the presence of hypertriglyceridemia on subsequent reexamination in both the univariate and multivariate models ($p<0.001$). The time from the last meal (postmeal time) also had a significant impact on the outcomes, independently of the non-fasting TG levels ($p=0.005$ in the bivariate model), whereas the variable itself had no significant impact in the univariate model. A multivariate logistic regression analysis revealed that body mass index, systolic blood pressure and the levels of total cholesterol and HDL cholesterol were independently associated with the outcomes (Table 2).

**Predictive Performance with Respect to Hypertriglyceridemia in the Non-Fasting Population**

As shown in Fig.2A, the multivariate model in which the health checkup data were entered together (the full multivariate model) had an area under the ROC curve of as high as 0.84 (95% CI 0.82-0.87). A similar predictive performance was found in the model whose explanatory variables were limited to significant and independent variables (the simplified multivariate model). The area under the ROC curve in this model was 0.84 (95% CI 0.81-0.86).

On the other hand, interestingly, the non-fasting TG levels by themselves exhibited substantially high predictive performance. Their area under the ROC curve was 0.83 (95% CI 0.80-0.85), which was not inferior to that of the multivariate model ($p=0.342$ vs. the full multivariate model, and $p=0.501$ vs. the simplified multivariate model) or the bivariate model including the TG levels and postmeal time ($p=0.850$) (Fig. 2A).
Hypertriglyceridemia in Patients Undergoing Health Checkups

While investigating the model performance, we further explored whether variable transformation could enhance the model's performance. The postmeal time distribution was right-skewed, and the variable was log-transformed. In the bivariate model where the log-transformed non-fasting triglycerides were adjusted for the log-transformed postmeal time, the log-transformed postmeal time exhibited a significant impact.

**Distribution of the Postmeal Time and Reassessment of Predictive Performance**

In the analyses performed above, the variable postmeal time was treated without any transformation. Its original data were not normally distributed, which may have affected the current statistical findings. Although the logistic regression itself makes no assumption about the distribution of the independent variables, normality would yield a more improved model performance. We therefore further investigated whether variable transformation would improve the model performance.

The distribution of the postmeal time in the population was right-skewed, and the variable was log-transformed. In the bivariate model in which the log-transformed non-fasting triglycerides levels were adjusted for the log-transformed postmeal time, the log-transformed postmeal time exhibited a significant impact.

**Fig. 2. Predictive performance for hypertriglyceridemia in the non-fasting population**

A: The ROC curves of the initial non-fasting health checkup data for hypertriglyceridemia (subsequent fasting TG measurements ≥ 1.7 mmol/l). Bold solid line, non-fasting TG levels alone; bold shaded line, the bivariate model including the non-fasting TG levels and postmeal time; thin solid line, the full multivariate model in which the initial health checkup data were entered together; thin shaded line, the simplified multivariate model whose explanatory variables were limited to significant and independent variables (see Table 2). B: The sensitivity and specificity values provided by arbitrary non-fasting TG cutoff points. The bold solid lines represent the sensitivity and specificity and the thin solid lines represent the 95% CIs. C: Predictive accuracy for hypertriglyceridemia in simulated non-fasting populations with its varied prevalence. The non-fasting TG cutoff points and their sensitivity and specificity values are shown. The simulated non-fasting populations were those with a 30- (thin lines), 35- (solid lines) and 40-percent (bold lines) prevalence of hypertriglyceridemia.
association with hypertriglyceridemia ($p=0.033$). The adjusted odds ratio per interquartile range was 1.33 (95% CI 1.02-1.74). However, the model did not improve the predictive performance evaluated with the area under the ROC curve. This value was 0.83 (95% CI 0.80-0.85), which was quite similar to that of the non-fasting triglycerides levels alone, i.e., 0.83 (95% CI 0.80-0.85). In addition, the full multivariate model in which other variables were additionally entered provided a similar predictive performance. The area under the ROC curve of this model was 0.84 (95% CI 0.82-0.87). These findings suggest that the postmeal time did not improve model performance, even after variable transformation.

### Cutoff Point of the Non-Fasting Triglyceride Levels

These findings indicate that the non-fasting TG levels by themselves are a simple and reliable predictor of hypertriglyceridemia. We therefore subsequently assessed the predictive accuracy given by an arbitrary cutoff point of the non-fasting TG levels and searched for the optimal cutoff point. As demonstrated in Fig. 2B, the cutoff point where the sensitivity and specificity values intersected was 2.0 mmol/l, whose sensitivity and specificity were 75% (95% CI 71-80%) and 75% (95% CI 72-78%), respectively. On the other hand, when 2.3 mmol/l, a Western cutoff point proposed in the AHA statement, was adopted, the specificity was increased to 84% (95% CI 81-86%) and the sensitivity was reduced to 65% (95% CI 60-69%).

#### Influence of the Postmeal Time on the Cutoff Point for Hypertriglyceridemia

The predictive accuracy of each non-fasting TG cutoff point described above was obtained for the entire non-fasting population. Given the independent impact of the postmeal time (Table 2), the predictive accuracy would vary if one were to focus not on the entire population, but rather on a subgroup with a certain postmeal time. We therefore additionally assessed the predictive accuracy in the subgroups with varied postmeal times. The assessments were based on the bivariate model including the TG levels and postmeal time (see Table 2).

The findings are summarized in Table 3. The TG cutoff point of 2.0 mmol/l was associated with a...
higher sensitivity and lower specificity in the subgroup participating right after their last meal and a lower sensitivity and higher specificity in the subgroup participating several hours after their last meal. For instance, in the subgroup with a postmeal time of seven hours, the sensitivity was reduced to 63%, whereas the specificity was 84%. Lowering the TG cutoff point to 1.7 mmol/l in the subgroup improved the sensitivity to 74%, with a specificity of 77%. On the other hand, in the subgroup with a postmeal time of one hour, a TG cutoff point of 2.0 mmol/l had a sensitivity of 84% and a specificity of 68%. The sensitivity and specificity values became closer to each other at the point of 2.1 mmol/l in the subgroup; a larger TG cutoff point, e.g., 2.3 mmol/l, was associated with a lower sensitivity (70%) and higher specificity (79%).

We also recalculated the predictive accuracy of the TG cutoff point at each postmeal time using a revised model with the log-transformed postmeal time. The results are presented in Table 4. Similar to the original findings (Table 3), the recalculation (Table 4) showed that a TG cutoff point of 2.0 mmol/l was associated with a higher sensitivity and lower specificity in the subgroup participating right after their last meal and a lower sensitivity and higher specificity in the subgroup participating several hours after their last meal.

**Predictive Performance with Respect to Hypertriglyceridemia in Simulated Non-Fasting Populations**

Since the predictive accuracy was expected to be influenced by the distribution of the TG levels and the prevalence of hypertriglyceridemia, we additionally assessed the predictive accuracy in simulated population models. The simulated populations were developed on the basis of the univariate logistic regression model including the TG levels and the hypothesized normality of their log-transformed distribution.

The simulation revealed that a low prevalence of hypertriglyceridemia was associated with a low TG level as an optimal cutoff point in the population, whereas a high prevalence was associated with a high TG cutoff point (Fig. 2C). For instance, in the population with a 30% prevalence of hypertriglyceridemia, the optimal TG cutoff point was 1.8 mmol/l, with a sensitivity and specificity of 73% each. On the other hand, in the population with a 40% prevalence, the optimal cutoff point was 2.1 mmol/l, with a sensitivity and specificity of 76%. The cutoff point of 2.3 mmol/l was therefore optimal when the prevalence of hypertriglyceridemia was as high as 45%.

**Discussion**

The current study revealed that the non-fasting TG levels by themselves had a tolerable performance for predicting reexamination-detected hypertriglyceridemia and that a non-fasting TG level of 2.0 mmol/l appears to be an optimal cutoff point for Japanese employees.

Several large prospective cohorts recently identified the non-fasting TG levels to be potentially superior in predicting future cardiovascular events compared with the fasting TG levels and some recent interventional trials have targeted postprandial triglyceride excursion. Nonetheless, to date, the optimal threshold of the non-fasting TG level by itself is still under discussion, and the latest scientific statement has proposed a non-fasting TG cutoff point commensurate with the normal range of the fasting TG level (< 1.7 mmol/l). Furthermore, the definition of metabolic syndrome recommends using the fasting TG levels, not the non-fasting levels. In clinical practice, hypertriglyceridemia is still determined based on a fasting TG level of ≥ 1.7 mmol/l. It is true that a number of previous studies have already investigated the relationship between the fasting and postprandial TG levels. However, in these studies, the subjects were asked to consume a prescribed test meal with a certain fat content and nutritional composition. Such conditions are far from practical health care settings. In health checkups conducted at the workplace, the amount of food intake and intensity of exercise before TG measurement varies considerably from participant to participant. These factors can considerably influence the measurements. It was of health care necessity to assess the association between the real-world non-fasting TG levels and the fasting TG levels in Japanese employees.

The current study revealed that the non-fasting TG levels by themselves have tolerable performance for predicting sustained hypertriglyceridemia. Although the non-fasting TG measurements had a relatively low correlation with the reexamined fasting TG measurements, their area under the ROC curve for predicting sustained hypertriglyceridemia was as high as 0.83 (Fig. 2A). Interestingly, a subsequent investigation revealed that the cutoff point was 2.0 mmol/l, which is lower than the 2.3 mmol/l a Western cutoff point proposed in a recent AHA statement. The AHA statement suggested that in patients with a non-fasting TG level of < 2.3 mmol/l in screening, no further testing for hypertriglyceridemia is indicated. However, in the current study population, this cutoff point had a sensitivity of as low as 65% and a specificity of
84%. This 65% sensitivity, or 35% false-negative rate, means that approximately one-third of subjects with hypertriglyceridemia would remain undiagnosed, if the recommendation of the AHA was applied in the present population. Our additional investigations also demonstrated that the sensitivity remained low when the population was limited to subjects with a short postmeal time (Table 3). These findings indicate that a cutoff point lower than 2.3 mmol/l, e.g. 2.0 mmol/l, is appropriate for Japanese employees.

Furthermore, the current study showed that the sensitivity was further reduced when the prevalence of hypertriglyceridemia in the population was simulated to be low (Fig. 2C). As is well known, metabolic abnormalities can vary by area and community, even within one ethnic population. Although no precise data are currently available regarding prefectural differences in the TG distribution in Japan, recent national surveys have revealed that the prevalence of obesity varies across Japanese prefectures. Given that hypertriglyceridemia is highly associated with the body mass index, one can safely expect to observe prefectural variation in the TG distribution in Japan. To reduce oversight of hypertriglyceridemia in such low-prevalence populations, it is of practical validity to lower the non-fasting TG cutoff point or to provide further stratification of patients with a non-fasting TG level <2.0 mmol/l. In contrast, when the prevalence of hypertriglyceridemia is higher, a higher TG cutoff point is suitable. The simulation showed that a cutoff point of 2.3 mmol/l is optimal when the prevalence of hypertriglyceridemia is as high as 45%. Although it seems rare that a today’s Japanese general population would have such an extremely high prevalence of hypertriglyceridemia, future possible increases in the prevalence of hypertriglyceridemia in Japan would validate the application of the Western cutoff point, i.e., 2.3 mmol/l, to the Japanese general population.

The current study is associated with several limitations. First, the sample size was relatively small. However, for a predictive performance of 70-80%, the current sample size could detect differences of ~4% with a power 1-β equal to 0.8. We believe that this difference is clinically permissible. Second, the current study recruited only Japanese employees and it remains to be revealed whether the current findings are applicable to other ethnic groups. Future investigations in other ethnic workers are required. Third, men accounted for as much as 87% of the study population. Therefore, the characteristics of women may not have been sufficiently reflected, and the application of our findings may be limited to similar male-dominant workplaces. However, the multivariate regression model (Table 2) showed that sex differences did not have an independent impact on the presence of hypertriglyceridemia, which indicates a relatively small influence of sex differences on the outcomes. Fourth and finally, the reexaminations of the triglycerides levels were conducted four months after the initial check-ups. Therefore, seasonal variation may have affected the results. However, the reexamined fasting triglycerides levels were not significantly different from the initial fasting triglycerides levels in the fasting population. We believe that these findings suggest a small effect of seasonal variation on the current findings.

**Conclusion**

Non-fasting TG measurements by themselves have a tolerable performance for predicting sustained hypertriglyceridemia in health care practice. It would be safe to propose 2.0 mmol/l as the non-fasting TG cutoff point for Japanese employees.

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**Notice**

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