TC, LDL, HDL, TC/HDL and LDL/HDL to evaluate the best monitoring test.

METHODS

Study participants

Between January and December 2005, we consecutively enrolled all people attending our Centre for Preventive Medicine at St Luke's International Hospital in Tokyo, Japan for the health check-up programme. The purpose of this programme is to promote public health through early detection of chronic diseases and disease risk factors. In Japan, the industrial Safety and Health Law obliges all workers and their family to undergo an annual health check-up in their workplaces. About 30 companies and local government organisations in Tokyo, Japan have made a contract with our centre to provide this check-up for their employees. Thus, at our centre, around 80% of participants are employees and their dependents of various companies and local government organisations in Tokyo, Japan. The cost of the medical examination is largely paid for by the employers. Since many participants are expected to have repeated examinations, we took advantage of this opportunity to conduct a follow-up study. The remaining 20% of participants are citizens of Tokyo who individually registered for the programme and paid for it without company sponsorship.

Data collection

We collected data from adults (>20 years) who had undergone an annual health check-up from 2005 to 2008 at the Centre for Preventive Medicine in St Luke's International Hospital in Tokyo, Japan. We excluded people who took cholesterol-lowering drugs at baseline (figure 1). Two investigators independently extracted and recorded information using a structured data form. A consensus was reached after discussion for any points of disagreement. St Luke's International Hospital ethical committee institutional review board approved all aspects of this study. To preserve patient confidentiality, direct patient identifiers were not collected as part of the dataset.

Measurements

An annual check-up consists of demographic information, medical history, initial evaluation (vital signs and laboratory data) and treatments provided. Laboratory data includes lipids (TC, LDL cholesterol, HDL cholesterol and triglyceride), fasting plasma glucose, HbA1c and thyroid-related hormones. Venous blood was drawn for measurements after an overnight fast and analysed at a central laboratory. Direct LDL and direct HDL measurements were performed in the Central Laboratory at the Centre for Preventive Medicine in St Luke's International Hospital by the LDL-cholesterol kit and HDL-cholesterol kit, respectively, provided by Sekisui Medical (Tokyo, Japan).

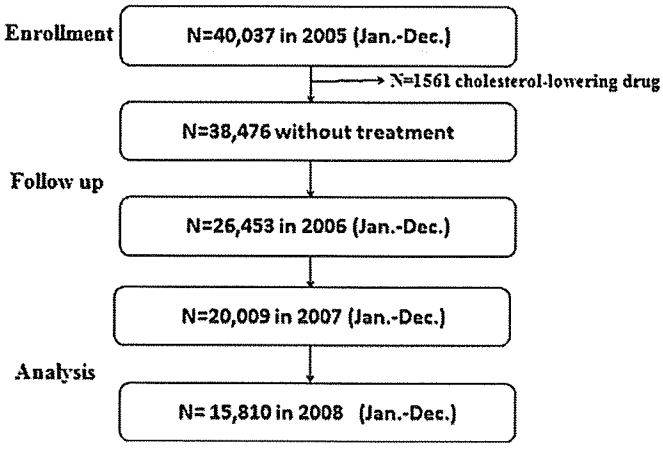


Figure 1 Flow diagram.

Long-term true change and short-term within-person variations

We used the direct method to estimate variations in long-term true change among patients and short-term within-person variation.[23] We calculated the variance of differences between the baseline value in 2005 and each subsequent year. Based on the 'variogram' method, we used a linear extrapolation backward from the longer-term measurements and evaluated what the apparent variance would be at baseline.[17] By subtracting this variance at baseline (equal to twice short-term within-person variation) from this variance of change, we estimated the true long-term change among patients.

Censored values

Some patients in our study started taking cholesterol-lowering drugs after baseline. To avoid including changes caused by cholesterol-lowering treatment while minimising selection bias, we 'censored' such data and replaced subsequent values with the previous one for each following measurement ('last observation carried forward'). For the sensitivity analysis, we also excluded all observations from patients who started taking a cholesterol-lowering drug.

Detecting the ratio of signal (long-term changes) to noise (within-person variations)

We used the S/N ratio to estimate the optimal interval and the best measure for re-screening.[17] A true increase of a patient's cholesterol level consists of the average change of the whole group over time (signal) and the short-term within-person variation around the average change (noise). When monitoring, we aim to detect the people who drift from the average population. This would be reflected as an increase in long-term variation of the overall population. Therefore, the long-term variation will also be part of the signal. In a good monitoring test, the signal needs to be large relative to noise; thus we calculated the S/N ratio by dividing signal by noise and estimated the optimal re-screening interval when the ratio was >1.

Statistical methods

All analyses were conducted by SPSS statistical software V.15.0J (SPSS Japan, Tokyo, Japan). Responses were analysed using descriptive statistics, including mean, variance, SD and percentages. A coefficient of variance was calculated by the SD divided by the mean cholesterol level at baseline. The 95% CIs were calculated using normal approximation methods.

RESULTS

Demographic data

From January 2005 to July 2008, 15 810 people underwent annual check-ups (figure 1). The mean age of patients was 49.3 years old (SD 12.2, range 21–92) and 53% of patients were male. Other primary characteristics of patients are shown in table 1. The average TC, LDL cholesterol and HDL cholesterol level at baseline were 5.3 mmol/l (SD 0.9), 3.0 mmol/l (SD 0.8) and 1.6 mmol/l (SD 0.4), respectively. The mean ratio TC/HDL and LDL/HDL level at baseline were 3.5 (SD 1.0) and 2.0 (SD 0.8), respectively. Figure 2 shows the trends of each mean lipid level from 2005 to 2008.

Table 1 Baseline demographic characteristics

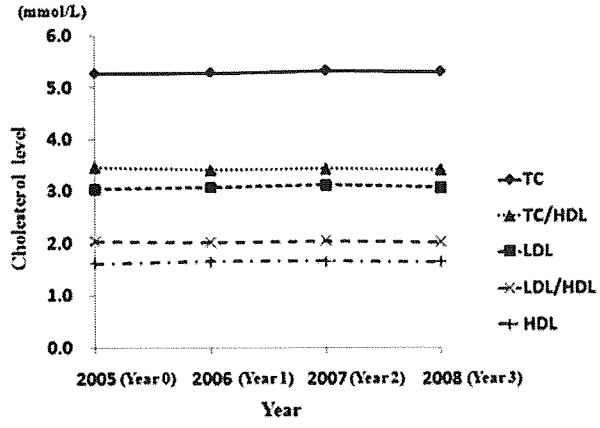
	Population with 3 years follow-up (n=15810)	Population at enrolment (n=38476)
Age (years), mean (SD)	49.3 (12.2)	47.0 (12.2)
Range (years)	21–92	20–98
Male, n (%)	8362 (52.9)	19947 (51.8)
Body mass index (kg/m^2), mean (SD)	22.5 (3.2)	22.4 (3.2)
Total cholesterol (mmol/l), mean (SD)	5.3 (0.9)	5.3 (0.8)
Triglyceride (mmol/l), mean (SD)	1.1 (0.8)	1.1 (0.9)
Blood pressure (mm Hg), mean (SD)		
Systolic	118.7 (17.5)	117.5 (17.4)
Diastolic	73.8 (11.2)	73.0 (11.2)
HbA1c (%), mean (SD)	5.1 (0.6)	5.1 (0.6)
Current smokers, n (%)	2637 (16.7)	7385 (19.2)
Alcohol, n (%)	9584 (60.6)	23762 (61.8)

Short-term, within-person variation

Figure 3 shows the direct estimates of the variance of change in each of five lipoprotein profiles over 4 years. Based on this figure, a linear backward extrapolation of the variogram method estimated that the variances of difference among individual cholesterol levels at baseline were 0.24, 0.16, 0.03 mmol^2/l^2, 0.16 and 0.10 for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively. The SDs of the short-term variations (square root of half the variance of the difference) were 0.35, 0.28, 0.13 mmol/l, 0.28 and 0.22 for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively. In addition, the coefficients of variation were 6.4%, 9.4%, 8.0%, 7.9% and 10.6% for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively.

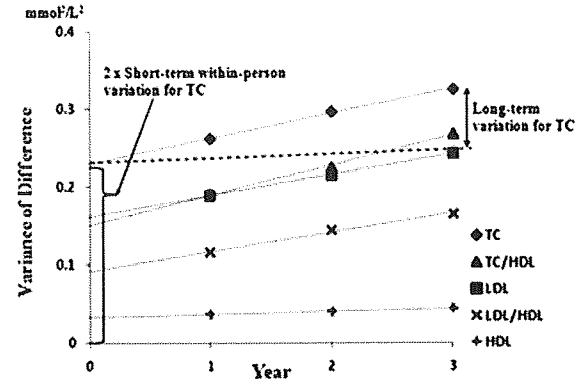
Long-term, true change variation

Figure 3 indicates the increase in variance of differences for all lipoprotein profiles over time. We divided the variances of difference into two components—short-term within-person variation at baseline and long-term variation. The long-term variation increased over time from 0 at baseline to 0.10 (SD 0.32), 0.08 (SD 0.29), 0.012 (SD 0.11) mmol^2/l^2, 0.12 (SD 0.35) and 0.07 (SD 0.27) by year 3 for TC, LDL, HDL, TC/HDL and LDL/HDL, respectively.



TC: total cholesterol, LDL: low-density lipoprotein cholesterol, HDL: high- density lipoprotein cholesterol

Figure 2 Cholesterol mean levels by years. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol.



TC: total cholesterol, LDL: low-density lipoprotein cholesterol, HDL: high- density lipoprotein cholesterol

Figure 3 Variance of difference among individual cholesterol levels over 4 years. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol.

The signal-to-noise ratio

The S/N ratios of the two lipid ratios by 3 years (TC/HDL 1.6 and LDL/HDL 1.5) were >1 and were better than that of single standard lipids (TC 0.8, LDL 0.99, HDL 0.7) (table 2). When values were divided into two groups based on TC level at baseline (<5.0 mmol/l and ≥5.0 mmol/l), the variance of differences also increased over time (figure 4). However, the S/N ratio in the group with a TC level ≥5.0 mmol/l was only slightly higher than that in the group with a TC level <5.0 mmol/l because the within-person variance was also higher. The S/N ratios of two lipids ratios (TC/HDL and LDL/HDL) were also higher than those of other single standard lipid measure in both groups.

DISCUSSION

Summary of findings

This large population survey of adults not taking cholesterol-lowering drugs suggested that the lipid ratios of TC/HDL and LDL/HDL are the best monitoring predictors for re-screening to identify those at risk for CVD. The optimal interval for re-screening should be in the region of 3 years or more.

Comparison with other reports and implications

The estimated within-person coefficient of variation (CV) of 6.4% for TC levels is comparable to values found in the previous studies.[24 25] In the MRC Mild Hypertension Trial (n=14 600),

Table 2 Estimated short-term and long-term variation of lipoprotein profiles

	TC	LDL	HDL	TC/HDL	LDL/HDL
'Signal (S)': Long-term variation					
Year 1	0.03	0.03	0.004	0.04	0.02
Year 3	0.10	0.08	0.012	0.12	0.07
'Noise (N)': Short-term within-person variation (CV, %)	0.12 (6.4)	0.08 (9.4)	0.02 (8.0)	0.08 (7.9)	0.05 (10.6)
S/N ratio					
Year 1	0.3	0.4	0.2	0.5	0.4
Year 3	0.8	0.99	0.7	1.6	1.5

CV, coefficient of variation; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; S/N, signal-to-noise; TC, total cholesterol.

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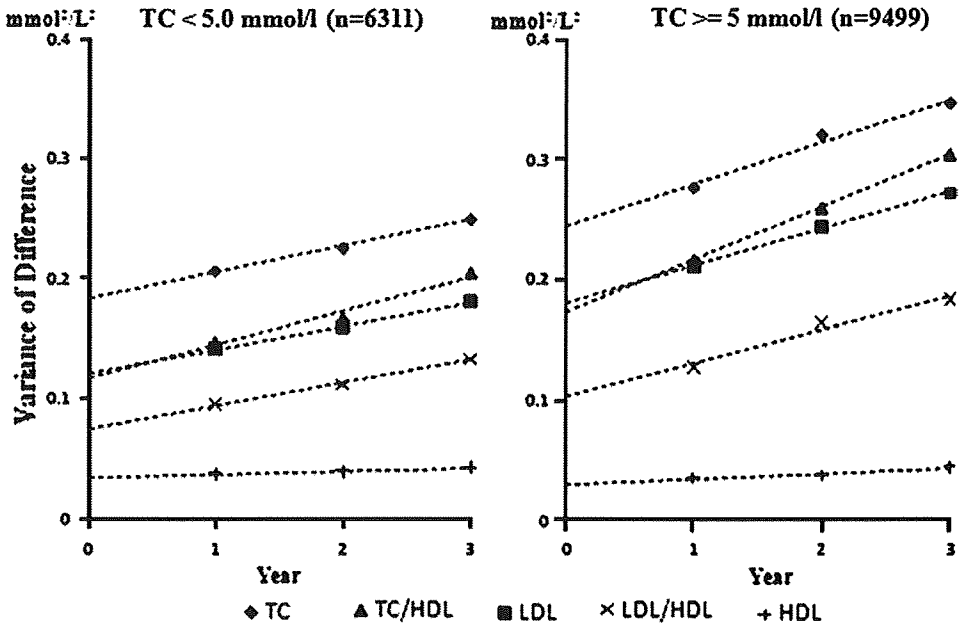

Figure 4 Variance of difference among individual cholesterol levels over 4 years by TC level at baseline. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LDL/HDL, ratio of LDL to HDL; TC, total cholesterol; TC/HDL, ratio of TC to HDL.

Thompson and Pocock[24] showed that for measurements 1 year apart, the within-person CV was 7%. In a meta-analysis of 30 studies, Smith *et al*[25] reported that the within-person CV for TC averaged 6.1% (95% CI 5.6% to 6.6%). However, previous studies reported that within-person variations increased with the sampling interval[25–28] and were influenced by the analytical methods.[25] For example, a study of 41 healthy volunteers[26] showed that for a median of 24 h, CV was 2–3%, whereas for 4 days or longer, it increased to 4–5%.

Our study showed that the estimated within-person CV for LDL (9.4%) was slightly higher than TC (6.4%) and HDL (8.0%). The results are comparable with the previously mentioned meta-analysis.[25] Smith *et al*[25] estimated that biological CVs were 9.5% (95% CI 8.1% to 10.7%), 6.1% (95% CI 5.6% to 6.6%) and 7.4% (95% CI 6.7% to 8.1%) for LDL, TC and HDL, respectively. Although we directly measured LDL, in contrast to the previous study[25] in which LDL was calculated by Friedewald equation, the direct LDL assay could not reduce the variability in LDL compared with the conventional LDL calculation.[29]

Our survey indicates that most of the variation in the first few years is due to short-term within-person variation as the long-term change of variation per year slightly increased. For example, the long-term change of variation for TC from baseline to 3 years later is smaller than short-term within-person variation based on a 0.8 S/N ratio for TC at 3 years in our study. Thus, if a patient is in a relatively stable condition, as was our screening population, measuring too frequently, such as every year, is potentially misleading and random fluctuations that occur in clinical measurements may mislead us into changing treatment unnecessarily.[12 17]

Based on the S/N ratio in our study, we suggest that the interval of re-screening for dyslipidaemia could be at least 3 years for adults not taking cholesterol-lowering drugs. These intervals are almost compatible with those in most current guidelines,[3 15] which are based on expert opinion. However, to determine the optimal interval of the individual level, we should consider the change of patients' lifestyle and treatment during their monitoring. On the other hand, risk factors of CVD, such as blood pressure and diabetes, should be taken into consideration for the overall risk assessments; however, in this study, we have focused on the variation of lipid profile in this increase over time and its impact on the assessment of lipid re-screening to evaluate the interval.

Our survey showed that the two lipid ratios are better monitoring predictors than single standard lipids including TC, LDL and HDL since their S/N ratios (1.6 for TC/HDL and 1.5 for LDL/HDL) at 3 years are higher than those of other lipids measures (0.8 for TC and 0.99 for LDL). As for initial risk measurement, several previous cohort studies,[20–22 30] a meta-analysis study,[31] and the Joint British Societies' (JBS 2) guidelines[32] suggest that lipid ratios (TC/HDL and LDL/HDL) also have greater independent predictive values for CHD than individual serum TC or LDL level, whereas current guidelines[3 13 15] for primary prevention of CHD do not emphasise the use of these lipids ratios for screening. In choosing a good monitoring tool, in addition to the clinical validity of the initial risk measurements, the S/N ratio needs to be high (at least >1.0) to address potential false-positive results due to short-term within-person variation.[12 17] Therefore, the ratio of TC/HDL or LDL/HDL might be used not only as an initial risk assessment, but also as a monitoring measurement over time.

In this study, we did not examine the other initial risk measurements of lipids, such as apoA, apoB and apoB/apoA ratio, since we were interested in the screening of lipids measured routinely in many clinical practice setting. However, similar research would be worthwhile for the apolipoproteins and other biomarkers of CVD risk to evaluate their optimal interval. Some guidelines recommend that LDL is calculated non-directly rather than measured directly. Thus, we carried out our analysis with the direct LDL measurements and also estimated non-direct LDL using the Friedewald formula. We concluded that the values are comparable and, therefore, reported only the results of direct LDL in our study.

Limitations

Our survey has several limitations. First, we collected data from only one institution in Tokyo, Japan. Although the sample size is large, findings might not be generalised to other populations. Second, there may be some change in variation because of the need to impute future values in patients who began taking cholesterol-lowering drugs. However, this is unlikely to make a large

difference to our conclusions because of its small proportion (4.8%). Third, a substantial proportion of patients were not followed up for all 4 years. If the rate of change of cholesterol was different for those patients, our results might be biased. Finally, although we used the direct method to estimate within-person variation, we did not use other models for analysis, such as a linear mixed model. However, we think that the direct method results in higher estimates of long-term variation because it is more conservative in indicating the likelihood of early change,[17] and therefore more likely to report shorter monitoring intervals.

CONCLUSION

The SN ratios of a single lipid measure (TC, LDL and HDL) are weak over 3 years and decisions based on these measures are potentially misleading. The ratios of TC/HDL and LDL/HDL are better measures for both initial assessment of CVD risk and for continuing monitoring. The interval should be more than 3 years for monitoring assessment.

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Contributors OT, PPG, RP: conception and design, or analysis and interpretation of data and drafting the article or revising it critically for important intellectual content and final approval of the version to be published. TS, JS, SH and TF: revising the article critically for important intellectual content and final approval of the version to be published.

Competing interests None.

Ethics approval This study was conducted with the approval of the St Luke's International Hospital ethical committee Institutional Review Board.

Provenance and peer review Not commissioned; not externally peer reviewed.

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The Latent Risk of Acidosis in Commercially Available Total Parenteral Nutrition (TPN) Products: a Randomized Clinical Trial in Postoperative Patients

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Summary **To evaluate the latent risk of acidosis in commercially available total parenteral nutrition (TPN) products, three types of commercially available TPN products were compared in postoperative patients. Sixty-four hospitalized patients with gastro-intestinal disease who undertook curative gastro intestinal resection were studied prospectively and administered with TPN solutions. Three types of commercially available TPN products were assigned randomly to eligible patients. Serial studies of blood acid-base status, serum electrolytes, and urinary acid-base status were conducted in the three groups administered with different TPN solutions. Patients received appropriate electrolytic solutions on the operation day and TPN solution from 2 to 7 days after operation. There were no differences among any of the serum electrolytes in the three groups. In one group, urinary pH decreased slightly and urinary net acid excretion (NAE) increased significantly after administration. This TPN product contains about 40 mEq/L of non-metabolizable acid to avoid the Maillard reaction that produces a complex of glucose and amino acids. Urinary NAE did not change in the other two groups. These TPN products do not use non-metabolizable acid to adjust pH. The present results suggest that the non-metabolizable acid may be a risk factor of metabolic acidosis.**

Key Words**: acidosis, total parenteral nutrition, Maillard reaction, acid-base imbalance, Humans**

Introduction

It is well known that malnutrition generates a predisposition for postoperative complications, increased incidence of infection [*1*], and prolonged hospital stays [*2*]. Metabolic disturbances occur in malnourished patients undergoing

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major surgery and patients with total parenteral nutrition (TPN) [*3*, *4*]. Acid-base imbalance, *i.e.*, metabolic acidosis resulting from infusates of intravenous nutrition, is observed frequently during TPN therapy [*5*]. Further acidosis occurs because of metabolic abnormalities, such as thiamine deficiency, and an excess of lactic acid induced by the bolus injection of D-fructose, as well as an excess infusion of anionic components such as chloride salts provided by the administration of synthetic L-amino acids [*6–8*]. Moreover, acidosis could be related to either the excess amount of titratable acidity in the infusates or hydrogen ions released by the metabolism of nitrogen sources [*9*]. The problem may be overcome by the use of thiamine hydrochloride, management of the infusion rate, or adding free salts or acetate of cationic amino acid to the preparation [*1*]. However, even with such interventions hyperchloremic metabolic acidosis has been reported during TPN therapy in Japan [*10*]. Previously, it was reported that the acid load with hydrochloric acid in TPN solutions may cause severe hyperchloremic metabolic acidosis in rabbits [*11*], although acetic acid may not produce acidemia for patients, because hydrogen ions from the acetic acid are neutralized by bicarbonate ions generated from the metabolism of acetate ions. However, this hypothesis has not yet been proven by clinical research. In addition, the regulation of the kind or the amount of acid for adjusting the pH is not prescribed by the guidelines of the American Society for Parenteral and Enteral Nutrition (ASPEN) or the Japanese Society for Parenteral and Enteral Nutrition (JSPEN).

This study investigated the effects of three types of commercial TPN products on plasma acid-base balance.

Materials and Methods

Study population

The study was approved by the institutional review board of Nagoya University Hospital, and the patients gave written informed consent before enrollment. It was assumed that the annual incidence of acidosis was lower than 5%. In this situation, the sample size was calculated by the coordinator of the Critical Appraisal Skills Program JAPAN (CASPjp: http://caspjp.umin.ac.jp). Patients with gastrointestinal carcinoma who had undergone curative resection, such as gastrectomy, proctocolectomy, or cholecystectomy, and were admitted to the first surgical unit of Nagoya University Hospital were enrolled. Because patients with renal dysfunction may have an increased risk of acidosis, those with renal insufficiency (50 mL/min: calculated creatinine clearance using the Cockcroft-Gault formula) were excluded. Patients with metabolic acidosis or pulmonary complications were also excluded.

Nutritional management

All patients were managed according to a standard treatment protocol. Central venous catheters were placed and all patients received a crystalloid infusion (4.5% dextrose and 0.2% sodium chloride fluid: Solita T3® Ajinomoto Pharmaceuticals) before their operations. After the operation, eligible patients were administered TPN solutions. The compositions of the three TPN solutions used in this study are shown in Table 1, and these were based on the guidelines of ASPEN and JSPEN.

TPN product randomization

After written consent was obtained from the patients before operation, the attending physician called the CASPjp call center and the TPN products were assigned randomly using a computer-generated random number. Sixty-four patients who had undergone curative resection were randomized into the three TPN product groups. The TPN solutions used were three general commercial products: Aminotoripa® (AMINO: Branched chain amino acid (BCAA) rich solution with glucose, fructose, and xylitol solution in a separate cavity bag; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan),

Table 1. The composition of the three TPN solutions

	AMINO	PN	UNI
N^+ (mEq/L)	38.9	45.5	40
K^+ (mEq/L)	30	27.3	27
Mg^{2+} (mEq/L)	5.6	5.5	6
Ca^{2+} (mEq/L)	5.6	7.3	6
Cl^- (mEq/L)	38.9	45.5	59
SO_4^{2-} (mEq/L)	5.6	5.5	
$Acetate^-$ (mEq/L)	60	36.4	10
$Gluconate^-$ (mEq/L)	5.6	7.3	6
$Lactate^-$ (mEq/L)	—	—	35
$Malate^{2-}$ (mEq/L)	—	—	17
P (mmol/L)	6.7	7.3	8.1
Zn (μmol/L)	10	18.2	20
Glucose (g/L)	111.3	163.6	175
Fructose (g/L)	55.3	—	—
Xylitol (g/L)	28	—	—
Total free amino acid (g/L)	33.3	27.3	30
pH	5.56	5.1	4.36
Titratable acidity (mEq/L)	24.3	31.9	44.1
Sodium sulfite (g/L)	0.4	0.04	0.48
HCL(mEq/L)	—	—	35.1–39.1

AMINO: Branched chain amino acid (BCAA) rich solution and glucose, fructose and xylitol solution in a separate cavity bag; Aminotoripa®; PN: Milk composition amino acid solution and glucose solution contained in a separate cavity bag; PNtwin®; UNI: BCAA rich solution and glucose solution in same cavity bag; Unicaliq®

PNtwin® (PN: Milk composition amino acid solution and glucose solution contained in a separate cavity bag; Ajinomoto Pharma Co., Ltd., Tokyo, Japan), and Unicaliq® (UNI: BCAA rich solution and glucose solution in same cavity bag; Terumo Corp., Tokyo, Japan). Patients received appropriate electrolytic solutions on operation day and TPN solution from 2 to 7 days after operation. All patients received multivitamins during this study. Blood and urine samples were collected before operation and 1, 3, 5, and 7 days after operation. Serum electrolytes, creatinine, blood urea nitrogen (BUN), lactic acid, pyruvic acid, and blood acid-base status were calculated by using standard automated laboratory techniques. Twenty-four hour urine collections for the measurements of urine electrolytes, pH, creatinine, and urinary NAE were also performed. Urinary NAE was determined by a titrimetric method [*12*] and was the sum of titratable acid and ammonium concentrations minus the bicarbonate concentration. The titratable endpoint pH was 7.40 at 0 Pa as a PCO_2.

Outcome measures

This randomized clinical study was conducted to discover the acidosis risk of TPN therapy, and the primary outcome measure was acidosis as an adverse event. However, considering the patients' safety, it was difficult to measure the harm of TPN therapy using a randomized clinical study method. Therefore, this study initially evaluated the acidosis risk in animal subjects, and urinary acid excretion was confirmed as a risk factor of acidosis. NAE was correlative with arterial blood pH ($p<0.0001$). Thus, urinary total acid excretion used as a surrogate outcome of the acidosis risk during TPN therapy.

Statistical analysis

Efficacy was analyzed according to the intention to treat approach. All statistical analyses were performed using StatView for Windows software (Version 5.0, SAS Institute, Cary, NC). All data were presented as means ± s.e. Student's *t* test was used for the comparison of data; a *p* value of less than 0.05 was considered statistically significant.

Results

Of the 76 patients in the surgical ward who received curative operations during the study period, 12 were excluded because of renal insufficiency. Sixty-four eligible patients were assigned randomly to the three groups. The demographics for each group were similar (Table 2). Consent was sought from the 64 eligible patients; all patients agreed to participate in this study. Twenty one, 22, and 21 of the 64 patients were allocated to the AMINO, PN, and UNI groups, respectively. The three groups of patients showed no important differences in baseline characteristics. No patient was withdrawn from the study after randomization. All patient data were included in this study.

The time courses of plasma pH, HCO_3^-, pCO_2, and blood base excess (BE) levels in the patients after administration of the TPN solutions are shown in Figure 1. The pH of arterial blood increased significantly in the AMINO and PN group after administration. The pCO_2 of arterial blood decreased significantly in the AMINO and PN group at 6 days after administration compared with postoperative day (POD) 1. The HCO_3^- concentration of arterial blood increased significantly in the PN group 1 day after administration. BE increased significantly in the AMINO and PN groups 1 day after administration. There were no significant differences in anion gap among the three groups during the

Table 2. The characteristics of patients at entry to the study

Characteristic	AMINO ($n=21$)	PN ($n=22$)	UNI ($n=21$)
Age (years)	60.5 ± 2.6	55.7 ± 2.9	62.1 ± 2.6
Height (cm)	162.9 ± 2.0	161.5 ± 1.7	157.7 ± 1.8
Weight (kg)	69.7 ± 2.0	56.9 ± 2.1	53.2 ± 2.5
Serum creatinine (mg/dL)	0.83 ± 0.04	0.80 ± 0.04	0.76 ± 0.05
Creatinine clearance (mL/min)	75.1 ± 3.6	83.9 ± 5.9	73.8 ± 5.1
Gender (male/female)	7/14	7/15	9/12
Type of resection gastrectomy	4	9	6
proctocolectomy	8	4	7
hepatectomy	2	4	1
pancreatectomy	2		3
cholecystectomy	2	2	1
others	3	3	3

Data are shown as mean ± s.e. Creatinine clearance calculated by using the Cockcroft–Gault formula.

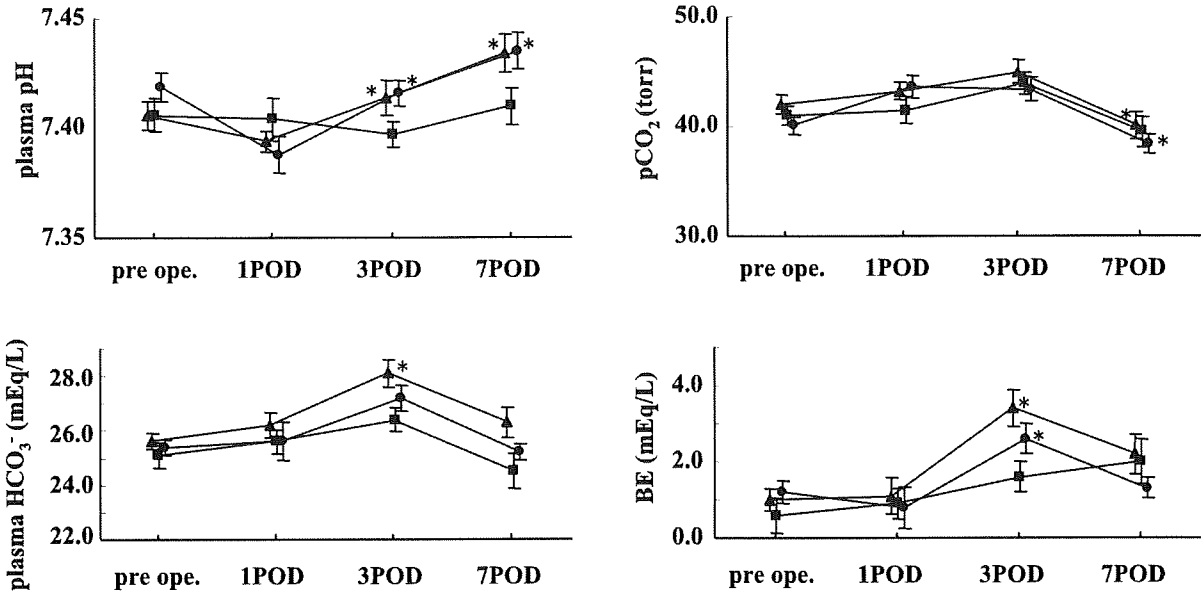

Fig. 1. Time courses of plasma pH, plasma HCO_3^-, pCO_2, and BE levels after administration of AMINO (circle), PN (triangle), and UNI (square) TPN solutions. Values are mean ± s.e. *$p<0.05$ vs POD 1. BE; blood base excess, POD: postoperative day.

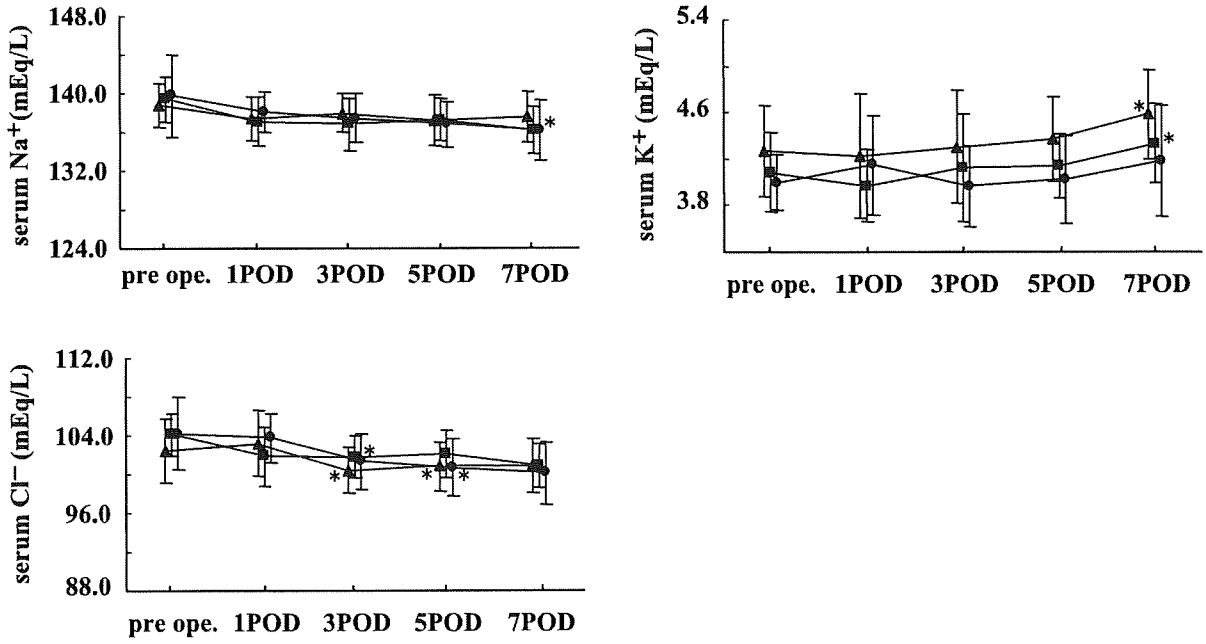

Fig. 2. Time courses of serum electrolyte levels after administration of AMINO (circle), PN (triangle), and UNI (square) TPN solutions. Values are mean ± s.e. *$p<0.05$ vs POD 1.

study period. No patients suffered from metabolic alkalosis or acidosis. All patients did not change their body weight during this study.

The time courses of serum electrolyte levels after administration of the TPN solutions are shown in Fig. 2. The concentrations of serum electrolytes such as Na^+, K^+, and Cl^-, changed slightly but were within normal limits. There were no significant changes in the concentration of serum creatinine, BUN, urine electrolytes, and urine creatinine during this study (data not shown).

The time courses of urine pH and NAE levels after administration are shown in Figure 3. Urinary pH did not change in the AMINO and PN groups, but decreased in the UNI group after administration, whereas urinary NAE

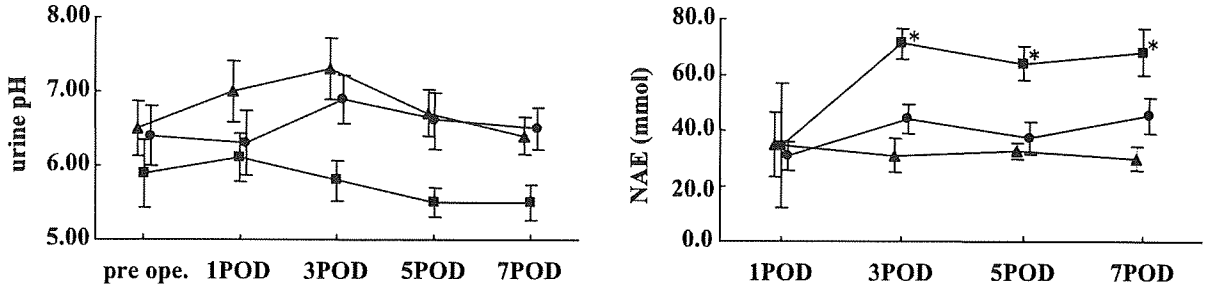

Fig. 3. Time courses of urine pH and NAE levels after administration of AMINO (circle), PN (triangle), and UNI (square) TPN solutions. Values are mean ± s.e. *p<0.05 vs POD 1. NAE; net acid excretion.

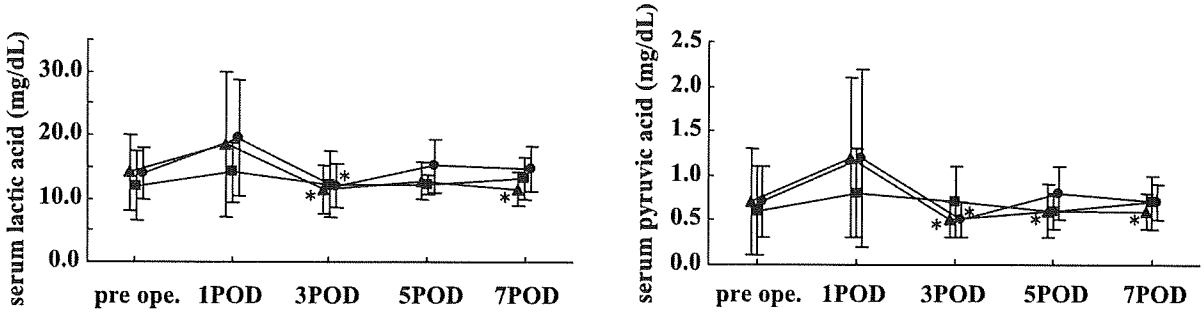

Fig. 4. Time courses of serum lactic and pyruvic acid levels after administration of AMINO (circle), PN (triangle), and UNI (square) TPN solutions. Values are mean ± s.e. *p<0.05 vs POD 1.

increased significantly in the UNI group after administration.

The time courses of lactic acid and pyruvic acid levels are shown in Fig. 4. The serum concentration of lactic acid decreased significantly in the AMINO group at POD 3 and in the PN group at POD 3 and 7 compared to POD 1. The serum concentration of pyruvic acid decreased significantly in the AMINO group at POD 3 and in the PN group on POD 3, 5, and 7 compared to POD 1. There were no significant changes in the serum concentration of lactic acid or pyruvic acid in the UNI groups.

Discussion

Acidosis during TPN therapy could be related to the presence of hydrochloric salts in synthetic L-amino-acid preparations [*5–8*]. ASPEN and JSPEN have developed clinical guidelines for TPN therapy. However, these guidelines have not commented on the risk of the acid load induced from pH adjustment agents in TPN solutions.

Recently, hydrochloric acid has been added to bagged commercial TPN solutions to avoid Maillard reaction, which is induced by D-glucose and amino acids, and the UNI solution uses hydrochloric salts of synthetic L-amino-acid to avoid this reaction. Organic acids such as acetic acid are added to the TPN solutions to stabilize the pH of the products after heat sterilization [*13*]. Therefore, two types of acids are added to commercial TPN solutions to maintain the quality of the formula. As a result, the titratable acidity of the nutrient solution consists of hydrochloric acid and organic acids. In general, titratable acidity is higher in solutions containing hydrochloric salts, and the adjusted TPN solutions have higher titratable acidity compared to the standard solutions. Terashima *et al.* suggested that metabolic acidosis is caused by the high titratable acidity induced from not only non-metabolizable acids but also from metabolizable acids in commercial TPN solutions [*9*]. This study focused on acids in TPN solutions as a cause of metabolic acidosis and investigated the effect of non-metabolizable and metabolizable acids on the plasma acid-base balance. The present findings suggested that the amount of titratable acidity is not related to the incidence of acid load. Only non-metabolizable acids such as hydrochloric acid influence the patient's acid load.

Metabolic acidosis is a pH imbalance in which the body has accumulated too much acid and does not have enough bicarbonate to effectively neutralize the effects of the acid. Previously, we reported that the acid load with hydrochloric acid in TPN solutions may cause severe hyperchloremic metabolic acidosis in rabbits [*11*]. In the present study, urinary pH decreased slightly and NAE increased significantly after administration in UNI group, but other two groups did not change urinary pH and NAE. Urine becomes

more acidic when the body is in acidosis. Since urine is a waste, the acid in the urine are lost for the body and this contributes to return the body pH to a normal value. However, there is no regulation that pharmaceutical companies should indicate the amount of added acid in the attached documents for their products. This situation is dangerous for physicians because they cannot determine the risk of acidosis when they order TPN prescriptions. Therefore, information regarding the potential inorganic acid content in commercial TPN solutions should be included in the attached documents for TPN products.

The present study focused on acids in TPN solutions as a cause of metabolic acidosis and investigated the effect of metabolizable and non-metabolizable acids on the plasma acid-base balance. The present results suggest that the amount of titratable acidity is not related to the incidence of acid load. Only non-metabolizable acids such as hydrochloric acid influence serum pH in patients. Non-metabolizable acid may be a risk factor of metabolic acidosis. Therefore, pharmaceutical companies should inform medical professionals of the amount of non-metabolizable acid in TPN solutions to help to avoid metabolic acidosis.

Abbreviations

TPN, total parenteral nutrition; NAE, net acid excretion; CASPjp, Critical Appraisal Skills Programme JAPAN; BCAA, Branched chain amino acid; BUN, blood urea nitrogen; TA, titratable acid; BE, base excess; Aminotoripa®, AMINO; PNtwin®, PN; Unicaliq®, UNI; POD, postoperative day.

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