sary, as is the need to design intensive treatment to improve endothelial dysfunction.

A weak correlation between EMP and hsCRP resulted in statistical modification of interaction between EMP and hsCRP. EMP levels correlated to some extent with various inflammatory markers, because inflammatory cytokines can induce the release of EMP, and the latter, in turn, promote endothelial injury, leading to endothelial dysfunction (11).

Study limitations. One limitation of the present study is the relatively small number of patients in a single center. However, this should result in underestimation, stressing the need for further multicenter studies in a larger population to confirm the present results. There is no consensus about measurement of EMP for assessment of endothelial damage and prothrombotic state at this stage, and microparticles are still used only for research purposes. There is a need to standardize the EMP assay for the development and establishment of routine clinical tests, because measurement of CD144-EMP could be potentially useful for the evaluation of endothelial dysfunction. The number of this study population was not estimated by power calculation. It is effective and necessary to have a plan for the number of patients required for a prospective study.

Conclusions

Endothelial dysfunction leading to cardiovascular complications can be assessed quantitatively by measurement of plasma levels of CD144-EMP. Moreover, a multiple biomarkers strategy that includes endothelial dysfunction assessed by CD144-EMP can provide better risk stratification of cardiovascular events and, hence, more thorough clinical assessment of patients who might benefit from more aggressive treatment strategies that improve prognosis.

Reprint requests and correspondence: Dr. Seigo Sugiyama, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto City 860-8556, Japan. E-mail: ssugiyam@gpo.kumamoto-u.ac.jp.

REFERENCES

1. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation 2004;109:IV6–19.
2. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355:2631–9.
3. Zethelius B, Berglund L, Sundstrom J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med 2008;358:2107–16.
4. Widlansky ME, Gokce N, Keaney JF Jr., Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003;42:1149–60.
5. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899–906.
6. Chan SY, Mancini GB, Kuramoto L, Schulzer M, Frohlich J, Ignaszewski A. The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. J Am Coll Cardiol 2003;42:1037–43.
7. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol 2002;40:505–10.
8. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257–65.
9. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007;115:1285–95.
10. Kuvin JT, Karas RH. Clinical utility of endothelial function testing: ready for prime time? Circulation 2003;107:3243–7.
11. Boulanger CM, Amabile N, Tedgui A. Circulating microparticles: a potential prognostic marker for atherosclerotic vascular disease. Hypertension 2006;48:180–6.
12. VanWijk MJ, VanBavel E, Sturk A, Nieuwland R. Microparticles in cardiovascular diseases. Cardiovasc Res 2003;59:277–87.
13. Koga H, Sugiyama S, Kugiyama K, et al. Elevated levels of VE-cadherin-positive endothelial microparticles in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 2005;45:1622–30.
14. Shet AS. Characterizing blood microparticles: technical aspects and challenges. Vasc Health Risk Manag 2008;4:769–74.
15. Grundy SM, Balady GJ, Criqui MH, et al. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. Circulation 1998;97:1876–87.
16. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388–91.
17. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2003;26 Suppl 1:S5–20.
18. Imai E, Matsuo S, Makino H, et al. Chronic Kidney Disease Japan Cohort (CKD-JAC) study: design and methods. Hypertens Res 2008;31:1101–7.
19. Omland T, Sabatine MS, Jablonski KA, et al. Prognostic value of B-type natriuretic peptides in patients with stable coronary artery disease: the PEACE trial. J Am Coll Cardiol 2007;50:205–14.
20. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
21. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23:2109–23.
22. D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. Am Heart J 2000;139:272–81.
23. Grønnesby JK, Borgan O. A method for checking regression models in survival analysis based on the risk score. Lifetime Data Anal 1996;2:315–28.
24. Koenig W, Sund M, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg cohort study, 1984 to 1992. Circulation 1999;99:237–42.
25. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.
26. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387–97.

27. Omland T, Richards AM, Wergeland R, Vik-Mo H. B-type natriuretic peptide and long-term survival in patients with stable coronary artery disease. Am J Cardiol 2005;95:24–8.
28. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA 2004;291:1978–86.
29. Boos CJ, Balakrishnan B, Blann AD, Lip GY. The relationship of circulating endothelial cells to plasma indices of endothelial damage/dysfunction and apoptosis in acute coronary syndromes: implications for prognosis. J Thromb Haemost 2008;6:1841–50.
30. Amabile N, Guerin AP, Leroyer A, et al. Circulating endothelial microparticles are associated with vascular dysfunction in patients with end-stage renal failure. J Am Soc Nephrol 2005;16:3381–8.
31. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. Circulation 2003;108:1664–72.
32. Sugiyama S, Kugiyama K, Aikawa M, Nakamura S, Ogawa H, Libby P. Hypochlorous acid, a macrophage product, induces endothelial apoptosis and tissue factor expression: involvement of myeloperoxidase-mediated oxidant in plaque erosion and thrombogenesis. Arterioscler Thromb Vasc Biol 2004;24:1309–14.

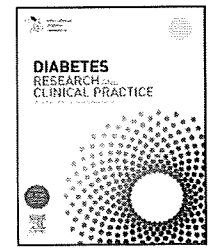
Key Words: biomarkers ▪ endothelium ▪ microparticles ▪ follow-up studies ▪ coronary heart disease.

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation



Vital sign triage to rule out diabetic ketoacidosis and non-ketotic hyperosmolar syndrome in hyperglycemic patients

Yasuharu Tokuda [a,*], *Fumio Omata* [b], *Yusuke Tsugawa* [c], *Kyouko Maesato* [d], *Kazuhisa Momotura* [e], *Atsuko Fujinuma* [e], *Gerald H. Stein* [f], *E. Francis Cook* [g]

[a] *Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan*
[b] *Gastroenterology Center, St. Luke's International Hospital, Tokyo, Japan*
[c] *Department of Medicine, St. Luke's International Hospital, Tokyo, Japan*
[d] *Department of Medicine, Shonan Kamakura General Hospital, Kanagawa, Japan*
[e] *Department of Medicine, Okinawa Chubu Hospital, Okinawa, Japan*
[f] *Department of Medicine, College of Medicine, University of Florida, Gainesville, FL, USA*
[g] *Department of Epidemiology, Harvard School of Public Health, Boston, USA*

ARTICLE INFO

Article history:
Received 9 August 2009
Received in revised form
12 November 2009
Accepted 24 November 2009
Published on line 22 December 2009

Keywords:
Vital sign
Diabetic ketoacidosis
Non-ketotic hyperosmolar syndrome
Triage
Recursive partitioning analysis

ABSTRACT

Aims: To develop a prediction algorithm to rule out diabetic ketoacidosis (DKA) and non-ketotic hyperosmolar syndrome (NKHS) based on vital signs for early triage of patients with diabetes.

Methods: The subjects were consecutive adult diabetic patients with hyperglycemia (blood glucose ≥250 mg/dl) who presented at an emergency department. Based on a derivation sample (n = 392, 70% of 544 patients at a hospital in Okinawa), recursive partitioning analysis was used to develop a tree-based algorithm. Validation was conducted using the other 30% of the patients in Okinawa (n = 152, internal validation) and patients at a hospital in Tokyo (n = 95, external validation).

Results: Three risk groups for DKA/NKHS were identified: a high-risk group of patients with glucose >400 mg/dl or systolic blood pressure <100 mmHg; a low risk group of patients with glucose ≤400 mg/dl and normal vital signs (systolic blood pressure ≥100 mmHg, pulse ≤90/min, and respiratory rate ≤20/min); and an intermediate risk group. The prevalences of DKA/NKHS were 2% (derivation set), 0% (internal validation set), and 0% (external validation set) in the low risk group, respectively.

Conclusions: Our algorithm may help DKA/NKHS triage and patients with normal vital signs can be initially triaged as low risk for DKA/NKHS.

1. Introduction

Diabetic ketoacidosis (DKA) is an acute life-threatening complication in type 1 and type 2 diabetes [1–3]. Clinical presentations of DKA are sometimes non-specific and mimic other acute diseases [4], but DKA patients usually present with vital sign disturbances due to hemodynamic and metabolic derangement [5,6]. Tachycardia of DKA is a sign of dehydration, hypovolemia, or accompanying conditions associated with DKA such as infection or electrolyte imbalance [6]. Kussmaul's respiration reflects a deep respiratory effort plus tachypnea [7], and this characteristic respiration in DKA patients leads to compensatory respiratory alkalosis for alleviating metabolic acidosis [5]. Blood pressure in DKA

* *Corresponding author at:* 3-2-7 Miya-machi, Mito City, Ibaraki 310-0015, Japan. Tel.: +81 29 231 2371; fax: +81 29 221 5137.
E-mail addresses: tokuyasu@orange.ocn.ne.jp, yasuharu.tokuda@gmail.com (Y. Tokuda).
0168-8227/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.diabres.2009.11.020

patients may also be lower than the normal range when hypovolemia is severe or when sepsis is present. Body temperature may be either higher than the normal range due to accompanying infection or lower in some cases with severe dehydration or advanced sepsis [8].

On the other hand, non-ketotic hyperosmolar syndrome (NKHS), which causes a similar hemodynamic derangement (severe hyperosmolar dehydration without significant ketoacidosis), is relatively rare but can have greater mortality than DKA. Both DKA and NKHS are considered as typical states of diabetic emergency and need urgent diagnosis and management.

Since DKA/NKHS may occur when patients with diabetes have vital sign disturbances, initial triage for ruling-out DKA/NKHS based on vital signs can be performed in an emergency department or outpatient clinic [9]. However, a model is required for rapid evaluation of the risk for DKA/NKHS in patients with diabetes and to assure routine clinical examination for acute conditions. Thus, our objective was to develop a triage model to stratify the risk of DKA/NKHS using initial vital signs and blood glucose concentrations based on simple tests such as the fingerstick glucose test in patients with diabetes presenting at an emergency department.

2. Methods

2.1. Subjects

We conducted medical record reviews for the four-year period from January 2000 to December 2003 at Okinawa Chubu Hospital, a 550-bed community teaching hospital serving a population of 400,000 in Okinawa, Japan; and for the two-year period from January 2005 to December 2006 at St. Luke's International Hospital, a 520-bed community teaching hospital serving a population of 300,000 in Tokyo, Japan. The inclusion criteria were (1) consecutive adult (≥18-year-old) patients at the emergency department, (2) clinical history of diabetes, (3) initial blood glucose concentrations of ≥250 mg/dl (≥13.9 mmol/l) using a fingerstick glucometer (Okinawa Chubu Hospital) or a quick blood glucose test (St. Luke's International Hospital), and (4) blood gas analysis performed for evaluation of the presence of DKA. The study was approved by the Institutional Review Boards of the two hospitals.

2.2. Data collection

Data were collected for demographics, initial vital signs, blood glucose and laboratory tests. In the two hospitals, emergency department nurses receive educational sessions for accurate vital sign measurement before serving in triage roles. Upon patient arrival at the emergency department, triage nurses measured and recorded systolic and diastolic blood pressure, pulse, respiratory rate and body temperature, with the pulse and respiratory rates measured over 30 s and doubled. The triage nurses also routinely measured blood glucose using a fingerstick glucometer for patients with a self-declared history of diabetes.

2.3. Criteria for DKA/NKHS

DKA was judged to be present if a patient met all of the following three criteria: (1) blood glucose ≥250 mg/dl (≥13.9 mmol/l), (2) metabolic acidosis with pH ≤7.30, or a serum bicarbonate concentration ≤18 mequiv./l in arterial or venous blood, and (3) positive ketonemia (elevated concentration of serum acetoacetate or β-hydroxybutyrate). These criteria were based on the working classification established by Kitabchi et al. [4,10,11]. NKHS was clinically diagnosed by the presence of severe hyperglycemia and serum hyperosmolarity and absence of ketonemia.

2.4. Statistical analysis

For comparison of demographics, vital signs and blood glucose between DKA/NKHS and non-DKA/NKHS patients, a t-test was used for continuous data and a chi-square test for binary data. To develop the triage model, we used a split-sample strategy for data from Okinawa Chubu Hospital, in which 70% of the patients were randomly sampled and used to derive an algorithm using recursive partitioning analysis based on vital sign variables and blood glucose concentrations, and the remaining 30% were used as an internal validation set [12]. Data from St. Luke's International Hospital were used for external validation of the algorithm.

We used a recursive partitioning analysis to build a prediction algorithm. This technique generates a classification tree with series of binary splits, in which patients are assigned to mutually exclusive subgroups according to a set of predictors. When applied to our group data, each binary split in a tree produced two subgroups, one containing a relatively high proportion of DKA/NKHS patients, and the other, a relatively high proportion of non-DKA/NKHS patients. We then interpreted the combination of these binary splits as a prediction algorithm for classifying patients according to the probability of DKA/NKHS.

Entropy, a measure of impurity of a node, was used as the node splitting criterion to identify the cutoff point for the best separation of the two subgroups. This index selects the partition with the greatest purity by measuring the amount of variance in the proportion of DKA/NKHS patients between each potential pair from the partition. It reaches a minimum value when only one class is present at a subgroup node. The partitioning starts after evaluating each predictor for its potential to separate subgroups and selects the best predictor with the most pure division for the first split. This procedure is then repeated for each of the two subgroups that are generated from the first split, again evaluating all potential cutoff points of each variable to identify the predictor that provides the best separation.

In the recursive partitioning analysis, vital sign data were grouped using clinically reasonable cutoff points: 90, 100, 110 and 120 mmHg for systolic blood pressure; 80, 90, 100 and 110/min for pulse rate; and 20, 22, 24 and 26/min for respiratory rate. Blood glucose concentrations were grouped using cutoff levels of 350, 400, 450 and 500 mg/dl. The model outcome was the prevalence of DKA/NKHS among terminal nodes. Entropy criteria were used for node splitting to reduce node impurity [13]. Several terminal nodes were grouped into three risk levels

(high, intermediate and low) based on the DKA/NKHS prevalence of each node. Since our goal was to generate a triage rule that would not miss DKA/NKHS among diabetic patients, the misclassification cost for labeling DKA/NKHS patients as non-DKA/NKHS was set at 15 times higher than that for labeling non-DKA/NKHS patients as DKA/NKHS. Varying misclassification costs in this manner tends to result in a final model with higher sensitivity [13].

DKA/NKHS prevalence was evaluated within a 95% confidence interval (CI) in each classified group and the characteristics of the final model were assessed by calculating the sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio with 95% CIs. An exact binomial method was used to obtain all 95% CIs. CART v. 5.0 (Salford Systems, San Diego, CA) was used for recursive partitioning analysis and SAS v. 9.1 (SAS Institute, Cary, NC) for general statistics. All p-values were two-sided and $p < 0.05$ was considered to be statistically significant.

3. Results

Data for 544 patients from Okinawa Chubu Hospital were used in derivation of the algorithm or for internal validation. The mean age of the patients was 59 years old and 287 (53%) were male. Among these patients, 134 (24.6%) met the criteria for DKA/NKHS (120 DKA and14 NKHS). The mean age of the DKA/NKHS patients (53 years old) was significantly lower than that (62 years old) of the non-DKA/NKHS patients ($p < 0.001$). The DKA/NKHS patients included a significantly higher percentage of males ($p = 0.001$) and had a higher median glucose concentration (498 vs. 399 mg/dl, $p < 0.001$) compared to the non-DKA/NKHS patients. In the non-DKA/NKHS patients, the common clinical conditions based on diagnostic records by physicians at the emergency department ($n \geq 10$) included respiratory disease ($n = 51$), musculoskeletal disorder ($n = 31$), urologic disease ($n = 30$), vertigo or dizziness ($n = 20$), non-specific hyperglycemia ($n = 20$), non-specific abdominal pain ($n = 18$), soft-tissue infection ($n = 14$), stroke ($n = 13$), coronary artery disease ($n = 12$), heart failure ($n = 11$) and neuropathic pain ($n = 10$).

Data for 95 patients from St. Luke's International Hospital were used for external validation of the algorithm. The mean age of the patients was 69 years old (range, 21–106), 45 (46%) were men, and 17 (18%) met the criteria for DKA/NKHS (12 DKA and 5 NKHS). The mean age of the DKA/NKHS patients (63 years old) did not differ significantly from that (71 years old) of the non-DKA/NKHS patients ($p = 0.15$), and there was no gender difference between the DKA/NKHS and non-DKA/NKHS patients from St. Luke's International Hospital ($p = 0.604$).

Demographics/laboratory data and vital signs of DKA/NKHS and non-DKA/NKHS patients are shown in Tables 1 and 2, respectively. At Okinawa Chubu Hospital, DKA/NKHS patients had higher pulse and respiratory rates and lower systolic and diastolic blood pressure compared to non-DKA/NKHS patients. There was no difference in body temperature between the groups. At St. Luke's International Hospital, DKA/NKHS patients had a significantly greater pulse rate and lower systolic/diastolic blood pressure, but the respiratory rate did not differ between the DKA/NKHS and non-DKA/NKHS groups.

Recursive partitioning analysis generated four classification splits for the high, intermediate and low risk groups

Table 1 – Demographic and laboratory data in patients with and without DKA/NKHS[a].

	DKA/NKHS ($n = 134$)	Non-DKA/NKHS ($n = 410$)	p-Value
Okinawa Chubu Hospital (derivation or internal validation, $N = 544$)			
Age, yr	53 ± 18	62 ± 17	<0.001
Male gender, n (%)	87 (65)	200 (49)	0.001
Glucose, mg/dl	498 ± 163	399 ± 126	<0.001
BUN, mg/dl	44 ± 27	17 ± 10	<0.001
Creatinine, mg/dl	2.7 ± 2.0	1.2 ± 1.1	<0.001
Arterial pH	7.20 ± 0.16	7.41 ± 0.09	<0.001
Arterial pCO_2, mmHg	23 ± 11	37 ± 7.9	<0.001
Arterial bicarbonate, mequiv./l	11 ± 7.7	24 ± 5.2	<0.001
	DKA/NKHS ($n = 17$)	Non-DKA/NKHS ($n = 78$)	p-Value
St. Lukes International Hospital (external validation, $N = 95$)			
Age, yr	63 ± 22	71 ± 14	0.15
Male gender, n (%)	7 (41)	38 (49)	0.57
Glucose, mg/dl	759 ± 287	364 ± 120	<0.001
BUN, mg/dl	39 ± 24	32 ± 20	0.16
Creatinine, mg/dl	1.4 ± 0.63	1.4 ± 1.7	0.86
Arterial pH	7.25 ± 0.11	7.37 ± 0.14	0.002
Arterial pCO_2, mmHg	26 ± 12	40 ± 14	<0.001

DKA, diabetic ketoacidosis; NKHS, non-ketotic hyperosmolar syndrome. BUN, blood urea nitrogen.
[a] Values are shown as mean ± standard deviation when not specified otherwise.

Table 2 – Vital signs between patients with and without DKA/NKHS[a].

	DKA/NKHS (n = 134)	Non-DKA/NKHS (n = 410)	p-Value
Okinawa Chubu Hospital (derivation or internal validation, N = 544)			
SBP, mmHg	116 ± 37	138 ± 29	<0.001
DBP, mmHg	60 ± 27	73 ± 15	<0.001
PR, /min	109 ± 21	92 ± 17	<0.001
RR, /min	27 ± 8	22 ± 4	<0.001
BT, °C	36.7 ± 1.2	36.8 ± 1.6	0.95
	DKA/NKHS (n = 17)	Non-DKA/NKHS (n = 78)	p-Value
St. Lukes International Hospital (external validation, N = 95)			
SBP, mmHg	114 ± 19	139 ± 35	0.003
DBP, mmHg	56 ± 25	73 ± 24	0.011
PR, /min	111 ± 14	99 ± 23	0.01
RR, /min	23 ± 7	21 ± 6	0.285
BT, °C	36.8 ± 0.9	36.9 ± 1.0	0.874

SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; RR, respiratory rate; BT, body temperature; DKA, diabetic ketoacidosis; NKHS, non-ketotic hyperosmolar syndrome.
[a] Values are shown as mean ± standard deviation.

(Fig. 1). The high-risk group included patients with glucose concentrations >400 mg/dl (first split); and of the remaining patients, those with systolic blood pressure <100 mmHg (second split). Among the non-high-risk patients, the intermediate risk group included patients with pulse rate >90/min (third split), and of the remaining patients, those with a respiratory rate >20/min (fourth split). Patients not meeting any of these criteria were placed in the low risk group.

The prevalence of DKA/NKHS in the low, intermediate and high-risk groups is shown in Table 2. In the low risk group, there were two patients with DKA/NKHS [2%; 95% confidence interval (CI), 0–10%] in the derivation set, none in the internal validation set (0%; 95% CI, 0–8%), and none in the external validation set (0%; 95% CI, 0–21%). In contrast, in the high-risk group, there were 75 patients with DKA/NKHS (50%; 95% CI, 42–59%) in the derivation set, 21 in the internal validation set (51%; 95% CI, 35–67%), and 16 in the external validation set (36%; 95% CI, 22–52%).

Classification characteristics for diabetic ketoacidosis between high and intermediate-low risk groups and between high-intermediate and low risk groups are shown in Table 3. Using the cutoff point for high vs. intermediate-low risk gave specificities of 75% (derivation), 83% (internal validation), and 64% (external validation), whereas the cutoff point for high-intermediate vs. low risk gave sensitivities of 98% (derivation) and 100% (both internal and external validation). Overall, the relatively low specificity was a trade-off for high sensitivity in this model.

The model misclassified two patients with DKA/NKHS in the derivation set into the low risk group. These patients were

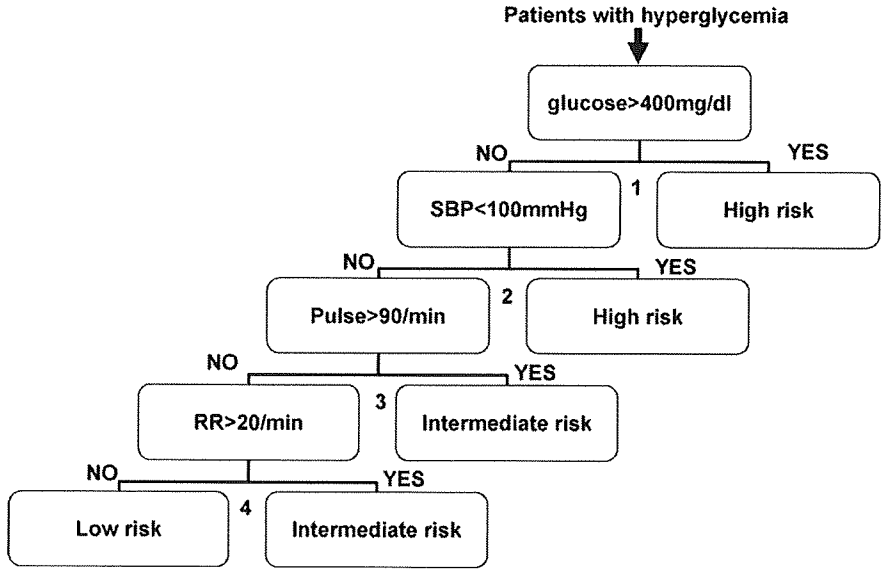


Fig. 1 – Triage algorithm for classifying diabetic patients into three different risk groups. Abbreviations: SBP, systolic blood pressure; RR, respiratory rate. The numbers indicate the classification splits.

Table 3 – Prevalence of DKA/NKHS in risk groups in each population set.

Risk group	No. of patients, *n*	Patients with DKA/NKHS, *n*	Prevalence of DKA/NKHS, %	(95% CI)
Derivation set (*N* = 392)				
High risk	149	75	50	(42–59)
Intermediate risk	174	23	13	(9–19)
Low risk	69	2	2	(0–10)
Internal validation set (*N* = 152)				
High risk	41	21	51	(35–67)
Intermediate risk	77	13	16	(9–27)
Low risk	34	0	0	(0–8)
External validation set (*N* = 95)				
High risk	44	16	36	(22–52)
Intermediate risk	35	1	3	(0–15)
Low risk	16	0	0	(0–21)

CI, confidence interval; DKA, diabetic ketoacidosis; NKHS, non-ketotic hyperosmolar syndrome.

Table 4 – Classification characteristics of the algorithm for DKA/NKHS in each population set.

Characteristic	High-risk group vs. intermediate-low risk group	High-intermediate risk group vs. low risk group
Derivation set (*N* = 392)		
Sensitivity, % (95% CI)	75 (65–83)	98 (93–100)
Specificity, % (95% CI)	75 (69–80)	23 (18–28)
Internal validation set (*N* = 152)		
Sensitivity, % (95% CI)	62 (44–79)	100 (92–100)
Specificity, % (95% CI)	83 (75–89)	29 (21–38)
External validation set (*N* = 95)		
Sensitivity, % (95% CI)	94 (71–100)	100 (80–100)
Specificity, % (95% CI)	64 (52–75)	21 (12–31)

CI, confidence interval; DKA, diabetic ketoacidosis; NKHS, non-ketotic hyperosmolar syndrome.

a 69-year-old woman with schizophrenia and blood pressure 140/70 mmHg, pulse rate 84/min, and respiratory rate 20/min; and a 62-year-old woman with hip fracture and blood pressure 110/60 mmHg, pulse rate 72/min, and respiratory rate 20/min. Therefore, these patients had respiratory rates close to the cutoff point between the low and intermediate risk groups. The model did not misclassify any DKA/NKHS patients into the low risk group in the internal and external validation sets (Table 4).

4. Discussion

The results show that our model could be helpful for DKA/NKHS triage in an emergency department. Based on common data such as vital signs and blood glucose, the model classifies diabetic patients into three risk groups for DKA/NKHS. Patients with diabetes can be triaged safely as low risk when they have blood glucose ≤400 mg/dl and normal vital signs, whereas patients in the high-risk group have about a 50% probability for DKA/NKHS. Our risk-averse model seems to be clinically reasonable, since it is important to avoid false negative triage in assessment of DKA/NKHS, which is potentially life-threatening and requires early detection and aggressive treatment [9,14].

Our study followed mostly standard methodology for developing clinical prediction rules [19]. We defined the outcome clearly and used common clinical data so that a future prospective study can be performed to determine the generalizability of the model. The model is also clinically reasonable since it is compatible with the pathophysiology of DKA/NKHS. Furthermore, the classification algorithm has a simple structure and is easy for physicians and emergency department staff to use, as illustrated in Fig. 1. Physicians have long recognized the importance of vital sign observations and vital sign measurement has proven to be useful for detecting serious diseases during triage in emergency departments [15,16]. However, these studies have focused on acute general conditions, rather than individual diseases, and our study may be the first to provide evidence on the important role of vital sign measurement for DKA/NKHS triage.

In diabetic patients with suspected DKA, blood gas analysis is the test of choice [17,18], since DKA can be excluded based on a normal pH and normal bicarbonate concentration. However, use of our simple triage algorithm may reduce the immediate need for blood gas testing for low risk patients with diabetes. Our algorithm may also have roles outside hospital emergency departments. Depending on the local health care structure, private outpatient clinics may not have technical equipment for blood gas testing, but glucose analyzer kits are usually available in these clinics. The triage algorithm may help to decide whether to transfer diabetic patients to an emergency department for suspected DKA/NKHS. Additionally, emergency medical technicians can be educated in the use

of the triage algorithm to determine the severity of hyperglycemia, as well as the risk of DKA/NKHS.

There is a debate about the reliability of noninvasive vital sign measurements, since the reproducibility of these measurements in a clinical setting by trained observers can show significant inter-observer variability [20]. Thus, this inherent variability should be recognized through careful interpretation of vital signs, especially for respiratory rate measurement. However, another recent study showed improved reliability of vital signs when measured by well-trained nurses in a triage booth in an emergency department [21]. Thus, vital sign measurements by well-trained nurses appear to be reliable. Future studies may be needed for analyzing reproducibility of vital signs measurements in patients with DKA/NKHS.

There may be a selection bias in this study, since we excluded patients who did not undergo blood gas testing based on the decision of an emergency physician. However, the vital signs of these patients were usually within or close to normal limits due to mild conditions, which led the physician to judge them unlikely to have DKA/NKHS, especially for patients with mild hyperglycemia of about 250–300 mg/dl [22,23]. Thus, we suspect that most of these patients would have fallen into the low risk category in our model and that none would have developed DKA/NKHS. Therefore, exclusion of these patients should not change the results significantly. Another limitation in this study is that we could not collect data for co-morbidity of diabetes and precipitating factors for DKA/NKHS. The presence of these factors in patients with diabetes can lead to the greater risk for DKA/NKHS. Future studies are needed for incorporating these factors for developing a prediction model for DKA/NKHS.

In summary, we developed a simple and sensitive triage algorithm for classification of patients with diabetes into risk-stratified groups for DKA/NKHS. Our study reinforces the important medical tradition of evaluating vital signs. To effectively triage patients with diabetes at risk for DKA/NKHS, the algorithm should be used in combination with individualized clinical judgments by health care teams.

Acknowledgments

We thank the nurses, interns, residents and staff of the Department of Emergency Medicine, Okinawa Chubu Hospital and St. Lukes International Hospital for their excellent clinical care of the diabetic patients. Dr. Y. Tokuda had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

[1] K. Ellemann, J.N. Soerensen, L. Pedersen, B. Edsberg, O.O. Andersen, Epidemiology and treatment of diabetic ketoacidosis in a community population, Diabetes Care 7 (1984) 528–532.
[2] O. Pinhas-Hamiel, L.M. Dolan, P.S. Zeitler, Diabetic ketoacidosis among obese African-American adolescents with NIDDM, Diabetes Care 20 (1997) 484–486.
[3] J. Valabhji, M. Watson, J. Cox, C. Poulter, C. Elwig, R.S. Elkeles, Type 2 diabetes presenting as diabetic ketoacidosis in adolescence, Diabet. Med. 20 (2003) 416–417.
[4] A.E. Kitabchi, B.M. Wall, Diabetic ketoacidosis, Med. Clin. North Am. 79 (1995) 9–37.
[5] J.Y. Guh, Y.H. Lai, L.K. Yu, S.J. Shin, J.H. Tsai, Evaluation of ventilatory responses in severe acidemia in diabetic ketoacidosis, Am. J. Nephrol. 17 (1997) 36–41.
[6] M.R. Burge, N. Garcia, C.R. Qualls, D.S. Schade, Differential effects of fasting and dehydration in the pathogenesis of diabetic ketoacidosis, Metabolism 50 (2001) 171–177.
[7] A. Minagar, W.J. Weiner, Adolf Kussmaul and his respiratory sign, J. Med. Biogr. 9 (2001) 81–183.
[8] J.M. Guerin, P. Meyer, J.M. Segrestaa, Hypothermia in diabetic ketoacidosis, Diabetes Care 10 (1987) 801–802.
[9] D.S. Bell, J. Alele, Diabetic ketoacidosis. Why early detection and aggressive treatment are crucial, Postgrad. Med. 101 (1997) 193–198, 203–204.
[10] A.E. Kitabchi, G.E. Umpierrez, M.B. Murphy, E.J. Barrett, R.A. Kreisberg, J.I. Malone, et al., Management of hyperglycemic crises in patients with diabetes, Diabetes Care 24 (2001) 131–153.
[11] A.E. Kitabchi, G.E. Umpierrez, M.B. Murphy, E.J. Barrett, R.A. Kreisberg, J.I. Malone, et al., Hyperglycemic crises in diabetes, Diabetes Care 27 (Suppl. 1) (2004) S94–102.
[12] L. Breiman, J. Friedman, R. Olshen, C. Stone, Classification and Regression Trees, Chapman & Hall CRC Press LLC, Boca Raton, FL, 1984.
[13] H. Zhang, B. Singer, Recursive Partitioning in the Health Sciences, Springer-Verlag, New York, 1999.
[14] R.D. Hardern, N.D. Quinn, Emergency management of diabetic ketoacidosis in adults, Emerg. Med. J. 20 (2003) 210–213.
[15] R.D. Waldrop, D.E. Harper, C. Mandry, Prospective assessment of triage in an urban emergency department, South Med. J. 90 (1997) 1208–1212.
[16] R.J. Cooper, D.L. Schriger, H.L. Flaherty, E.J. Lin, K.A. Hubbell, Effect of vital signs on triage decisions, Ann. Emerg. Med. 39 (2002) 223–232.
[17] Y. Gokel, S. Paydas, Z. Koseoglu, N. Alparslan, G. Seydaoglu, Comparison of blood gas and acid-base measurements in arterial and venous blood samples in patients with uremic acidosis and diabetic ketoacidosis in the emergency room, Am. J. Nephrol. 20 (2000) 319–323.
[18] Z. Hassan, D.M. Subramonyam, S. Thakore, Venous blood gas in adult patients with diabetic ketoacidosis, Emerg. Med. J. 20 (2003) 363–364.
[19] A. Laupacis, N. Sekar, I.G. Stiell, Clinical prediction rules. A review and suggested modifications of methodological standards, JAMA 277 (1997) 488–494.
[20] Z.V. Edmonds, W.R. Mower, L.M. Lovato, R. Lomeli, The reliability of vital sign measurements, Ann. Emerg. Med. 39 (2002) 233–237.
[21] A. Worster, L. Elliott, T.J. Bose, E. Chemeris, Reliability of vital signs measured at triage, Eur. J. Emerg. Med. 10 (2003) 108–110.
[22] M.F. Delaney, A. Zisman, W.M. Kettyle, Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome, Endocrinol. Metab. Clin. North Am. 29 (2000) 683–705, V.
[23] J.L. Chiasson, N. Aris-Jilwan, R. Belanger, S. Bertrand, H. Beauregard, J.M. Ekoé, et al., Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state, CMAJ 168 (2003) 859–866.

Diabetes Care Publish Ahead of Print, published online June 21, 2010

HbA1c to Detect Diabetes Mellitus in Healthy Adults: When Should We Re-check?

Osamu Takahashi, MD, MPH [1,2]; Andrew J. Farmer, D.M., F.R.C.G.P.[1]; Takuro Shimbo, MD [3]; Tsuguya Fukui, MD, MPH [2]; Paul P. Glasziou, MBBS, PhD [1]

[1]Department of Primary Health Care, University of Oxford, Oxford, UK; [2]Division of General Internal Medicine, Department of Medicine, St. Luke's International Hospital, Tokyo, Japan; [3] Department of Clinical Research and Informatics, International Medical Centre of Japan, Tokyo, Japan

Correspondence to:
Osamu Takahashi, MD, MPH
E-mail: otakahas@luke.or.jp

Submitted 31 March 2010 and accepted 12 June 2010.

Objective: To evaluate the optimal interval for re-checking HbA1c levels below diagnostic threshold of 6.5% for healthy adults.

Research Design and Methods: Retrospective cohort study. Participants were 16,313 apparently healthy Japanese adults not taking glucose-lowering medications at baseline. Annual HbA1c measures from 2005 to 2008 at the Center for Preventive Medicine, a community teaching hospital in Japan, estimated cumulative incidence of diabetes.

Results: Mean age (SD) of participants was 49.7 (12.3) years and 53% were male. Mean (SD) of HbA1c at baseline were 5.4 % (0.5). At three years, for those with HbA1c at baseline of less than 5.0 %, 5.0-5.4%, 5.5-5.9%, and 6.0-6.4%, cumulative incidence (95%CI) was 0.05% (0.001- 0.3), 0.05% (0.01 – 0.11), 1.2% (0.9 – 1.6), and 20% (18 – 23), respectively.

Conclusions: In those with an $HbA1_C$ under 6.0%, rescreening at intervals shorter than three years identifies few individuals (~1% or less) with an $HbA1_C \geq 6.5\%$.

Since fasting and post glucose challenge levels to predict risk of diabetic retinopathy, blood glucose levels have been the international standard for diagnosis (1). Recently a shift to haemoglobin A1c (HbA1c) for diagnosis has been proposed because HbA1c integrates longer term glucose levels and has better the pre-analytic stability (2).

The proposed diagnostic threshold of 6.5% was based on retinopathy risk at different levels of HbA1c (2). However, optimal frequency for repeating HbA1c has not been determined (3).

We used a large, longitudinal data set to explore the value of repeating HbA1c at different intervals to identify subjects who might progress above the threshold (≥6.5%).

METHODS

Study Participants. Between January and December 2005, we consecutively enrolled all adults (>20 years old) attending the Center for Preventive Medicine at St. Luke's International Hospital in Tokyo, Japan for the health check program. The program promotes early detection of chronic diseases and disease risk factors. We excluded people who took glucose-lowering medications at baseline

Data collection. We extracted data from records of people undergoing annual health checks from January 2005 to December, 2008. We excluded those without health check in year 1, 2 or 3. St. Luke's International Hospital Institutional Review Board approved the study.

Measurements. The annual health check collected demographic information and medical history with an initial evaluation (vital signs and laboratory data). Laboratory data included HbA1c, fasting plasma glucose (FPG), and lipids (total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Venous blood was drawn after an overnight fast and analyzed at the Central Laboratory at St. Luke's International Hospital. HbA1c assays were performed by an Automated Glycohemoglobin Analyzer HLC-723G (Tosoh, Tokyo, Japan) with a coefficient of variation (CV) of <1.34% and certified by the National Glycohemoglobin Standardization Program (4). We classified as possible diabetes persons with either a single measured HbA1c≥6.5% (5, 6) or self-reported

commencement of glucose-lowering treatment. As a sensitivity analysis, we used FPG≥126 mg/dl as one of the diagnostic criteria.

Statistical methods. Analyzes used SPSS software 15.0J (SPSS Japan, Tokyo, Japan), except 95% confidence intervals (CI) which were based on an exact binominal (7) using Stata version 10 (STATA Corp, College Station, TX).

RESULTS

From January 2005 to July 2008, 16,313 people of the enrolled population of 39,284 underwent annual checks. Mean age (SD) of participants was 49.7 (12.3) years; 53% were male. The mean (SD) body mass index was 22.5 (3.2) kg/m^2; fasting plasma glucose was 99.2 (12.7) mg/dl; HbA1c at baseline was 5.4 (0.5) %; total, LDL cholesterol, and HDL cholesterol level at baseline were 204.3 (33.8) mg/dl, 117.6 (29.7) mg/dl, and 62.4 (15.8) mg/dl, respectively; and systolic blood pressure 119 (18) mmHg and diastolic blood pressure 73 (11) mmHg. The trends of mean HbA1c levels for the entire cohort from 2005 to 2008 slightly increased over the three years (0.05% per year). The demographic characteristics of nonparticipants and participants were similar.

At 3 years the cumulative incidence of diabetes was 3.2 % (95%CI: 3.0 – 3.4). However, this varies greatly by initial level of HbA1c. At three years, for those with HbA1c of less than 5.0 %, 5.0-5.4%, 5.5-5.9%, and 6.0-6.4% at baseline, cumulative incidence (95%CI) was 0.05% (0.001- 0.3%), 0.05% (0.01 – 0.11%), 1.2% (0.9 – 1.6%), and 20% (18 – 23%), respectively and adding FPG≥126 mg/dl to the diagnostic criteria showed the similar results (Figure). Logistic regression suggested that only BMI (Odds Ratio 1.14/kg/m^2) and FPG (Odds Ratio 1.06/mg/dl) added to the baseline HbA1c; age, gender, SBP, and LDL were non-significant. The average coefficient of variation (CV) of $HbA1_C$ stratified by baseline HbA1c was 2.7% and did not differ among these subgroups.

DISCUSSION

This study confirms that the rise in HbA1c in a non-diabetic population is slow. Participants who are well under the diagnostic threshold of HbA1c of 6.5% are unlikely to exceed this within several years of follow-up.

Much of the increased detection of diabetes in those with a higher baseline HbA1c was at one year, and may be attributable to measurement error and short term variation in HbA1c. The CV (including within subject variation) varies between 2 and 5 % (8); a CV of 5% would mean a 95% measurement interval of a single HbA1c in this range would be +/- 0.6%. This degree of variation would lead to some individuals having sequential tests from just below to just above 6.5%. Although the variation could occur at all time points, this is much less likely in the 5.0-5.9% range.

Our findings echo the slow rise of HbA1c found in trials with diabetic patients. For example, in the UKPDS study the patients on diet alone had a rise of less than 0.2% per year (9). Our non-diabetic cohort had an even lower average change in HbA1c of 0.05% per year.

This study has several limitations. First, the follow-up is incomplete as not all participants came back ever year. This could be addressed by other analysis, such as a linear mixed model. However, any bias would be likely to favour those developing diabetes to re-attend. Second, a few participants (1.1%) began taking glucose-lowering drugs, but this is unlikely to make a large difference to our conclusions. Third, our data are from one institution in Tokyo, Japan, might not generalize to other populations. For example, adult mean BMI levels of 22-23 kg/m^2 are found in Africa and Asia, while levels of 25-27 kg/m^2 are prevalent across North America

and Europe and then BMI level could be related to the cumulative incidence of diabetes. Finally, although the ADA criteria recommend a repeat HbA1c test to confirm the diagnosis of type 2 diabetes (2), our study included only a single measurement of HbA1c.

In conclusion, for the purpose of detecting new cases of diabetes, in those with an initial HbA1c under 6.0%, rescreening at intervals shorter than three years identifies few individuals (~1% or less) with an HbA1c $\geq$ 6.5%. At $HbA1_C \geq 6\%$, rescreening even at a 1- year interval would be reasonable strategy to identify disease.

***Author Contributions*:** O.T wrote manuscript, AF wrote manuscript, PG wrote and reviewed manuscript and, TS and FT contributed discussion.

ACKNOWLEDGMENT

This work was supported in part by a UK National Institute for Health Research program grant and by a grant from the Ministry of Health, Labour, and Welfare of Japan. We would like to thank the following people: Sachiko Ohde, St. Luke's Life Science Institute, and Gautam A. Deshpande, St. Luke's Life Science Institute and University of Hawaii, for their helpful comments

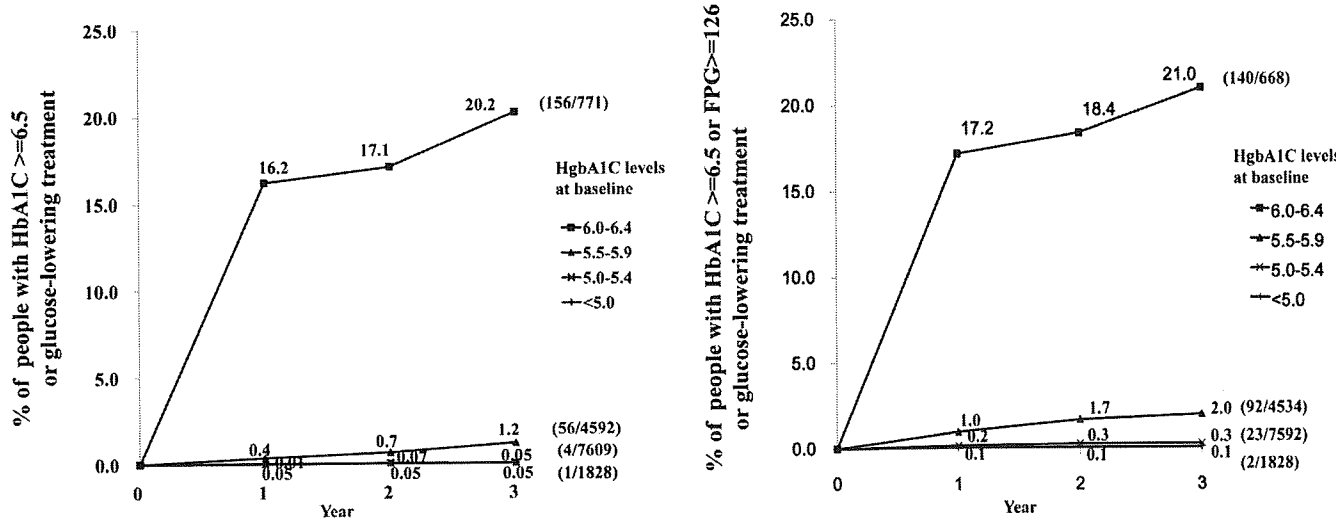
Conflict of Interest: None

REFERENCES

1. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20(7):1183-97.
2. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care.* 2009;32(7):1327-34.
3. Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J, Gregg E, Holman RR, Kirkman MS, Stern M, Tuomilehto J, Wareham NJ. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet.* 2010;375(9723):1365-74.
4. Terreni A, Paleari R, Caldini A, Ognibene A, Mosca A, Messeri G. Evaluation of the analytic performances of the new HPLC system HLC-723 G7 for the measurement of hemoglobin A1c. *Clin Biochem.* 2003;36(8):607-10.
5. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2010;33 Suppl 1:S62-9.
6. Bloomgarden ZT. A1C: recommendations, debates, and questions. *Diabetes Care.* 2009;32(12):e141-7.
7. Clopper SJ, Pearson ES. The use of confidence of fiducial limits illustrated in the case of the binominal. *Biometrika.* 1932;26:404-13.
8. Schwartz KL, Monsur JC, Bartoces MG, West PA, Neale AV. Correlation of same-visit HbA1c test with laboratory-based measurements: a MetroNet study. *BMC Fam Pract.* 2005;6:28.
9. United Kingdom Prospective Diabetes Study (UKPDS): Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ.* 1995;310(6972):83-8.

Legends

Figure: Percent of patients at annual re-checks with HbA1C above 6.5% or FPG above 126 mg/dl (by Baseline HbA1c)



Abbreviations: HbA1c, haemoglobin A1c, FPG, fasting plasma glucose

HEART

Lipid re-screening: what is the best measure and interval?

Osamu Takahashi, Paul P Glasziou, Rafael Perera, et al.

Heart 2010 96: 448-452 originally published online June 14, 2009
doi: 10.1136/hrt.2009.172619

Lipid re-screening: what is the best measure and interval?

Osamu Takahashi,[1,2] Paul P Glasziou,[1] Rafael Perera,[1] Takuro Shimbo,[3] Jiro Suwa,[4] Sonoe Hiramatsu,[4] Tsuguya Fukui[2]

See Editorial, p413

[1]Department of Primary Health Care, University of Oxford, Oxford, UK [2]Division of General Internal Medicine, Department of Medicine, St Luke's International Hospital, Tokyo, Japan [3]Department of Clinical Research and Informatics, International Medical Centre of Japan, Tokyo, Japan [4]Centre for Preventive Medicine, St Luke's International Hospital, Tokyo, Japan

Correspondence to
Osamu Takahashi, Department of Primary Health Care, University of Oxford, Old Road Campus, Roosevelt Drive, Headington, Oxford, OX3 7LF, UK; otakahas@luke.or.jp/otakahas@gmail.com

Accepted 2 June 2009
Published Online First 14 June 2009

ABSTRACT

Objectives To estimate the long-term true change variation ('signal') and short-term within-person variation ('noise') of the different lipid measures and evaluate the best measure and the optimal interval for lipid re-screening.

Design Retrospective cohort study from 2005 to 2008.

Setting A medical health check-up programme at a centre for preventive medicine in a teaching hospital in Tokyo, Japan.

Participants 15 810 apparently healthy Japanese adults not taking cholesterol-lowering drugs at baseline, with a mean body mass index of 22.5 kg/m^2 (SD 3.2).

Main outcome measures Annual measurement of the serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and calculation of the ratio of TC/HDL and LDL/HDL. Measurement of the ratio of long-term true change variation ('signal') to the short-term within-person variation ('noise') for each measure.

Results At baseline, participants (53% male) with a mean age of 49 years (range 21–92) and a mean TC level of 5.3 mmol/l (SD 0.9 mmol/l) had annual check-ups over 4 years. Short-term within-person variations of TC, LDL, HDL, TC/HDL, and LDL/HDL were 0.12 (coefficient of variation (CV) 6.4%), 0.08 (CV 9.4%), 0.02 (CV 8.0%) mmol^2/l^2, 0.08 (CV 7.9%) and 0.05 (CV 10.6%), respectively. The ratio of signal-to-noise at 3 years was largest for TC/HDL (1.6), followed by LDL/HDL (1.5), LDL (0.99), TC (0.8) and HDL (0.7), suggesting that cholesterol ratios are more sensitive re-screening measures.

Conclusion The signal-to-noise ratios of standard single lipid measures (TC, LDL and HDL) are weak over 3 years and decisions based on these measures are potentially misleading. The ratios, TC/HDL and LDL/HDL, seem to be better measures for monitoring assessments. The lipid re-screening interval should be >3 years for those not taking cholesterol-lowering drugs.

INTRODUCTION

Dyslipidaemia is common in industrialised countries,[1] including Japan,[2] and is an important modifiable risk factor for coronary heart disease (CHD) and cardiovascular disease (CVD).[3–5] Large randomised controlled studies and meta-analysis studies have established that cholesterol-lowering treatment reduces CHD morbidity and mortality,[3 6–8] Thus, cholesterol level screening is important for adults to identify those at risk of CVD and is widely available.[9 10]

Screening the cholesterol level includes interpretation of the initial level and also that of a series of sequential levels over time,[11] in which we should consider the variations of both short-term within-person and long-term among individuals in the population.[12] Lipid guidelines for primary prevention of CVD and CHD recommend a targeting level for lipid level and how to interpret initial measurements; however, they rarely specify subsequent monitoring in primary prevention, and guidelines vary in their recommendation. In the United Kingdom, the National Institute for Clinical Excellence[13 14] for the primary prevention of CVD recommends that people aged 40–74 years without a history of CVD should have total cholesterol (TC) and high-density lipoprotein cholesterol (HDL) measured; however, the optimal interval for these measurements is not provided.

On the other hand, in the United States, the National Cholesterol Education Program in Adults[3] recommends that all adults aged ≥20 years have a fasting lipoprotein profile that includes TC, low-density lipoprotein cholesterol (LDL), HDL and triglycerides once every 5 years. Moreover, the United States Preventive Services Task Force[15] suggests that doctors routinely screen men aged ≥35 years and women aged ≥45 years for lipid disorders. Again, however, the optimal re-screening interval is unclear. Even when guidelines suggest screening intervals, the basis for these suggestions is not provided and no guidelines consider within-person and long-term variation in their re-screening strategies.

Detecting dyslipidaemia and intervening early can reduce the impact but it also has some important drawbacks such as inconvenience and cost; in addition, false-positive results may be obtained that can lead to inappropriate action.[11 16] A good monitoring test should correlate with the final clinical outcomes but also differentiate changes in the condition (signal) from the background of measurement variability (noise).[12] Considering such variations could avoid leading to inappropriate intervention or minimise the harm.[12 17–19] Thus, in choosing test options, the signal-to-noise (S/N) ratio may be a key factor in determining the value of the test for monitoring.[16]

We, therefore, aimed to estimate the variation in long-term true changes in the different lipid profile measures and the short-term within-person variations and thus estimate the S/N ratio in cholesterol screening. Since several previous studies have suggested that lipid ratios (TC/HDL and LDL/HDL) have greater independent predictive values for CHD than serum TC or LDL levels,[20–22] we compared S/N ratio among different types of cholesterol measures, including

Heart 2010;**96**:448–452. doi:10.1136/hrt.2009.172619

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).

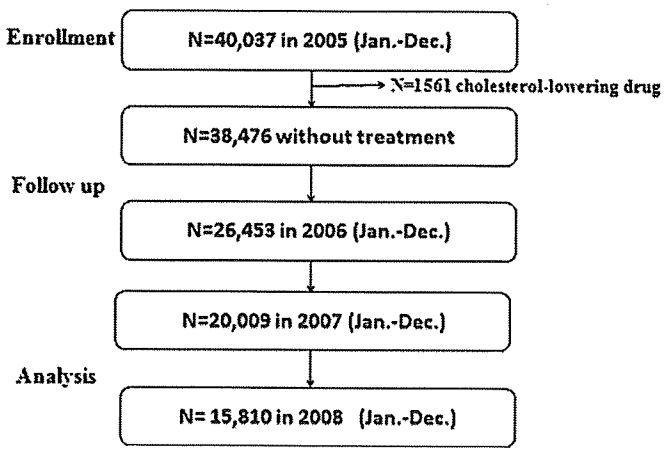


Figure 1 Flow diagram.

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

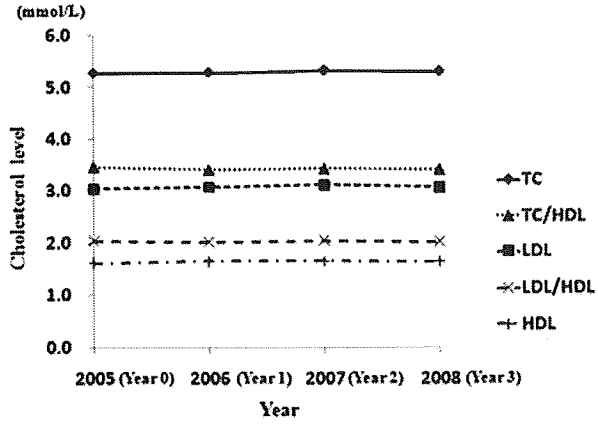
	Population with 3 years follow-up (n=15810)	Population at enrolment (n=38476)
Age (years), mean (SD)	49.3 (12.2)	47.0 (12.2)
Range (years)	21–92	20–98
Male, n (%)	8362 (52.9)	19947 (51.8)
Body mass index (kg/m^2), mean (SD)	22.5 (3.2)	22.4 (3.2)
Total cholesterol (mmol/l), mean (SD)	5.3 (0.9)	5.3 (0.8)
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.

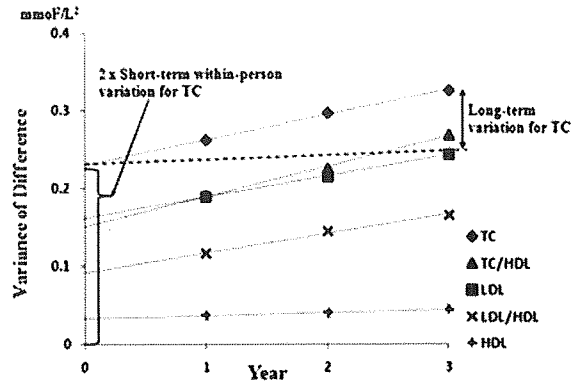
Long-term, true change variation

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	0.12	0.08	0.02	0.08	0.05
(CV, %)	(6.4)	(9.4)	(8.0)	(7.9)	(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.

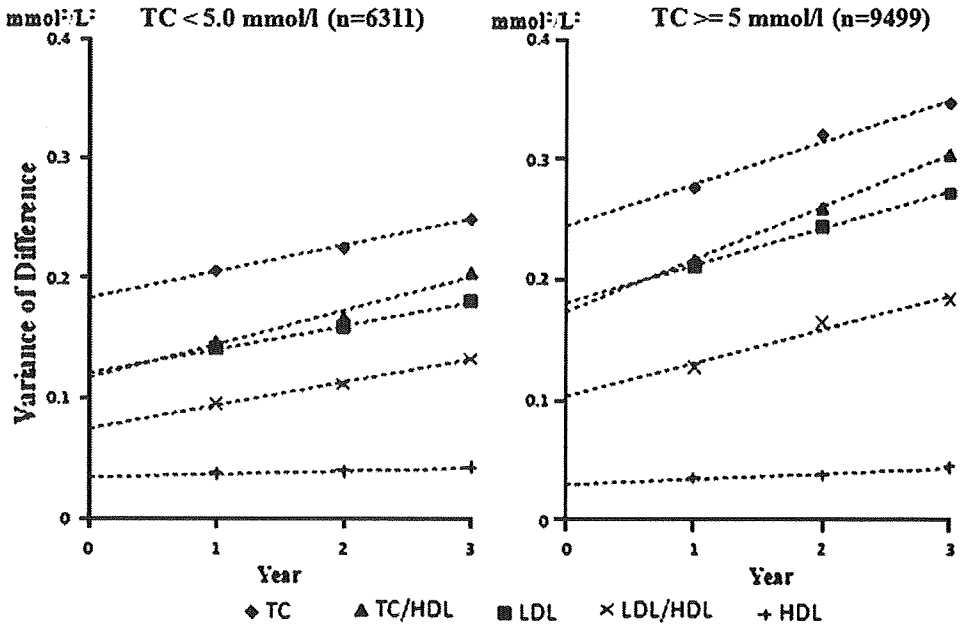


Figure 4 Variance of difference among individual cholesterol levels over 4 years by TC level at baseline. HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LDL/HDL, ratio of LDL to HDL; TC, total cholesterol; TC/HDL, ratio of TC to HDL.

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.

Acknowledgements This work was supported in part by a UK National Institute for Health Research programme grant and by the Japan Foundation for Emergency Medicine. We would like to thank Richard Stevens and Tomoya Okubo for their statistical support; Sachiko Ohde and Jacobs Joshua for their helpful comments.

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.

REFERENCES

1. **Hyre AD,** Muntner P, Menke A, *et al*. Trends in ATP-III-defined high blood cholesterol prevalence, awareness, treatment and control among U.S. adults. *Ann Epidemiol* 2007;**17**:548–55.
2. **Arai H,** Yamamoto A, Matsuzawa Y, *et al*. Prevalence of metabolic syndrome in the general Japanese population in 2000. *J Atheroscler Thromb* 2006;**13**:202–8.
3. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486–97.
4. **Teramoto T,** Sasaki J, Ueshima H, *et al*. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb* 2007;**14**:45–50.
5. **Okamura T,** Kokubo Y, Watanabe M, *et al*. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study. *Atherosclerosis* 2009;**203**:587–92.
6. **Costa J,** Borges M, David C, *et al*. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006;**332**:1115–24.
7. **Nakamura H,** Arakawa K, Itakura H, *et al*. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006;**368**:1155–63.
8. **Pignone M,** Phillips C, Mulrow C. Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials. *BMJ* 2000;**321**:983–6.
9. **MMWR.** Trends in Cholesterol Screening and Awareness of High Blood Cholesterol - United States, 1991-2003. *JAMA* 2005;**294**:2021–2.
10. H.E.A.R.T UK - The Nation's Cholesterol Charity. Available at http://www.heartuk.org.uk (accessed 6 January 2010).
11. **Del Mar C,** Doust J, Glasziou PP. *Clinical thinking; evidence, communication and decision-making* Oxford (UK): Blackwell Publishing Ltd. BMJ Books, 2006.
12. **Glasziou PP, Irwig L,** Aronson JK. *Evidence-based medical monitoring: from principles to practice* Oxford (UK): Blackwell Publishing, BMJ books, 2008.
13. National Institute for Health and Clinical Excellence (NICE) Clinical guideline. *Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease* 2008. Available at http://www.nice.org.uk/nicemedia/pdf/CG67NICEguideline.pdf (accessed 6 January 2010).
14. **Cooper A,** O'Flynn N. Risk assessment and lipid modification for primary and secondary prevention of cardiovasucular disease: summary of NICE guidance. *BMJ* 2008;**336**:1246–8.
15. **The U.S. Preventive Services Task Force (USPSTF).** Screening for lipid disorders in adults, 2008. Available at http://www.ahrq.gov/CLINIC/uspstf/uspschol.htm (accessed 6 January 2010).
16. **Glasziou P,** Irwig L, Mant D. Monitoring in chronic disease: a rational approach. *BMJ* 2005;**330**:644–8.
17. **Glasziou PP,** Irwig L, Heritier S, *et al*. Monitoring cholesterol levels: measurement error or true change? *Ann Intern Med* 2008;**148**:656–61.
18. **Bell KJ,** Irwig L, Craig JC, *et al*. Use of randomised trials to decide when to monitor response to new treatment. *BMJ* 2008;**336**:361–5.
19. **Bell KJ,** Hayen A, Macaskill P, *et al*. Mixed models showed no need for initial response monitoring after starting antihypertensive therapy. *J Clin Epidemiol* 2009;**62**:650–9.
20. **Kinosian B,** Glick H, Garland G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. *Ann Intern Med* 1994;**121**:641–7.
21. **Ridker PM,** Rifai N, Cook NR, *et al*. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 2005;**294**:326–33.
22. **Ingelsson E,** Schaefer EJ, Contois JH, *et al*. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA* 2007;**298**:776–85.
23. **Shepard DS.** Reliability of blood pressure measurements: implications for designing and evaluating programs to control hypertension. *J Chronic Dis* 1981;**34**:191–209.
24. **Thompson SG,** Pocock SJ. The variability of serum cholesterol measurements: implications for screening and monitoring. *J Clin Epidemiol* 1990;**43**:783–9.
25. **Smith SJ,** Cooper GR, Myers GL, *et al*. Biological variability in concentrations of serum lipids: sources of variation among results from published studies and composite predicted values. *Clin Chem* 1993;**39**:1012–22.
26. **Rotterdam EP,** Katan MB, Knuiman JT. Importance of time interval between repeated measurements of total or high-density lipoprotein cholesterol when estimating an individual's baseline concentrations. *Clin Chem* 1987;**33**:1913–15.
27. **Choudhury N,** Wall PM, Truswell AS. Effect of time between measurements on within-subject variability for total cholesterol and high-density lipoprotein cholesterol in women. *Clin Chem* 1994;**40**:710–15.
28. **Pereira MA,** Weggemans RM, Jacobs DR Jr, *et al*. Within-person variation in serum lipids: implications for clinical trials. *Int J Epidemiol* 2004;**33**:534–41.
29. **Schectman G,** Patsches M, Sasse EA. Variability in cholesterol measurements: comparison of calculated and direct LDL cholesterol determinations. *Clin Chem* 1996;**42**:732–7.
30. **Lemieux I,** Lamarche B, Couillard C, *et al*. Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: the Quebec Cardiovascular Study. *Arch Intern Med* 2001;**161**:2685–92.
31. **Prospective Studies Collaboration.** Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55000 vascular deaths. *Lancet* 2007;**370**:1829–39.
32. **British Cardiac Society BHS, Diabetes UK, HEART UK,** , *et al*. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;**91**(Suppl 5):v1–52.

Original Article J. Clin. Biochem. Nutr., 45, 68–73, July 2009

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

Katsuyoshi Kato[1,*], Shin-ichi Sugiura[2], Kohji Yano[1], Toshio Fukuoka[3], Akio Itoh[1], Masato Nagino[4], Toshitaka Nabeshima[5], and Kiyofumi Yamada[1]

[1]*Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan*
[2]*Department of Hospital Management Strategy and Planning, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan*
[3]*Department of Emergency Medicine and Intensive Care Unit, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan*
[4]*Division of Surgical Oncology Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan*
[5]*Department of Chemical Pharmacology, Meijo University Graduate School of Pharmaceutical Sciences, Nagoya 468-8503, Japan*

Received 27 November, 2008; Accepted 17 January, 2009

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

*To whom correspondence should be addressed.
Tel: 81-52-744-1958 Fax: 81-52-744-2948
E-mail: katsuy@med.nagoya-u.ac.jp