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STUDY OF PANCREAS FUNCTION FOR CARBOHYDRATE LOADING IN DIABETES WITH INSULIN RESISTANCE

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ABSTRACT:

Background: Authors have continued clinical practice and research of Calorie Restriction (CR), Low Carbohydrate Diet (LCD) and Morbus (M) value for long.

Subjects and Methods: Subjects were 32 type 2 diabetes mellitus (T2DM) with more than 10 μU/mL of fasting immunoreacitve insulin (IRI). Methods included fundamental tests such as glucose, IRI, homeostasis model assessment (HOMA)-R, HOMA-β, and so on.

Results: Obtained data were as follows: average age 57.6 ± 12.8 years old, average HbA1c 7.6%. Median values are: average glucose 166 mg/dL, M value 46.6, fasting glucose 140 mg/dL, fasting IRI 12.4 μU/mL, HOMA-R 4.5, HOMA-β 60.3. M value showed significant correlation with HOMA-R and HOMA-β ($p<0.01$). M value showed significant correlations with HbA1c, average glucose, HOMA-R, HOMA-β ($p<0.01$). For the responses of glucose and IRI for 70g of carbohydrate, Delta Ratio of insulinogenic index (IGI) and Area Under the Curves (AUC) Ratio of IGI were studied. Significant correlation existed between HOMA-β and AUC Ratio of IGI ($p<0.01$).

Discussion and Conclusion: These results suggested the relationship among average glucose, HbA1c, M value, HOMA-R, HOMA-β, IGI, Delta and AUC Ratio of IGI, and so on. These findings would become fundamental and reference data for the future study in this field.

Keywords: Morbus value (M value), Type 2 diabetes mellitus (T2DM), Calorie Restriction (CR), Homeostasis model assessment (HOMA), Insulinogenic Index (IGI), Area Under the Curve (AUC).

1 Introduction

The patients with diabetes has been increased in developed countries and developing countries [1]. In regard to clinical diabetic management, rather paradigm changes have been observed. American College of Physicians (ACP) proposed the change in standard value about HbA1c [2]. Furthermore, American Diabetes Association (ADA) presented the comments about the goals and treatment for diabetes [3].

In succession, the Prospective Urban Rural Epidemiology (PURE) studies were reported as large-scale epidemiological studies. They have covered about 140 thousands subjects in 600 communities from 18 countries [4]. Out of these studies, it was found that higher carbohydrate intake has an increased risk of total mortality (HR 1.28), and that reducing intake of carbohydrate would be recommended [5]. Moreover, standard guideline was presented from International Diabetes Federation (IDF) [6].

As to the nutritional therapy for diabetes, there have been various discussion about Low Carbohydrate Diet (LCD) and Calorie Restriction (CR) [7-9]. In Japan,

authors and colleagues have begun LCD, and treated lots of cases with clinical efficacy [10]. We have investigated related research concerning CR and/or LCD formula meals, elevated ketone bodies, Morbus (M) value, lipid metabolism, renal function [11-13]. In addition, three types of LCD meal were proposed, which are super, standard and petite LCDs [14]. Furthermore, we continued and developed LCD broadly in Japan by seminars, books and medical papers through Japanese LCD promotion association [15].

Along our clinical investigation concerning LCD and CR, we proposed new index that is simple and useful method. Similar to 75g oral glucose tolerance test (75gOGTT) and insulinogenic index (IGI) to carbohydrate 75g, we have tried to take advantage of breakfast of CR including Carbohydrate 70g (Carbo70). Corresponding to IGI-75gOGTT, IGI-Carbo70 was proposed and its clinical usefulness was investigated [16]. Along to this research direction, we developed the research in this study.

2 Subjects and Methods

We enrolled 32 patients with Type 2 Diabetes Mellitus (T2DM) in this study. As the background of the subjects, they were diagnosed as T2DM and/or in the diabetic state before the diagnosis of T2DM. For further evaluation and treatment, they were admitted to the hospital. On admission, they were not provided medicine for influencing blood glucose. Moreover, subjects were selected who showed fasting immunoreactive insulin (IRI) more than 10μU/mL. Subjects with IRI level 10μU/mL and less than 10μU/mL were excluded in this study.

As regard to the research methods, we have taken our formula protocol of diabetic evaluation. We decided to follow some certain criteria about this investigation.

a) Subjects were admitted to the hospital for 2 weeks. On the morning of day 2, basal data were obtained from the blood samples after overnight fasting. They include several biomarkers such as complete blood count, liver, renal function, lipid metabolism and so on. For diabetic aspect, HbA1c, glucose, IRI, C-peptide, M value, homeostasis model assessment of insulin resistance homeostasis model assessment of insulin resistance (HOMA-R) and homeostasis model assessment of β cell function (HOMA-β) were calculated.

b) For our diabetic research protocol program, CR and LCD were provided. Subjects have CR on day 1 and 2 and LCD from day 3 to 14. On the morning of day 2, subjects were provided CR breakfast with carbohydrate 70g. This breakfast has the content that PFC ratio was protein 15%, fat 25%, carbohydrate 60%, with 1400 kcal/day. It is along to the standard guideline in nutritional therapy which was proposed by Japan Diabetes Society (JDS) [17].

c) Similar to 75 gOGTT, 70g of carbohydrate in CR breakfast was given to the subjects. Blood samples were drawn for blood glucose and IRI on 0 and 30 min. During half an hour after the breakfast, subjects were to keep still on sitting position. From the data of glucose and IRI, the ratio of IRI response against glucose response was calculated.

d) Daily profile of blood glucose was investigated on day 2. The clock time was 08, 10, 12, 14, 17, 19, 22h, 7 times a day. Average blood glucose value and Morbus (M) value were calculated.

e) In our usual research protocol, CR meal is provided on day 1 and 2, and super LCD is provided from day 3 to 14. We have three types of LCD, which are super, standard and petite LCDs, in which the ratio of carbohydrate is 12%, 26%, 40%, respectively. In this study, we utilized the data from only day 2, and do not use data from day 3 to 14 or data from LCD.

2.1 Ratio of insulin/glucose response

Insulinogenic Index (IGI) has been known from the data of glucose and IRI on 0 and 30 min in 75gOGTT. Similar to this calculation, we have tried two kinds of calculating ratios for 70g of carbohydrate meal. As the formula of IGI shows delta (increment) of insulin (30min – 0 min) / delta (increment) of blood glucose (30min – 0min). In this report, this ratio is called as 'Delta Ratio of IGI for Carbo70'.

Another estimating method is from the usage of Area Under the Curves (AUC) of the glucose and IRI for 70g of carbohydrate. The ratio between IRI and glucose would be called as ' AUC Ratio of IGI for Carbo70'.

From described above, two ratios are defined as follows: Delta Ratio of IGI for Carbo70 is calculated as (IRI

at 30min – IRI at 0min)(μU/mL) / (Glucose at 30min – Glucose at 0min)(mg/dL).

Similarly, AUC Ratio of IGI for Carbo70 is calculated as (AUC of IRI for 0-30min) (μU/mL x h)/ (AUC of glucose for 0-30min)(mg/dL x h).

2.2 Daily profile of blood glucose

For blood glucose variability, daily profile of blood glucose in a day was studied on day 2. Blood samples were drawn and measured 7 times a day. The time were 08, 13, 12, 14, 17, 19, 22h.From these data, we calculated average blood glucose a day and also the level of M value according to the certain mathematical equation [18,19].

2.3 Morbus value

M value is the useful biomarker for glucose variability. Its characteristic benefit is expressing two aspects in clinical practice. One is the average blood glucose value obtained from 7 times a day, and another is mean amplitude of glycemic excursions (MAGE) [18-20]. Consequently, it is useful for research because of expressing simply one numerical value.

By mathematical equation, M value can be calculated easily as the logarithmic transformation. The significance of M value would be the expression of the glucose deviation from the ideal glucose variability [19-21].

The following steps are the calculation of the M value. At first, M = MBS + MW : M value is the total of MBS and MW. In addition, MW is (maximum blood glucose – minimum glucose)/20. Furthermore, MBS expresses the mean of MBSBS. Summarized these equations, MBSBS has been the individual M-value for each blood glucose, which is calculated as (absolute value of [10 × log (blood glucose level/120)])^3 [19-21].

As to the interpretation of the M value, the following would be the standard judgment. Generally speaking the value less than 180 is normal range, from 180 to 320 is borderline, and more than 320 is abnormal.

2.4 Statistical analysis

Regarding this study, the data were shown by the mean and standard deviation. In addition, some data were also shown as the median and quartile of 25% / 75%. When investigating the correlation with biomarkers, we used Spearman test for the judgment of the correlation coefficients. In these analyses, the computerized standard statistical tool for analytical evaluation was utilized [22].

2.5 Ethical Considerations

Current study was conducted in compliance with the ethical principles based upon the Declaration of Helsinki. In addition, other commentary was done in the Ethical Guidelines for Medical Research in Humans and in accordance with the Good Clinical Practice (GCP), associated with the consideration to the protection of subjects' human rights. Furthermore, there was adequate guideline for application, which was the "Ethical Guidelines for Epidemiology Research" by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare.

Author and colleagues have our ethical committee in the hospital. Several members including physician, nurse, pharmacist and other experts for the legal specialty attended and discussed. Regarding this study, we confirmed that current study was valid and agreed. Moreover, we have taken the informed consents and written paper agreements from the subjects. Current investigation has been registered for recognized study by National University Hospital Council of Japan (ID: #R000031211).

3 Results

3.1 Fundamental data

Enrolled subjects (n=32) revealed the basal data (Table 1). Average age was 57.6 ± 12.8 years old with 58 years old in median. Average HbA1c was 7.6%, while median value of HbA1c was 7.2%. Median value of average blood glucose and M value was 166 mg/dL and 46.6, respectively.

From the data of fasting glucose and IRI, HOMA-R and HOMA-β was calculated (Table 2). The median value of HOMA-R and HOMA-β was 4.5 and 60.3, respectively.

Table 1 Subjects and fundamental data

		Mean ± SD	Median [25%-75%]
Subjects	Number (M/F)	32 (12/20)	32 (12/20)
	Age (years old)	57.6 ±12.8	58 [51 – 66]
Glucose Profile	HbA1c (%)	7.6 ± 2.0	7.2 [6.1 – 8.2]
	Average Glucose (mg/dL)	171 ± 55.1	166 [121 – 197]
	M value	100 ± 134	46.6 [9.7 – 129]
Lipid metabolism	Triglyceride (mg/dL)	169 ± 112	140 [113 – 197]
	HDl-C (mg/dL)	51.5 ± 10.9	51.0 [43.8 – 57.5]
	LDL- C (mg/dL)	126 ± 31.4	123 [104 – 144]

Table 2 Estimation for HOMA- R and HOMA - β

		Mean ± SD	Median [25% - 75%]
HOMA calculation	Fasting glucose (mg/dL)	146 ± 36.5	140 [119 – 159]
	Fasting [R] (μU/mL)	13.9 ± 3.8	12.4 [11.6 – 16.0]
	HOMA – R	4.8 ± 1.6	4.5 [3.8 – 5.2]
	HOMA - β	77.5 ± 43.6	60.3 [45.2 – 93.8]

Table 3 Delta Ratio and AUC Ratio for Carbo 70

		Mean ± SD	Median [25% - 75%]
Insulinogenic Index	Glucose (0 min) (mg/dL)	146 ± 36.5	140 [119 – 159]
	Glucose (30 min) (mg/dL)	193 ± 46.2	186 [172 – 220]
	[R] (0 min) (μU/mL)	13.9 ± 3.8	12.4 [11.6 – 16.0]
	[R] (30min) (μU/mL)	37.7 ± 21.2	30.6 [24.4 – 51.1]
[R] Calculation	Delta Ratio	0.76 ± 0.98	0.45 [0.19 – 0.90]
	AUC Ratio	16.9 ± 10.6	13.6 [9.7 – 21.9]

3.2 IGI study for carbohydrate 70g

The responses of glucose and IRI for carbohydrate 70g were shown in Table 3. Median values of glucose for 0 vs 30min and IRI for 0 vs 30 min were 140mg/dL vs 186 mg/dL, 12.4μU/mL vs 30.6μU/mL, respectively. According to the 2 kinds of calculation of insulinogenic index (IGI), the median values were 0.45 in Delta Ratio and 13.6 in AUC Ratio, respectively.

3.3 Correlation of M value to glucose

Correlation of M value with HbA1c or average blood glucose were shown in Figure 1. There was significant correlation between M value and HbA1c ($p<0.01$) (Fig.1a). There was significant correlation between M value and average blood glucose ($p<0.01$) (Fig.1b).

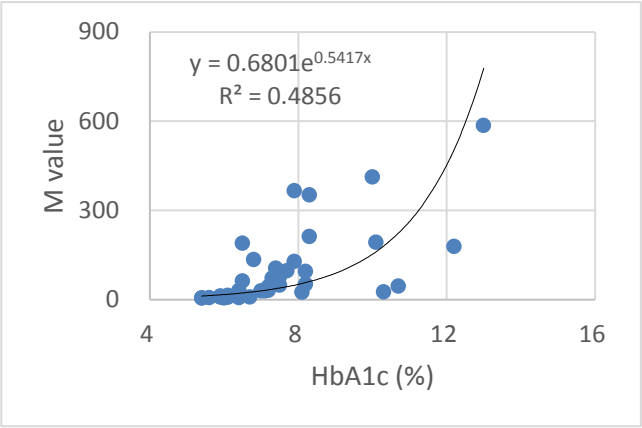

Figure 1(a): Correlation of M value with HbA1c. There was significant correlation between M value and HbA1c ($p<0.01$).

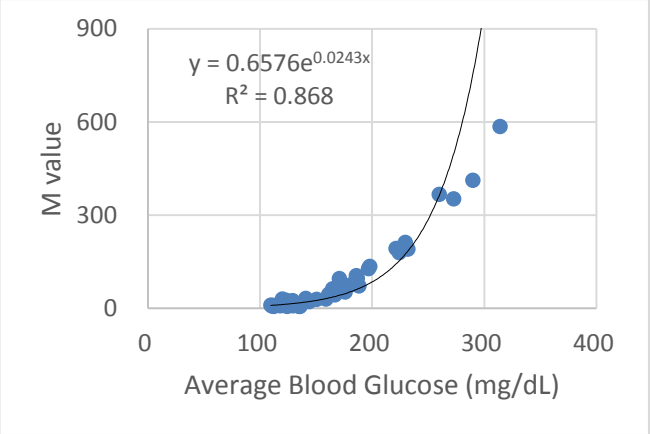

Figure 1(b): Correlation of M value with average blood glucose. There was significant correlation between M value and average blood glucose (p<0.01).

3.4 Correlation of M value with HOMA

Correlations of M value with 2 kinds of HOMA were shown in Figure 2. There was significant correlation between M value and HOMA-R (p<0.01) (Fig.2a). There was significant correlation between M value and HOMA-β (p<0.01) (Fig.2b).

3.5 Correlation of HOMA and IGI

Correlations of HOMA-β with Delta or AUC Ratio of IGI were shown in Fig.3. There was significant correlation between HOMA-β and Delta Ratio of IGI (p<0.01) (Fig.3a). In addition, There was significant correlation between HOMA-β and AUC Ratio of IGI (p<0.01) (Fig.3b).

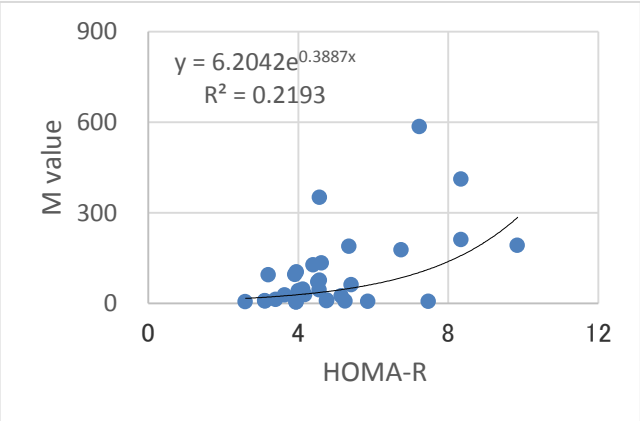

Figure 2(a): Correlation of M value with HOMA. There was significant correlation between M value and HOMA-R (p<0.01).

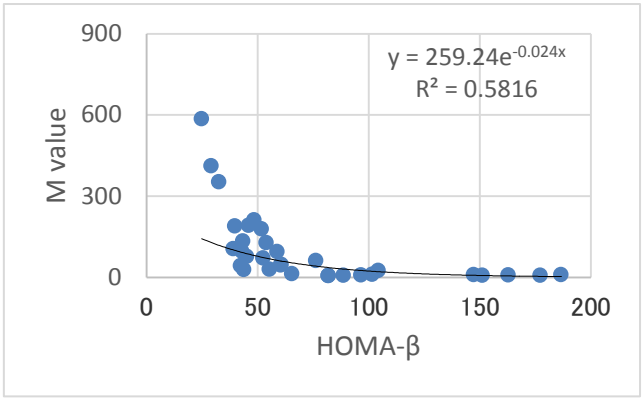

Figure 2(b): Correlation of M value with HOMA. There was significant correlation between M value and HOMA-β (p<0.01).

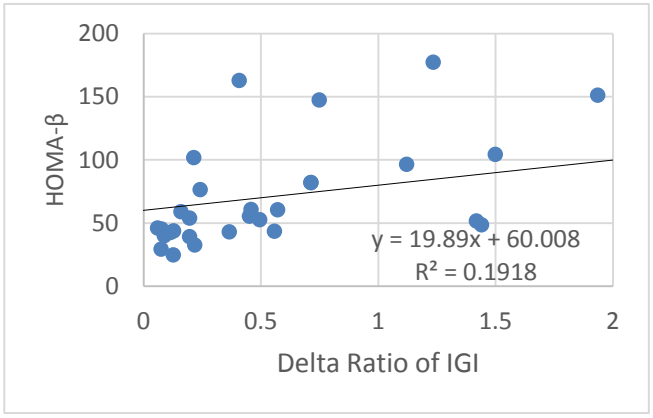

Figure 3 (a): Correlation of HOMA-β with Delta. There was not significant correlation between HOMA-β and Delta Ratio of IGI.

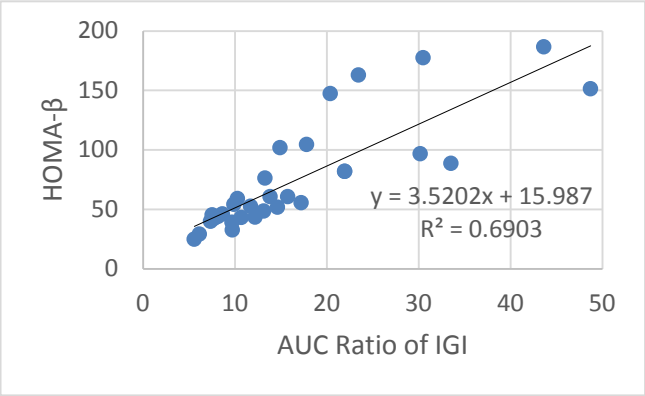

Figure 3(b): Correlation of HOMA-β with AUC Ratio of IGI. There was significant correlation between HOMA-β and AUC Ratio of IGI ($p<0.01$).

4 Discussion

Authors and colleagues have continued clinical research concerning LCD, CR and Morbus (M) value in various papers. Among them, one of the characteristic point for research would be the utilization of M value [18-20].

In the clinical practice for diabetes mellitus, there has been development of obtaining the glucose variability in several situations. For clarifying the blood glucose fluctuation, continuous blood glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG) have been used for years.

Moreover, in the case of detail research level, there are some parameters which can be calculated. On the basis of SMBG and CGM, they include standard deviation (SD), M value, average daily risk range (ADRR), and mean amplitude of glycemic excursions (MAGE) and so on [19-23] where they seemed to be beneficial as index of blood glucose fluctuation [23-25].

Taking most advantages of M value, pathophysiology of glucose variability has been investigated and clarified gradually [11, 13].

When comparing the average blood glucose level and the M value, the range of M value is broader and wider compared with that of value of blood glucose. That is one of the beneficial point of M value to utilize clinical research [26, 27]. It is because that M value expresses one numerical value, and that the level of M value means both average blood glucose and mean amplitude of glycemic excursions (MAGE) [28, 29].

In this study, various data concerning glucose variability and the responses of glucose and insulin against 70g of carbohydrate were found. From diabetic point of view, we would discuss and speculate fundamental data and detail findings about several correlations.

In the basic data of the subjects, the average value and the median value were almost equal in most items. On the other hand, there was a large difference between the average value and the median value only for the M value. The reason is probably due to the fact that the calculation formula for M value includes calculation to cube the difference value between measured glucose value and ideal glucose value.

The change and response in IRI for 70 g carbohydrate increased from 12.4 to 30.6 μU/mL on median. In this study, we restrict cases with fasting IRI more than 10 μU/mL. Studies restricting the range of IRI values like this report have been rather rare. As a result, we would not derive some speculation, but the result will become the basic data for future research in this field.

There was extremely high correlation coefficient between M value and average blood glucose. Its reason would be from the calculation method of M value, where average blood glucose is one of the several factors involved.

According to the value of R2 of M value with each HOMA, it was 0.22 in HOMA-R and 0.58 in HOMA-β [30]. HOMA-R showed a significant positive correlation ($p<0.01$), and HOMA-β showed a significant negative correlation ($p<0.01$). Among them, the correlation coefficient was higher in the latter HOMA-β. The reason would be probably from the fact that M value includes mean blood glucose and MAGE with close relationship with insulin secretion, and that HOMA-β represents pancreas function, leading to higher correlation coefficient in the latter [31, 32].

In current study, we investigated the correlation of biomarkers related to diabetes. The factors include HOMA-R and HOMA-β. Originally, HOMA was developed by Matthews [30]. By mathematical calculation, HOMA-R and HOMA-β are calculated from the balance between hepatic

glucose output and insulin secretion from fasting levels of glucose and insulin [33].

As the value of HOMA-R becomes higher, the insulin resistance becomes higher. Regarding the standard value of HOMA-R, it has been 1.73 or more with the presence of insulin resistance [34]. Subjects in this study were enrolled by the condition that fasting IRI was more than 10 μU/mL. Then, subjects seem to have insulin resistance. It is said that subjects indicating elevated HOMA-R are apt to suffer from myocardial infarction and cerebral infarction, regardless of diabetes. In other words, HOMA-R is not only for a judgment of insulin resistance but also for an indicator of cerebral cardiovascular events.

Regarding HOMA-β, it is estimated to suppose the ability of secretion of insulin from the pancreas. By previous reports, elevated HOMA-R value and decreased HOMA-β value have been independently and consistently associated with an increased diabetes risk [34, 35]. Compared the obtained data of HOMA-R and HOMA-β, most subjects in this study did not show normal ranges, suggesting both of the existence of insulin resistance and decreased β-function.

There were significant correlations between HOMA-β and both of Delta and AUC Ratio. The value of R2 in Delta vs AUC were 0.19 vs 0.69, respectively. The latter showed higher correlation coefficient, suggesting that AUC calculation would be more adequate than Delta calculation in the research point of view.

There have been several reports about clinical study of carbohydrate loading in breakfast. A trial of the international standard of test meal is found for the assessment of postprandial hyperglycemia [36]. This is called as Meal Tolerance Test (MTT) similar to GTT. There was another MTT which has carbohydrate 69g, similar to that of our investigation [37]. Among this report, glucose and IRI responses on 0 to 30 min were approximately 167 mg/dL to 230 mg/dL, and 12μU/mL to 37 μU/mL, respectively. When we speculate and calculate detail data, Delta Ratio vs AUC Ratio of IGI seemed to be 0.39 vs 12.3, respectively. These values seemed to be compatible for our data in the cases with rather fair responses.

As regard to the trials of Delta Ratio vs AUC Ratio of IGI, fundamental data have been accumulated at present. Current results would become the basal reference to develop this research in the future study.

For the limits of current research, several aspects would be considered. Diabetes related factors can be involved by investigating the relationship among them. Probable biomarkers may include blood value and urinary excretion of C-peptide, basal data of renal and liver function test, the changes of triglyceride, HDL-C, LDL-C and so on. Furthermore, trial research about MTT would be developed in the future.

4 Conclusion

In summary, 32 patients with T2DM were investigated. Glucose variability and responses of glucose and IRI for carbohydrate loading were studied. At present, obtained data would become fundamental reference for the future study. Further development of research in this field will be expected.

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Competing Interests:

The authors declare that they have no competing interests.

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