Marked recovery from glucotoxicity of β-cell function after medical nutrition therapy without pharmacotherapy in type 2 diabetic outpatients with extreme hyperglycemia: a pilot retrospective study

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Abstract. We investigated whether glucotoxicity of β-cell function could be eliminated after medical nutrition therapy (MNT) without forced correction of hyperglycemia by anti-diabetic medications including exogenous insulin administration. We analyzed newly diagnosed type 2 diabetic outpatients with hemoglobin A1c (HbA1c) of 10.1 ± 1.5%, who were treated by MNT at least for three months, without any aid of anti-diabetic medications. The β-cell function was calculated as the product of the ΔIns0–120/ΔGlu0–120 and the Matsuda index, where ΔIns0–120/ΔGlu0–120 represents the ratio of the incremental concentrations of insulin to those of glucose during the 0- to 120-min time periods under a 75-g oral glucose tolerance test. After MNT, HbA1c levels were reduced to 7.0 ± 1.0% (p < 0.001). The β-cell function was significantly improved (n = 13; p = 0.001; effect size d = 1.9). Fasting plasma glucose became below 7.0 mmol/L in 57% (8/13), and 120-minute plasma glucose became below 11.1 mmol/L in 43% (6/13). The β-cell function after MNT was significantly correlated with HbA1c levels achieved after MNT (Pearson’s correlation coefficient r = -0.62, p = 0.025). In conclusion, the β-cell dysfunction was ameliorated after MNT without glucose-lowering pharmacotherapy in newly diagnosed type 2 diabetic outpatients who presented extreme hyperglycemia.

Key words: Glucotoxicity, β-cell function, Medical nutrition therapy

Pancreatic β-cell function can be excessively deteriorated by sustained extreme hyperglycemia, which is well known as glucotoxicity [1]. The phenomenon is clinically common in patients with newly diagnosed type 2 diabetes who present extreme hyperglycemia, and forced correction of hyperglycemia by insulin therapy is often considered to ameliorate it [2]. The aim of the current study was to reveal whether the β-cell dysfunction could be ameliorated simply by medical nutrition therapy (MNT), without any aid of anti-diabetic medications including exogenous insulin administration.

Materials and Methods

This pilot study retrospectively analyzed newly diagnosed type 2 diabetic outpatients with hemoglobin A1c (HbA1c) ≥ 8%, who were initially treated by MNT without introducing any anti-diabetic medications at least for three months in Shiraiwa Medical Clinic, Osaka, Japan. Between June and December 2016, a total of 29 Japanese patients who first visited the clinic were newly diagnosed as type 2 diabetes. Of them, 14 patients were consecutively analyzed in the current study. Note that they were not suspected of being insulin-dependent, had dietary habits leaving room for improvement, had no history of anti-diabetic medications, and were treated by MNT at least for three months, without any aid of anti-diabetic medications.
treatment, and were free from marked comorbidities and complications. The risk of insulin dependence was practically judged based on comprehensive interpretations of plasma glucose levels, ketonuria, circulating insulin levels relative to glucose levels, and 24-hour urine C-peptide levels, although we did not set clear or definite criteria of all the laboratory parameters in clinical settings. Furthermore, such patients that had a marked discrepancy between plasma glucose levels and hemoglobin A1c levels, indicating a rapid deterioration of glucose metabolism, or presented rapidly worsening hyperglycemic symptoms were not included. All the 14 patients received MNT, which was provided by registered dietitians, without initiating anti-diabetic medications, at least for three months. MNT was a usual one which promoted and supported healthy eating patterns containing balanced foods with less focus on specific nutrients, and did not encourage excessive restriction of specific nutrients or calories. After three to five months, 13 of the 14 patients underwent a 75-g OGTT to re-assess their glucose metabolism. Note that in clinical settings, we made practical use of the OGTT data for planning the subsequent treatment strategies. In addition, we presented the data to patients, to show them how effective their lifestyle modification was for the improvement of glucose metabolism. The 75-g OGTT was therefore performed just in clinical practice, not primarily for study purpose.

Insulin sensitivity was assessed with the Matsuda index [3]. The β-cell function was calculated as the index of insulin secretion factored by insulin resistance, i.e., the product of ΔIns0–120/ΔGlu0–120 and the Matsuda index, where ΔIns0–120 and ΔGlu0–120 represent the mean incremental concentrations of plasma insulin and glucose during the 120-minute OGTT [4]. We also calculated ΔIns0–30/ΔGlu0–30 (so called insulinogenic index) as an index of the early insulin secretion, and its product with the Matsuda index as the corresponding index of β-cell function.

Data are presented as mean ± standard deviation (SD) for continuous variables, or as number (percentage) for discrete variables, if not otherwise mentioned. All statistical tests were two-sided and a p value of less than 0.05 was considered to be statistically significant. The significance of the change after MNT was assessed with the paired t-test. In addition to the p value, the effect size d are reported when required. The sample size of the current pilot study was enough to detect the 0.8-SD difference with a power of 80%.

The current study was in accordance with the principles of Declaration of Helsinki, and was approved by the ethics committees of Shiraiwa Medical Clinic and Osaka University Hospital. Since the current study was a retrospective research using only existing medical records, informed consent was exempted and instead relevant information regarding the study was open to the public, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Results

They were 52 ± 11 years old and 79% (11/14) were male. At the first visit, HbA1c was 10.1 ± 1.5% and 64% (9/14) were symptomatic (i.e., polydipsia and/or polyuria). Body mass index was 26.2 ± 4.2 kg/m². On the other hand, their 24-hour urine C-peptide levels were 120 ± 43 μg/day, indicating that none was considered to be insulin dependent. Ketonuria was found in three patients at baseline. However, their ketonuria was considered to come from extreme dietary restriction (calorie and carbohydrates) and long-hour fasting, rather than from insulin deficiency. Indeed, all of three patients had higher than 100 μg/day of 24-hour urine C-peptide levels.

The change of body weight, waist circumference, lipid profile, and liver function after MNT are summarized in Table 1. Physical exercise was increased in 4 of 14 patients, unchanged in 9 patients, and decreased in 1 patient. As shown in Fig. 1a, HbA1c was significantly lowered to 7.0 ± 1.0% after MNT (p < 0.001). A total of 10 patients (71%) achieved HbA1c < 7%, whereas HbA1c remained ≥ 8% after three-month MNT in the rest. Baseline HbA1c was not significantly different between those who achieved HbA1c < 7% and those who failed to (9.9 ± 1.5% vs 10.6 ± 1.6%; p = 0.516 by the Student’s t test). Neither was the prevalence of hyperglycemia-related symptoms at baseline (70% vs 75%; p = 1.00 by the Fisher’s exact test).

A re-performed 75-g OGTT showed a significant improvement of glucose tolerance with increased insulin levels (Fig. 1b). Fasting plasma glucose became below 126 mg/dL (7.0 mmol/L) in 57% (8/13), and 120-minute plasma glucose during the OGTT became below 200 mg/dL (11.1 mmol/L) in 43% (6/13).

The indices of insulin secretion, insulin sensitivity and β-cell function became significantly higher after MNT than at baseline (all p < 0.05), with the effect size
It is well recognized that glucotoxicity can be eliminated by forced correction of hyperglycemia [5]. Short-term exogenous insulin administration is therefore often considered as a practical management of newly diagnosed type 2 diabetes presenting extreme hyperglycemia [2]. Indeed, numerous clinical studies have reported that β-cell dysfunction is ameliorated after temporary insulin therapy in these patients [6-8]. However, it remained unclear whether β-cell function can recover by its own ability, without any aid of anti-diabetic pharmacotherapy.

The current findings indicated that MNT can ameliorate β-cell dysfunction to such an extent that many patients will achieve HbA1c goals without medications, and that some will become categorized as non-diabetic glucose tolerance. The improvement was likely expected irrespective of the baseline severity of

| Table 1 Change of clinical profiles other than glucose metabolism after MNT. |
|---------------------------------|----------------------|----------------------|----------------------|
|                                   | N | Baseline | After MNT | p value  |
|---------------------------------|---|----------|-----------|----------|
| Body weight (kg)                 | 14| 72.6 ± 14.3 | 68.0 ± 12.5 | < 0.001  |
| Body mass index (kg/m²)          | 14| 26.2 ± 4.2  | 24.6 ± 3.7  | < 0.001  |
| Waist circumference (cm)         | 7 | 96 ± 10    | 91 ± 9     | 0.012    |
| Aspartate aminotransferase (U/L) | 13| 27 ± 15    | 19 ± 6     | 0.040    |
| Alanine aminotransferase (U/L)   | 13| 37 ± 23    | 20 ± 11    | 0.004    |
| Total cholesterol (mg/dL)        | 13| 226 ± 53   | 208 ± 44   | 0.155    |
| LDL cholesterol (mg/dL)          | 10| 148 ± 23   | 140 ± 33   | 0.186    |
| HDL cholesterol (mg/dL)          | 13| 50 ± 12    | 51 ± 13    | 0.595    |
| Fasting triglyceride (mg/dL)     | 10| 93 ± 31    | 78 ± 16    | 0.173    |
| Non-HDL cholesterol (mg/dL)      | 13| 176 ± 47   | 157 ± 35   | 0.114    |

HDL, high-density lipoprotein; LDL, low-density lipoprotein. LDL cholesterol levels were estimated by the Friedewald’s equation.

Fig. 1 Glycemic control and glucose tolerance at baseline and after MNT
(a): HbA1c levels after MNT without pharmacotherapy. (b): Plasma glucose (left panel) and insulin levels (right panel) during a 75-g OGTT. White circles = profiles at baseline; black circles = profiles after MNT for three to five months. Asterisks indicate p < 0.05.
hyperglycemia. It is also of note that these improvement can be achieved in only several months. Although temporary insulin therapy has been often recommended for the purpose of eliminating glucotoxicity, appropriately provided MNT might be more cost-effective, i.e., as effective with lower cost.

Interestingly, the amelioration of β-cell dysfunction after MNT seemed greater than that of insulin resistance, as indicated by the effect size $d$. MNT might make a greater contribution to β-cell function than insulin sensitivity in patients with newly diagnosed type 2 diabetes who present extreme hyperglycemia.

This was a retrospective study and therefore many confounders would modify the current findings. In other words, the improvement of β-cell function observed in the current study could not be explained solely by the elimination of glucotoxicity. For example, body weight and waist circumference were significantly decreased after MNT. It was not surprising that the change of body composition would considerably contribute to the improvement of glucose metabolism. Accompanying change of exercise habits would also affect the improved metabolism. The secretion of incretin hormone, altered by the change of meal in amount, might also modify the recovery of β-cell function [9]. In addition, serum alanine aminotransferase and aspartate aminotransferase levels, which were markers of liver function, were also significantly reduced. The change of liver function would possibly be another modulator for the improvement of glucose metabolism in the current study population. Furthermore, lipid profiles showed a trend of improvement, although none reached statistical significance. It is reported that not only hyperglycemia but also hyperlipidemia affect insulin secretory capacity as well as insulin sensitivity [10, 11]. Lipid metabolisms might be considerably involved in the recovery of β-cell function too. The current non-significance might come from an insufficient sample size. In addition, we

![Graphs showing changes in insulin secretion, insulin sensitivity, and β-cell function](image)

**Fig. 2** Change of the indices of insulin secretion (a), insulin sensitivity (b), and β-cell function (c), as well as early phase insulin secretion (d) and its corresponding β-cell function (e)

One patient demonstrated a decrease of insulin level during the first 30 minutes at baseline so that insulinogenic index ($\Delta{\text{Ins}}_{0-30}/\Delta{\text{Glu}}_{0-30}$) could not be calculated. Therefore the change of the index (d) and its product with the Matsuda index (e) were assessed in the remaining 12 patients.
did not have data on other parameters such as free fatty acid levels. Further studies are needed to confirm the impact of lipid metabolism on glucose metabolism.

It should be noted that the current study just demonstrated a clinical course of patients whom we decided to treat with MNT alone. The patients were not suspected of being insulin dependent, had dietary habits leaving room for improvement, had no history of anti-diabetic treatment, and were free from marked comorbidities and complications. This was not the data demonstrating clinical outcomes in all newly diagnosed diabetic patients. There was a selection bias in this sense.

A major limitation of the current pilot study was that this was a single-center retrospective non-controlled study with a small sample size. Future prospective controlled studies with a sufficiently larger population are needed to validate the current findings and to further explore for clinical factors which distinguish responders and non-responders to MNT. Another limitation was that the β-cell function was assessed as a product of insulin secretion and sensitivity indices derived from an OGTT data. Although clinical studies demonstrated the usefulness overseas, the validity in a Japanese population remained unrevealed. However, in the current study, the change of insulin secretion index had a larger effect size than that of insulin sensitivity index. Given that the β-cell function is indicated by insulin secretion adjusted for insulin resistance, markedly improved insulin secretion under a small change of insulin resistance would support the amelioration of the β-cell dysfunction. Future studies are needed to validate the current findings.

In conclusion, β-cell function was considerably improved after MNT without any aid of anti-diabetic medications in newly diagnosed type 2 diabetic outpatients who presented extreme hyperglycemia.

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Disclosure

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