The Duration of Severe Insulin Omission is the Factor Most Closely Associated with the Microvascular Complications of Type 1 Diabetic Females with Clinical Eating Disorders

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ABSTRACT
Objective: To investigate which features of eating disorders are associated with retinopathy and nephropathy in Type 1 diabetic females with clinical eating disorders.
Method: Participants were 109 Type 1 diabetic females with clinical eating disorders diagnosed by the structured clinical interview for DSM-IV (bulimia nervosa [n = 70], binge-eating disorder [n = 28], anorexia nervosa [n = 7], and eating disorder not otherwise specified [n = 4]). Retinopathy and nephropathy were screened and demographic, medical, and eating disorder related factors were investigated. To identify the factors associated with each complication, logistic regression analysis was done.
Results: Duration of severe insulin omission and duration of Type 1 diabetes were significantly associated with retinopathy (odds ratios = 1.35 and 1.23, respectively) and nephropathy (odds ratio = 1.35 and 1.21, respectively) in multivariate regression analyses.
Conclusion: Of the various problematic behavioral factors related to eating disorders, the duration of severe insulin omission was the factor most closely associated with the retinopathy and nephropathy of Type 1 diabetic females with clinical eating disorders by multivariate analysis. This finding may help patients who deliberately omit insulin become aware of medical risk of insulin omission. © 2007 by Wiley Periodicals, Inc.

Keywords: binge eating; bulimia; complication; eating disorders; HbA1c; insulin omission; nephropathy; retinopathy; risk factor; Type 1 diabetes

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Introduction
The concurrence of an eating disorder with Type 1 diabetes is not rare and can lead to very serious medical problems. Previous research has reported that the prevalence of clinical eating disorders in young Type 1 diabetic females is 5–15%1–6 and that Type 1 diabetic patients with eating disorders have a poorer metabolic control and a higher prevalence of diabetic-related complications than those without.7–12 However, no reports have given a detailed account of which factors related to eating disorders are the most predictive of development of complications. Clarification of these factors would be useful in the management of these patients.

We have acquired much experience in the treatment of such patients, having treated 109 Type 1 diabetic females with clinical eating disorders, referred from throughout Japan, from 1994 to 2003. The majority were engaged in recurrent binge eating, either bulimia nervosa (BN) or binge-eating disorder (BED).7,8 The primary difference between BN and BED was the regular use of an “inappropriate compensatory behavior” (ICB) to prevent weight gain in BN.13 Our previous study showed that Type 1 diabetic females with BN had poorer metabolic control and higher rates of long-term complications than those with BED.7 The study also showed that those with BED had poorer metabolic control than those without eating disorders.
The findings of our previous study suggest that certain behavioral factors related to eating disorders, such as binge eating and various type of ICBs, are most associated with earlier onset/progression of microvascular complications.

As with diabetes, in which a longer duration is known to lead to a stronger possibility of the development of complications,\textsuperscript{14,15} not only the presence/absence of problematic behaviors but also the duration of behavior may be associated with the development of complications. It seems that the longer the duration of the problematic behavior, the stronger the influence of the behavior leading to complications.

The purpose of the current study was to investigate which features of eating disorders, especially the duration of each problematic behavior related to eating disorders, are associated with the onset/progression of the microvascular complications of Type 1 diabetic females with clinical eating disorders.

### Method

#### Participants

The participants were 109 Type 1 diabetic females with clinical eating disorders (BN, \( n = 70 \); BED, \( n = 28 \); anorexia nervosa (AN), \( n = 7 \); and eating disorder not otherwise specified (ED-NOS), \( n = 4 \)) referred from June 1994 to June 2003 to our outpatient clinic in the Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University for the treatment of eating disorders and Type 1 diabetes. The Diabetes Center at Tokyo Women's Medical University, the most specialized treatment center for diabetes in Japan, referred 79 of these 109 patients.

All participants had been diagnosed with Type 1 diabetes for at least 1 year. Eating disorders were diagnosed by the eating disorder module of the Structured Clinical Interview for DSM-IV (SCID-P).\textsuperscript{16}

#### History of Disordered Eating Behaviors

At the first visit, the participants underwent a detailed clinical interview concerning the history of disordered eating behaviors such as the duration of binge eating, severe insulin omission,\textsuperscript{3,7,8,17–19} self-induced vomiting, and laxative abuse.

Binge eating was defined as (1) eating, in a discrete of time, an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances, (2) a sense of lack of control over eating during the episode.\textsuperscript{13} Insulin omission, self-induced vomiting, and laxative abuse are the most common ICBs of Type 1 diabetic females with BN. The DSM-IV diagnostic criteria for BN recognizes binge eating and ICBs when both occur, on average, at least twice a week for 3 months. However, our experience with these patients has shown that insulin omission in Type 1 diabetic females with BN is usually done more frequently and in a more extreme way. Therefore, for insulin omission as ICB of BN, we have defined severe insulin omission as omission/reduction of at least one-quarter of the prescribed insulin, mainly for the purpose of preventing weight gain.\textsuperscript{8,20}

The patient history of such disordered eating behaviors, especially severe insulin omission, is difficult to determine precisely, because of lapses in the patient's memory and/or refusal/resistance to admitting doing these behaviors. However, as our patient interview done in a long and supportive counseling session (outpatient counseling at first visit\textsuperscript{20,21}), our patients tend to report their history honestly. Information from a letter of introduction from the referring physician is often helpful. We can cross-check the information related to us by the patient with the patient history and the HbA1c course reported by the referring physician. Moreover, about half of these patients undergo inpatient or outpatient treatment after the interview, thus we can make the history more precise as the treatment unfolds, even if the patient reported it inaccurately at first.

#### Blood Glucose Control and BMI

The HbA1c level, as an index of the average blood glucose level over a period of ~3 months, was measured by high-performance liquid chromatography at the first visit to our outpatient clinic. The normal range in our laboratory is 4.4–5.5%. Height and weight were measured and BMI (body mass index) was calculated.

#### Diabetic Retinopathy

The stage of diabetic retinopathy is diagnosed by the following process at the Diabetes Center at Tokyo Women's Medical University School of Medicine.\textsuperscript{15}

Each patient underwent fundus examination through dilated pupils by a specialist in ophthalmology at least once every 6–12 months. Simple retinopathy was defined as the presence of microaneurysms or dot hemorrhages. Patients with simple retinopathy underwent fundus examination every 4–6 months. For patients with avascular area or intraretinal microvascular abnormalities, signs of preproliferative retinopathy, fluorescence angiography was done. Proliferative retinopathy was confirmed by observation of retinal neovascularization.

Because this is the standard process for examining retinopathy in Japan and participants from hospitals other than Tokyo Women's Medical University were also
referred by diabetes specialists, most of our participants had undergone a similar process. The information was obtained from the medical records of the referring doctors.

Advanced retinopathy hereafter refers to preproliferative and proliferative retinopathy.

Diabetic Nephropathy
Nephropathy was diagnosed as the presence of microalbuminuria defined according to the following consensus statement of the American Diabetes Association.

Two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed one of the following diagnostic thresholds; 30–299 mg/24h in 24-h urine collection, 30–299 mg/g creatinine urinary albumin-to-creatinine ratio in spot collection, or 20–199 μg/min urinary albumin excretion in morning collection.

Data Analysis
Ordered logistic regression analysis was performed to analyze the association between each explanatory variable and retinopathy status (non, simple, and advanced retinopathy) allowing the estimation of odds ratio (OR) and corresponding 95% confidence interval (CI). Logistic regression analysis was used to test the association between binary nephropathy status and an explanatory variable.

Curvature of the relationship between the potential risk factors and the log odds of retinopathy or nephropathy was tested by including the square term of the explanatory variable. As no variable showed statistically significant curvature, all variables were included as continuous variables without transformation. Variables with a level of significance less than 0.20 by simple regression analysis were included as explanatory variables in the multiple regression model.

Results
History of ICBs and Binge Eating
Of 109 Type 1 diabetic females with clinical eating disorders, 106 (97.2%) had a current or past history of binge eating, 74 (67.9%) of severe insulin omission, 36 (33.0%) of self-induced vomiting, and 16 (14.7%) of laxative abuse.

The Association Between Each Clinical Characteristic and Retinopathy Status; Non, Simple, and Advanced Retinopathy (Simple Regression Analysis)
Table 1 shows the results of ordered logistic regression analysis. When the duration of Type 1 diabetes was adjusted, duration of severe insulin omission and duration of binge eating were significantly associated with retinopathy status and there was tendency toward an association between age and retinopathy status.

The Association Between Each Clinical Characteristics and Nephropathy Status (Simple Regression Analysis)
Table 2 shows the results of logistic regression analysis. When the duration of Type 1 diabetes was adjusted, duration of severe insulin omission and duration of binge eating were significantly associated with nephropathy status.

Multiple Regression Analysis
Tables 3 and 4 show the results of a multiple regression analysis, in which variables with a level of significance less than 0.20 by simple regression
Duration of severe insulin omission and duration of Type 1 diabetes were significantly associated with retinopathy (Table 3) and nephropathy (Table 4).

### Conclusion

The most notable finding in this research is that the duration of severe insulin omission is the factor most associated, by multiple regression analysis, with retinopathy and nephropathy in Type 1 diabetic females with clinical eating disorders. Although the duration of Type 1 diabetes was an equally important factor associated with retinopathy and nephropathy in these patients, it is a well-established risk factor for diabetic long-term complications.14,15

The design of this study does not ensure a cause-effect relationship between the duration of severe insulin omission and the onset of retinopathy and nephropathy. However, from a clinical point of view, we can speculate that the duration of severe insulin omission is a predictor of retinopathy and nephropathy. First, severe insulin omission generally preceded the onset of microvascular complications. Second, it is quite natural to think that severe insulin omission leads to very poor glycemic control, which in turn leads to microvascular complications. Third, it is highly unlikely that the onset of microvascular complications would lead to the beginning of severe insulin omission. In our experience we have found that after patients develop microvascular complications, some patients have increased motivation toward following their therapeutic regimen, although stopping insulin omission is quite difficult for most of these patients.

It has been reported that insulin omission is common in Type 1 diabetic females and is done for various reasons.17 It was also reported that patients who omitted insulin for weight-management purposes (weight-related omitters) did it more frequent and had poorer metabolic control and a higher rate of complications than non-weight-related omitters.17 In this study, we focused on the most severe insulin omission, omission of at least one-quarter of the prescribed insulin mainly for the purpose of preventing weight gain.

Previous research has reported that Type 1 diabetic patients with eating disorders manifested a higher prevalence of diabetic complications than patients without.7–12 However, no reports have given a detailed account of which behavioral factors related to eating disorders are the most associated

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**TABLE 2. Logistic regression analysis to analyze the association between each explanatory variable and nephropathy status**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR Adjusted for Duration of Type 1 Diabetes (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.08 (0.97–1.20)</td>
<td>0.17</td>
</tr>
<tr>
<td>Age at first visit</td>
<td>11.9 (5.2)</td>
<td>–</td>
</tr>
<tr>
<td>BMI</td>
<td>21.5 (3.2)</td>
<td>0.98 (0.84–1.35)</td>
</tr>
<tr>
<td>HbA1c at first visit</td>
<td>15.1 (6.5)</td>
<td>1.07 (0.88–1.30)</td>
</tr>
<tr>
<td>Duration of Type 1 diabetes</td>
<td>7.7 (4.2)</td>
<td>1.23 (1.04–1.46)</td>
</tr>
<tr>
<td>Duration of binge eating</td>
<td>6.6 (4.2)</td>
<td>1.39 (1.15–1.69)</td>
</tr>
<tr>
<td>Duration of severe insulin omission</td>
<td>2.2 (2.8)</td>
<td>1.23 (1.04–1.46)</td>
</tr>
<tr>
<td>Duration of severe insulin omission</td>
<td>3.7 (2.9)</td>
<td>1.23 (1.04–1.46)</td>
</tr>
<tr>
<td>Duration of self-induced vomiting</td>
<td>0.9 (1.9)</td>
<td>1.14 (0.94–1.38)</td>
</tr>
<tr>
<td>Duration of laxative abuse</td>
<td>0.3 (1.3)</td>
<td>1.17 (0.92–1.48)</td>
</tr>
</tbody>
</table>

### TABLE 3. Multiple regression analysis of factors associated with retinopathy of Type 1 diabetic females with clinical eating disorders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mutually Adjusted OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.10 (0.99–1.22)</td>
<td>0.09</td>
</tr>
<tr>
<td>Duration of Type 1 diabetes</td>
<td>1.23 (1.10–1.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of binge eating</td>
<td>1.15 (0.97–1.36)</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of severe insulin omission</td>
<td>1.35 (1.14–1.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of self-induced vomiting</td>
<td>1.02 (0.84–1.24)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

### TABLE 4. Multiple regression analysis of factors associated with nephropathy of Type 1 diabetic females with clinical eating disorders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mutually Adjusted OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (0.93–1.21)</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration of Type 1 diabetes</td>
<td>1.21 (1.06–1.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of binge eating</td>
<td>1.05 (0.84–1.31)</td>
<td>0.67</td>
</tr>
<tr>
<td>Duration of severe insulin omission</td>
<td>1.35 (1.08–1.69)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of self-induced vomiting</td>
<td>1.01 (0.81–1.26)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Odds ratio for every one unit (year) increase of the variable.
with earlier onset/progression of complications. This study is the first to investigate the relevant factors. It revealed that the duration of severe insulin omission was the behavioral factor most strongly associated with retinopathy and nephropathy.

The most important reason for this finding is probably the devastating effect of severe insulin omission on metabolic control. We previously reported that a higher HbA1c level was most associated with the presence of severe insulin omission in Type 1 diabetic females with binge eating.7 Therefore, for the participants of this study, the period during which the patient was engaged in severe insulin omission corresponded with the period of highest HbA1c. As a higher HbA1c level is a well-established risk factor for diabetic complications,23 it is logical that a longer duration would lead to a higher probability of complications.

There was no significant association between HbA1c at the first visit and microvascular complications. The reason why the duration of severe insulin omission was significant but HbA1c at the first visit was not would seem to be that the former is more representative of a general history of poor metabolic control than the latter. That is, although HbA1c at the first visit shows only one short period (a few months) of metabolic control, the duration of severe insulin omission indicates both extremely poor metabolic control and its duration.

The stoppage of severe insulin omission is critical to slowing the onset/progression of diabetic microvascular complications. However, it is very difficult to stop once omission has become habitual, because severe insulin omission is deeply bound with the maintenance and deterioration of eating disorders. In a previous study, we reported that Type 1 diabetic females with BN who did only severe insulin omission as an ICB showed lower subjective distress on psychological tests than those who did another ICB.8 Low subjective distress does not lead to the motivation necessary for behavioral change.

Eating disorders concurrent with Type 1 diabetes have been reported to be persistent12,24 and very difficult to treat.25–28 Peveler and Fairburn reported that the success rate of treatment for BN patients with Type 1 diabetes was lower than for nondiabetic BN patients.25 We reported our integrated inpatient therapy for Type 1 diabetic females with BN and a good prognosis for them, including a high recovery rate of eating disorder and improvement of metabolic control.20,21 However, long-term inpatient therapy in a specialized unit is necessary.

Rodin et al. stated that “effective strategies for prevention and early intervention for disordered eating in young women with diabetes should be a priority.”9 However, although their brief intervention was associated with a reduction in disturbed eating attitudes and behavior, it was not associated with a significant reduction in either HbA1c levels or deliberate insulin omission for weight control.26 There is an urgent necessity to develop further interventions that have more significant impact on metabolic control and other diabetes-related outcomes.

It is necessary for clinicians who manage young Type 1 diabetic females to be aware that the remarkably poor glycemic control of their patients is often related to the eating disorder and that severe insulin omission is the most influential behavioral factor related to poorest glycemic control and microvascular complications. Clinicians must carefully and in a timely manner inform patients who are engaged in severe insulin omission of the potential risk that this behavior has of causing microvascular complications. Moreover, it is important to give this information beforehand to patients who have not yet engaged in severe insulin omission but who may be vulnerable to such omission in the future, such as young Type 1 diabetic females who are over-concerned with body weight. Clinicians must not let the patients develop a false sense of weight security by the use of insulin omission, but should strive to motivate the patient to administer insulin properly by giving them the necessary information.

The current research involves some limitations. First, some of the data are based on a case history reported by the patients, hence recall bias is difficult to avoid. We designed special methods to minimize the bias, as explained in the “History of disordered eating behaviors” in Method. Another limitation originates from the fact that an eating disorder concurrent with Type 1 diabetes is a rare disease. We have acquired much experience in the treatment of Type 1 diabetic females with clinical eating disorders, but it is very difficult to design a prospective cohort study about this disease. Even with these limitations, we think it is meaningful that this cross-sectional study suggested that severe insulin omission is the most important predictor of retinopathy and nephropathy. A prospective study will be necessary to fully elucidate these issues.

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References


