Clinical Characteristics of Subjects with Sulfonylurea-Dependent Type 2 Diabetes

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**Background:** Even though several oral anti-diabetic drugs (OAD) with various modes of action are replacing sulfonylurea (SU), some patients seem to be dependent on SU for adequate glycemic control. Therefore, we evaluated the clinical characteristics of such patients.

**Methods:** We selected the patients with type 2 diabetes who met following criteria from 2009 to 2014 at Seoul National University Hospital: glycated hemoglobin (HbA1c) was maintained below 7.5% for at least 6 months under small dose of SU (glimepiride ≤2 mg/day or equivalent dose); after discontinuation of SU, HbA1c increased ≥1.2% within 3 months or ≥1.5% within 6 months; and after resuming SU, HbA1c reduction was ≥0.8% or reduction of fasting plasma glucose was ≥40 mg/dL within 3 months. Patients with impaired hepatic or renal function, and steroid users were excluded.

**Results:** Nineteen subjects were enrolled: after averaged 4.8±1.5 months of SU-free period, HbA1c increased from 6.7%±0.4% to 8.8%±0.8% even though adding other OAD such as gliptins. However, HbA1c decreased to 7.4%±0.7% after resuming SU within 2.4±0.8 months. There was no sexual predominance. Despite their old age (67±11 years) and long duration of diabetes (18±10 years), fasting C-peptide was relatively well-reserved (3.9±2.6 ng/mL), and nephropathy was not observed (albumin-creatinine ratio 21.2±16.6 mg/g and estimated glomerular filtration rate 75.8±18.0 mL/min/1.73 m²). Strong family history was also noted (73.7%).

**Conclusion:** Despite hypoglycemia risk of SU, it seemed indispensable for a subset of patients with regard to insulin secretion. Genetic influences would be evaluated.

**Keywords:** Sulfonylurea; Diabetes mellitus; Insulin secretion

**INTRODUCTION**

It is necessary to control serum glucose tightly to prevent microvascular complications in type 2 diabetes mellitus (T2DM), and many guidelines recommend target glycated hemoglobin (HbA1c) less than 6.5% to 7% [1,2]. However, in several studies, intensive glycemic control was reported to increase mortality, without significant reduction in cardiovascular events [3]. Although mechanisms for association between intensive glycemic control and increased mortality are not yet established, one possibility is hypoglycemia [4]. Even though hypoglycemia might not directly cause fatal outcome, it is known to induce hypoglycemia unawareness and to decrease quality of life [5,6]. So not only glucose lowering effects but also risk of hy-
poglycemia should be an important factor in the treatment of T2DM. Among oral anti-diabetic drugs (OAD), sulfonylureas (SU), gliptins and incretin based therapy stimulate insulin secretion, and can cause hypoglycemia.

SU is one of the most prescribed OAD and has strong glycemic control effects. However, it has risk of severe hypoglycemia, and higher mortality has been reported to be associated with SU compared with metformin [7,8]. In addition, several OAD have been developed with different modes of actions, what can replace SU. Therefore, SU is losing ground as mono-therapy, although it is still actively prescribed for combination with other OAD [9]. But we detected that some patients seemed to be extremely dependent on SU for glycemic control. They were very responsive to just small doses of SU and demonstrated stable glycemic control, but when the SU were stopped, glucose levels dramatically deteriorated and were not recovered until SU were resumed. Therefore, we researched those subjects and evaluated their clinical characteristics.

**METHODS**

We retrospectively sorted patients with T2DM under SU from 2009 to 2014 by searching electrical medical record. Among these patients, we selected patients who met following criteria: (1) subjects whose HbA1c was maintained below 7.5% for at least 6 months under small dose of SU (glimepiride ≤ 2 mg/day or equivalent dose); (2) after discontinuation of SU with/without compensation by adding or dosing-up of other OAD, HbA1c increased ≥ 1.2% within 3 months or ≥ 1.5% within 6 months; and (3) within 3 months of SU resuming, HbA1c reduction was ≥ 0.8% or fasting plasma glucose reduction was ≥ 40 mg/dL. Conversion of SU into glimepiride-equivalent dose is presented in Table 1 [10,11]. Exclusion criteria were as follows: impaired renal function (serum creatinine > 1.4 mg/dL or estimated glomerular filtration rate [eGFR] < 50 mL/min/1.73 m²), clinically relevant hepatic diseases, and medications which would affect glycemic control such as glucocorticoid. Other medical history, family history of diabetes mellitus (DM), anthropometric data and biochemical measures were reviewed from the electrical medical record. This study was conducted according to the Declaration of Helsinki and the principles of Good Clinical Practice. The Institutional Review Board of Seoul National University Hospital approved this study, and written informed consent was exempted as it was a retrospective descriptive study (IRB No. 1407-103-596).

**Table 1. Conversion of Sulfonylurea into Glimepiride-Equivalent Dose [10,11]**

| Variable                  | Equivalent dose, mg/day |
|---------------------------|-------------------------|
| Glimepiride               | 1                       |
| Gliclazide                | 80                      |
| Gliclazide-modified release| 30                     |
| Glibenclamide             | 5                       |

**Table 2. Changes in Glycemia according to SU and Concurrent Antidiabetic Medications**

| Variable                      | (A) Baseline | (B) After SU-free period (4.8±1.5 mo) | (C) After SU re-use (2.4±0.8 mo) | Post hoc analysis by Tukey’s multiple comparison test, if repeated measures ANOVA P<0.05 |
|-------------------------------|-------------|--------------------------------------|----------------------------------|-------------------------------------------------|
| FPG, mg/dL                    | 129.2±20.2  | 206.0±47.5                           | 142.4±23.6                       | <0.0001 <0.0001 NS                               |
| Glycated hemoglobin, %        | 6.7±0.4     | 8.8±0.8                              | 7.4±0.7                         | <0.0001 <0.0001 <0.001                           |
| SU as glimepiride-equivalent, mg/day | 1.0±0.6 | 0                                    | 1.3±0.8                         | <0.001 <0.001 NS                               |
| Concurrent antidiabetic agents, mg/day |          |                                      |                                  |                                                  |
| Metformin                     | 1,390±590 (n=17) | 1,400±510 (n=19)                  | 1,290±530 (n=18)                | NA NA NA                                        |
| Pioglitazone                  | 15±0 (n=4)  | 14±3 (n=7)                           | 15±0 (n=4)                      | NA NA NA                                        |
| DPP-4 inhibitors              | 100±0 (n=5) | 94±17 (n=9)                          | 90±22 (n=5)                     | <0.05 <0.05 NS                                  |

Values are expressed as mean±SD.

SU, sulfonylurea; ANOVA, analysis of variance; FPG, fasting plasma glucose; NS, not significant; NA, not applicable; DPP-4, dipeptidyl peptidase-4.

*a Conversion factors in Table 1; *b Sitagliptin or vildagliptin; *c There were 2 cases of saxagliptin, and the 5 mg of saxagliptin was regarded as 100 mg of sitagliptin.
RESULTS

We enrolled 19 patients with T2DM who showed dependence on SU. We confirmed the dependence by statistical evaluation of the changes in glycemia according to OAD changes. As shown in Table 2, concurrent OAD at baseline were metformin (n=17, 89.5%), pioglitazone (n=4, 21.1%), and dipeptidyl peptidase-4 (DPP-4) inhibitors (n=5, 26.3%). For comparisons, we converted doses of various SU into glimepiride-equivalent (Table 1). When the SU was stopped in the subjects, it was compensated by adding or dosing-up of metformin, pioglitazone, and DPP-4 inhibitors in 10 patients. As a result, use of DPP-4 inhibitors significantly increased in the total subjects, according to the repeated measures analysis of variance (P<0.05 for A vs. B) (Table 2). After 4.8±1.5 months of SU-free period, HbA1c increased from 6.7%±0.4% to 8.8%±0.8% (P<0.0001 for A vs. B) even though the increase in DPP-4 inhibitors. The patients resumed SU along with re-reduction in DPP-4 inhibitors (P<0.05 for B vs. C), and then the HbA1c decreased to 7.4%±0.7% after 2.4±0.8 months (P<0.0001 for B vs. C). Therefore, these subjects were dependent on SU and it could not be replaceable by DPP-inhibitors.

Next, we examined their clinical and laboratory characteristics (Table 3). Averaged age was 67±11 years and male was 58%. The mean body mass index (BMI) was 25.1±3.1 kg/m², duration of DM was 18±10 years. There was strong 1st-degree familial history of DM (73.7%). Averaged HbA1c was 6.7%±0.4% and fasting C-peptide was 3.9±2.6 ng/mL. Mean duration of SU use was 12 years, and the 2nd generation of SU, glimepiride and gliclazide comprised about 75% of the prescription.

DISCUSSION

As mentioned in the introduction, position of SU is being weakened these days, because of the concerns about hypoglycemia and potential risk for cardiovascular events. In addition, novel classes of anti-diabetic agents have been developed which could replace the SU. However, we identified there is a subset of patients for whom SU is indispensable. It may be different from SU sensitivity, because the subjects needed just a small dose of SU to maintain or recover acceptable glycemic control and agents other than SU could not replace it (Table 2). As long as we know, this paper is the first description on the SU-dependent patients with T2DM.

According to our study, we found several remarkable clinical characteristics of the subjects with SU dependence. First, there was a strong family history of DM suggesting genetic influences on this feature. For Koreans, reported family history in T2DM subjects over 50 years old was under 40% [12-14]. And, although the mean duration of DM was as long as 18 years, basal insulin secretion estimated from fasting C-peptide was favorable. In Asian T2DM patients with mean BMI of 24 to 25 kg/m², fasting C-peptide was reported from 1.4 to 2.7 ng/mL, with 5 to 9 years of relatively short duration of DM [12,13,15]. In those reports, HbA1c was over 8% and it could be a confounding factor for interpreting C-peptide. Another finding was that diabetic nephropathy was ignorable. Considering their age and DM duration, urine albumin/creatinine ratio was negligible and eGFR was well-maintained [16,17]. In summary, SU-dependent subjects with T2DM in this pilot study had strong genetic background, well-reserved insulin secretion and were free from diabetic nephropathy in spite of long duration of diabetes.

SU binds to the SU receptor 1 (SUR1), leading to closure of ATP-sensitive Kir6.2 potassium channels and insulin secretion.

| Variable | Value |
|----------|-------|
| Age, yr | 67±11 |
| Male sex, % | 57.9 |
| Weight, kg | 65.3±10.6 |
| Body mass index, kg/m² | 25.1±3.1 |
| Duration of diabetes, yr | 18±10 |
| DM in 1st degree family, % | 73.7 |
| Systolic blood pressure, mm Hg | 134.9±14.6 |
| Diastolic blood pressure, mm Hg | 76.2±12.1 |
| Glycated hemoglobin, % | 6.7±0.4 |
| Fasting serum glucose, mg/dL | 129.2±20.2 |
| C-peptide (n=10), ng/mL | 3.9±2.6 |
| Total cholesterol, mg/dL | 150.8±35.3 |
| Triglyceride, mg/dL | 113.5±51.8 |
| Urine albumin/creatinine ratio, mg/g | 21.2±16.6 |
| eGFR, mL/min/1.73 m² | 75.8±18.0 |
| SU duration, yr | 12±9 |
| SU, number (%)/mean dose, mg/day | Glimepiride 8 (42.1)/1.1±0.8, Gliclazide 4 (21.1)/70.0±20.0, Gliclazide modified release 2 (10.5)/30.0, Glibenclamide 5 (26.3)/2.5±1.5 |

Values are expressed as mean±SD. SU, sulfonylurea; eGFR, estimated glomerular filtration rate.
Mutations of Kir6.2 and SUR1 genes are known to induce neonatal diabetes, and some of these patients were demonstrated to successful transfer from insulin to SU [19]. Therefore, as presumed from the strong family history, dependence to SU in T2DM would be related with genetic factors, too. Further genetic studies are proceeding with our subjects, and confirmation of the clinical and genetic characteristics in larger population would be required.

The present study has several limitations. First, the main shortcoming of our study is small number of sample size without a control group. Therefore, our definition of the SU dependence is lack of comparison target, and the description of clinical characteristics is statistically weak. Also, the inherent methodological problem of a retrospective study design is another weakness. However, the strength of this study is using selected patients who not only presented good responsiveness to SU but also became deteriorated with poor glycemic control after discontinuation or replaced by other OAD, which suggests not “good response” but “dependence” to SU. Future prospective, controlled trials are required to confirm these preliminary findings.

In conclusion, despite several concerns including the risk of hypoglycemia, SU is essential for a subset of patients, and the mechanisms may involve genetic influence regarding insulin secretion.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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