EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2015;30:509-513
http://dx.doi.org/10.3803/EnM.2015.30.4.509
pISSN 2093-596X · eISSN 2093-5978

Clinical Characteristics of Subjects with Sulfonylurea-Dependent Type 2 Diabetes

Se Hee Min, Soo Heon Kwak, Young Min Cho, Kyong Soo Park, Hye Seung Jung

Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

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 m^2). 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-

Received: 20 March 2015, **Revised**: 20 May 2015, **Accepted:** 2 July 2015
Corresponding author: Hye Seung Jung
Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-0240, **Fax:** +82-2-762-9662, **E-mail:** junghs@snu.ac.kr

poglycemia should be an important factor in the treatment of T2DM. Among oral anti-diabetic drugs (OAD), sulfonylureas (SU), glinides 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 monotherapy, 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.

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

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 m^2), 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 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 $P<0.05$		
				P for A vs. B	*P* for B vs. C	*P* for A vs. C
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[a]	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)[b]	94±17 (*n*=9)[b,c]	90±22 (*n*=5)[b]	<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 and *post hoc* analysis (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/m^2, 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.

Table 3. Characteristics of the SU-Dependent Subjects (n=19)

Variable	Value
Age, yr	67±11
Male sex, %	57.9
Weight, kg	65.3±10.6
Body mass index, kg/m^2	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 m^2	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.

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/m^2, 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

[18]. 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.

ACKNOWLEDGMENTS

This study was supported by a grant from the Innovative Research Institute for Cell Therapy (A062260).

REFERENCES

1. Standards of medical care in diabetes: 2015: summary of revisions. Diabetes Care 2015;38 Suppl:S4.
2. Ko SH, Kim SR, Kim DJ, Oh SJ, Lee HJ, Shim KH, et al. 2011 Clinical practice guidelines for type 2 diabetes in Korea. Diabetes Metab J 2011;35:431-6.
3. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
4. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 2012;35:1897-901.
5. Williams SA, Pollack MF, Dibonaventura M. Effects of hypoglycemia on health-related quality of life, treatment satisfaction and healthcare resource utilization in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2011;91:363-70.
6. Cryer PE. Banting Lecture. Hypoglycemia: the limiting factor in the management of IDDM. Diabetes 1994;43:1378-89.
7. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J 2011;32:1900-8.
8. Wheeler S, Moore K, Forsberg CW, Riley K, Floyd JS, Smith NL, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia 2013;56:1934-43.
9. Oishi M, Yamazaki K, Okuguchi F, Sugimoto H, Kanatsuka A, Kashiwagi A, et al. Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). J Diabetes Investig 2014;5:581-7.
10. University of Kentuchy. Sulfonylurea dosage conversion table [Internet]. Lexington: University of Kentuchy; c2002 [updated 2006 Aug 13; cited 2015 Mar 12]. Available from: http://www.hosp.uky.edu/pharmacy/formulary/formtools/sulfonylurea.htm.
11. Kimberley Standard Drug List. Switching sulphonylureas [Internet]. Broome: Kimberley Aboriginal Medical Services Council; c2010 [cited 2015 Mar 12]. Available from: http://www.ksdl.kamsc.org.au/dtp/switching_sulphonylureas.html.
12. Jeong SU, Kang DG, Lee DH, Lee KW, Lim DM, Kim BJ, et al. Clinical characteristics of type 2 diabetes patients according to family history of diabetes. Korean Diabetes J 2010;34:222-8.
13. Park JY, Lee KU, Kim CH, Kim HK, Hong SK, Park KS, et al. Past and current obesity in Koreans with non-insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 1997;35:49-56.
14. Koo BK, Kim SW, Yi KH, Park KS, Moon MK. Changing relative contribution of abdominal obesity and a family history of diabetes on prevalence of diabetes mellitus in Korean men and women aged 30-49 years from 2001 to 2010. J Diabetes 2015;7:465-72.

15. Chan WB, Tong PC, Chow CC, So WY, Ng MC, Ma RC, et al. The associations of body mass index, C-peptide and metabolic status in Chinese type 2 diabetic patients. Diabet Med 2004;21:349-53.
16. Lee WJ, Sobrin L, Lee MJ, Kang MH, Seong M, Cho H. The relationship between diabetic retinopathy and diabetic nephropathy in a population-based study in Korea (KNHANES V-2, 3). Invest Ophthalmol Vis Sci 2014;55:6547-53.
17. Rim TH, Byun IH, Kim HS, Lee SY, Yoon JS. Factors associated with diabetic retinopathy and nephropathy screening in Korea: the Third and Fourth Korea National Health and Nutrition Examination Survey (KNHANES III and IV). J Korean Med Sci 2013;28:814-20.
18. Holt RI. Textbook of diabetes. 4th ed. Chichester: Wiley-Blackwell; 2010. p. 460-1.
19. Rafiq M, Flanagan SE, Patch AM, Shields BM, Ellard S, Hattersley AT, et al. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. Diabetes Care 2008;31:204-9.