Fasting insulin levels correlate with the frequency of hypoglycemic events in people with type 2 diabetes on treatment with sulfonylureas: A pilot study

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Abstract:
AIMS AND OBJECTIVES: We aimed to explore whether fasting insulin levels correlate with the risk of hypoglycemia in people with Type 2 diabetes (T2D) receiving sulfonylureas (SUs).

MATERIALS AND METHODS: Our study included 58 individuals with T2D who had been on treatment with SUs, but not insulin, for more than 2 years. Confirmed hypoglycemic episodes during the past year were self-reported by the patients, and a potential relationship of hypoglycemic event frequency with fasting insulin levels was investigated.

RESULTS: Fasting insulin concentrations were found to have a low positive and statistically significant correlation with the number of cases of mild hypoglycemia per year ($\rho = 0.279/P = 0.034$) and a moderately positive and statistically significant correlation with the number of severe hypoglycemic events per month ($\rho = 0.349/P = 0.007$) and per year ($\rho = 0.39/P = 0.002$).

CONCLUSION: Our results suggest that fasting insulin levels might be a predictor of the risk of hypoglycemia in people with T2D on treatment with SUs.

Keywords: Fasting insulin, hypoglycemia, sulfonylureas, type 2 diabetes

Introduction

Diabetes mellitus is a common disease which may cause severe complications and have a negative impact on the quality of life and life expectancy. A number of novel treatments have been established for the management of Type 2 diabetes mellitus (T2D) during the past years. However, sulfonylureas (SUs) are still considered to be the second most prescribed therapeutic class for T2D, following metformin.[1]

SUs are, in general, well-tolerated drugs. Their most common side effect, as demonstrated by both clinical trials and daily practice, is hypoglycemia.[2,3] Several studies taking into account the consequences of hypoglycemic episodes such as road traffic accidents, fall-related injuries, need for hospitalization, and patients’ reduced work productivity showed that hypoglycemia is associated with a significant financial burden not only for the patients and their families but also for the national health systems, as well.[4,5] Furthermore, meta-analyses have pointed toward a significant relationship between severe hypoglycemia and increased risk for...
Severe hypoglycemia is defined as the situation where a patient has low blood glucose concentrations and, at the same time, cognitive impairment requiring external assistance for recovery (to raise glucose levels and regain full consciousness). It is estimated that the incidence of severe hypoglycemic events in people with T2D who are on treatment with SUs is 0.9 events per 100 patient-years. As suggested by the results of the United Kingdom Prospective Diabetes Study, major hypoglycemic events are more frequently observed among patients being on therapy with insulin. A recent meta-analysis demonstrated that among patients treated with SUs, those receiving gliclazide had a lower risk of severe hypoglycemia. Moreover, the GUIDE study proved a significantly lower percentage of documented hypoglycemia (glucose <55 mg/dl) in patients treated with gliclazide modified release (MR) than those receiving glimepiride (3.7% vs. 8.9%, P = 0.003).

SUs have been previously shown to increase fasting insulin levels in individuals with T2D receiving these agents. Whether this increase is related to a greater risk of hypoglycemia has not yet been sufficiently elucidated. The primary aim of this study was to assess the correlation between fasting insulin concentrations and the incidence of hypoglycemia in patients with T2D on treatment with SUs. In addition, we investigated how specific SUs are differentiated in terms of risk of hypoglycemia and their relationship to fasting insulin concentrations.

Materials and Methods

Our data were collected from patients followed up at the diabetes center and the general practice outpatient clinic of Papanikolaou General Hospital of Thessaloniki, Greece, from September 2017 to September 2018. The sample consisted of 58 patients with T2D who had been on treatment with SUs for more than 2 years. Exclusion criteria were the following: glomerular filtration rate <30 ml/min/1.73 m², concomitant treatment with insulin, corticosteroids or other drugs affecting insulin concentrations, history of hepatic failure, and thyroid dysfunction. Patients who agreed to participate had their somatometric profile and full medical history taken.

Blood samples were collected in the morning, following a 12-h fasting period, and subsequently, the samples were centrifuged and both the serum and plasma were maintained at −20°C. Laboratory parameters were determined during the same day of blood sampling. Parameters measured were fasting glucose, glycated hemoglobin (HbA1c), fasting plasma insulin, urea, creatinine, thyroid-stimulating hormone (TSH), and free thyroxine. Direct chemiluminescence immunoassay was used to determine insulin and TSH concentrations, while HbA1c and glucose values were photometrically measured.

Confirmed hypoglycemic episodes during the past year were self-reported by the patients on a retrospective basis by completing the “Hypoglycemia Patient Questionnaire” weighted scoring system of the American Diabetes Association, as previously described. In brief, this questionnaire includes questions regarding the frequency of confirmed hypoglycemic episodes, severe or not, during varying time periods, and the way they are managed. In this present study, a severe episode of hypoglycemia was defined as the one where the patient needed another’s person help to manage hypoglycemia, whereas mild or moderate episode was defined as the one where the patient could not mentally focus and had to stop his or her activity to take a snack, candies, or juice.

Continuous variables were reported as mean ± standard deviation and the corresponding 95% confidence interval. The correlation between SUs’ dosage and various clinical and laboratory parameters was tested using the Pearson correlation coefficient and the Spearman’s (rho) correlation. P < 0.05 was defined as a level of significance. SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the data.

The study conforms with the Declaration of Helsinki and its later amendments. Participants were fully informed about the aim and the nature of the study and written consent was obtained prior to their participation. The protocol of the study was approved by the Ethical Committee of Papanikolaou General Hospital of Thessaloniki (approval number 28-7-2017/1007).

Results

Demographic, anthropometric, and biochemical data of patients recruited in the study are presented in Table 1. About 51.7% (n = 30) of the participants were on treatment with glimepiride (average daily dose 4.6 mg) and 48.3% (n = 28) were receiving gliclazide MR (average daily dose 60.5 mg). Apart from SUs, 93.1% (n = 54) of the participants enrolled were on concomitant treatment with metformin, 39.7% (n = 23) with a dipeptidyl peptidase-4 (DPP-4) inhibitor, 24.1% (n = 14) with a glucagon-like peptide-1 agonist, 15.8% (n = 9) with a sodium-glucose co-transporter-2 inhibitor, and 12.1% (n = 7) with pioglitazone. The most common triple combination in our cohort was metformin, SU, and a DPP-4 inhibitor, with 22.4% (n = 13) of participants receiving such a regimen.
of participants was measured to be 7.1% ± 0.6%, and the mean fasting glucose was 122.3 ± 29.9 mg/dl.

Fasting insulin concentrations were found to have a low positive, statistically significant correlation with the number of annual cases of mild hypoglycemia ($\rho = 0.279/ P = 0.034$) and a moderate positive, statistically significant correlation with the number of cases of severe hypoglycemia per year ($\rho = 0.39/ P = 0.002$) and per month ($\rho = 0.349/ P = 0.007$). For each additional unit of plasma insulin concentrations, cases of severe hypoglycemia were estimated to be by 0.008 ($P = 0.001$) in absolute value per month and by 0.015 ($P < 0.001$) in absolute value per year. However, the mean fasting insulin concentrations were comparable between patients treated with glimepiride and those treated with gliclazide MR ($17.7 \pm 14.3$ mIU/ml, respectively, $P = 0.591$).

Patients receiving glimepiride presented a statistically significant higher median value of episodes of mild hypoglycemia during both the last month ($P < 0.001$) and the last year ($P < 0.001$) than those treated with gliclazide MR [Table 2]. Episodes of severe hypoglycemia were only reported by patients receiving glimepiride, whereas no such episodes were recorded among individuals treated with gliclazide MR.

Glimepiride, in particular, was found to have a strong positive, statistically significant correlation with the number of severe cases of hypoglycemia per year ($\rho = 0.541/ P = 0.002$), as well as, a moderate positive, statistically significant correlation with the number of mild cases of hypoglycemia per month ($\rho = 0.452/ P = 0.012$) and per year ($\rho = 0.452/ P = 0.024$). Furthermore, for every mg increase in the dose of glimepiride, the number of severe hypoglycemic episodes per year was increased by 0.168 ($P = 0.001$) in absolute value. In contrast, gliclazide MR was not shown to be significantly related to any of the above parameters.

The results of the present study demonstrate a positive correlation between fasting plasma insulin levels and the frequency of mild and severe hypoglycemic episodes in patients treated with SUs. They also confirm previous findings according to which various SUs are significantly differentiated with respect to their safety profiles. As shown by a recently published meta-analysis,\textsuperscript{[14]} patients treated with glimepiride are at greater risk for severe and mild hypoglycemia compared to those receiving gliclazide. Our results are in contrast to those of another recent publication by Hope \textit{et al},\textsuperscript{[15]} in which low random nonfasting c-peptide levels were found to correlate with increased glucose variability and hypoglycemia in a cohort of T2D patients. However, this study solely included a population of insulin-treated individuals; therefore, its findings are not applicable to people with T2D receiving oral hypoglycemic agents.

This study has a number of limitations worth noting. The main one is the small sample size, restricting the accurate determination of a fasting insulin cutoff value, that could effectively predict the risk of hypoglycemia in individuals managed with SUs. Despite the differences in the incidence of hypoglycemia observed between patients treated with different SUs, mean fasting insulin levels in the two groups were comparable; this should be primarily attributed to the small number of patients investigated, not providing adequate power...
to detect statistical significance. In addition, SUs are known to reduce crucial neuroendocrine and metabolic counterregulatory defenses during hypoglycemia, including glucagon, catecholamines, and endogenous glucose production responses,[16] suggesting that the mechanisms involved in SU-provoked hypoglycemia are not exclusively insulin mediated.

A large proportion of participants in this study (79.3%) were overweight or obese. Insulin concentrations in people with T2D are dependent on a variety of factors, including BMI, waist circumference,[17] and antidiabetic treatment received.[18] Although the coadministration of other, apart from SUs, antidiabetic agents in our cohort might be a confounder, patients with T2D exclusively treated with SUs are relatively few in the daily clinical setting, a fact that restricted the inclusion of a large number of such patients in our sample. The same limitation applies for body weight as well, considering that only a 10% of people with T2D are within the normal BMI range. Adjustment for confounding effects of these factors in future trials would provide a clearer understanding of the relationship between endogenous insulin production and hypoglycemia. Moreover, self-report of hypoglycemia may not be totally accurate, thus under- or overestimating the exact incidence. Finally, due to its retrospective, cross-sectional design, this study is unable to infer causality.

**Conclusion**

Our work highlights, for the first time in the literature, an association between fasting plasma insulin concentrations and the risk of hypoglycemia, in individuals treated with SUs. This work should be primarily considered as a pilot study, calling for further larger, randomized studies to replicate our findings. From a clinical perspective, estimation of fasting insulin concentrations in this group of patients could possibly work as an easily performed, widely available, and relatively inexpensive tool to predict hypoglycemia. Detection of individuals being at high risk could facilitate effective prevention strategies, such as drug dose adjustment and proper patient counseling.[19]

Despite their disadvantages, SUs are a widely used class of antidiabetic medications. Their low cost, in combination with the vast experience obtained from their use over the years, renders them a valuable choice for T2D management, always in a setting of an individualized and patient-centered therapeutic approach. Besides, recent recommendations for T2D management do not exclude the use of SUs and suggest them when the cost of treatment is a major issue, such as in low-income countries.[20] For the aforementioned reasons, and despite the development of newer and promising treatment choices, the research in the field of SUs is worth to be continued, highlighting novel aspects of an old therapeutic class.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Acharya KG, Shah KN, Solanki ND, Rana DA. Evaluation of antidiabetic prescriptions, cost and adherence to treatment guidelines: A prospective, cross-sectional study at a tertiary care teaching hospital. J Basic Clin Pharm 2013;4:82-7.

2. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev 2001;17:467-73.

3. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: A comparison of glyburide with other secretagogues and with insulin. Diabetes Care 2007;30:389-94.

4. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: A population-based study of health service resource use. Diabetes Care 2003;26:1176-80.

5. Allicar MP, Mégas F, Houzard S, Baroux A, Le Thai F, Augendre-Ferrante B. Frequency and costs of hospital stays for hypoglycemia in France in 1995. Presse Med 2000;29:657-61.

6. Yeh JS, Sung SH, Huang HM, Yang HL, You IK, Chuang SY, et al. Hypoglycemia and risk of vascular events and mortality: A systematic review and meta-analysis. Acta Diabetol 2016;53:377-92.

7. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: Systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533.

8. Frier B, Schernthaner G, Heller S. Hypoglycaemia and cardiovascular risks. Diabetes Care 2011;34:1327-7.

9. Sequist ER, Anderson J, Chilst B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and the Endocrine Society. J Clin Endocrinol Metab 2013;98:1845-59.

10. United Kingdom Prospective Diabetes Study 24: A 6-year, randomized, controlled trial comparing SU, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Prospective Diabetes Study Group. Ann Intern Med 1998;128:165-75.

11. Landman GW, de Bock GH, van Hateren KJ, van Dijk PR, Groener KH, Gans RO, et al. Safety and efficacy of gliclazide as treatment for type 2 diabetes: A systematic review and meta-analysis of randomized trials. PLoS One 2014;9:e82880.

12. Schernthaner G, Grimaldi A, DiMario U, Drzewoski J, Kempler P, Kvaflí M, et al. GUIDE study: Double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004;34:535-42.

13. Greenfield MS, Doberne L, Rosenthal M, Schulz B, Widstrom A, Reaven GM. Effect of sulfonylurea treatment on in vivo insulin secretion and action in patients with non-insulin-dependent diabetes mellitus. Diabetes 1982;31:307-12.
14. Andersen SE, Christensen M. Hypoglycaemia when adding sulphonylurea to metformin: A systematic review and network meta-analysis. Br J Clin Pharmacol 2016;82:1291-302.

15. Hope SV, Knight BA, Shields BM, Hill AV, Choudhary P, Strain WD, et al. Random non-fasting C-peptide testing can identify patients with insulin-treated type 2 diabetes at high risk of hypoglycaemia. Diabetologia 2018;61:66-74.

16. Joy NG, Tate DB, Davis SN. Counterregulatory responses to hypoglycemia differ between glimepiride and glyburide in non diabetic individuals. Metabolism 2015;64:729-37.

17. Matsuba I, Saito K, Takai M, Hirao K, Sone H; Japan Diabetes Clinical Data Management Study Group. Fasting insulin levels and metabolic risk factors in type 2 diabetic patients at the first visit in Japan: A 10-year, nationwide, observational study (JDDM). Diabetes Care 2012;35:1853-7.

18. Ravikumar B, Gerrard J, Dalla Man C, Firbank MJ, Lane A, English PT, et al. Pioglitazone decreases fasting and postprandial endogenous glucose production in proportion to decrease in hepatic triglyceride content. Diabetes 2008;57:2288-95.

19. Koufakis T, Karras SN, Kotsa K. The place of sulfonylureas in the modern treatment of Type 2 Diabetes Mellitus: The end of an era or the beginning of a new one? J Pharmacol Pharmacother 2018;9:40-1.

20. Davies MJ, D’Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.