EDITORIAL

Iatrogenic hypoglycemia and quality of life in patients with type 2 diabetes mellitus

Hipoglucemia iatrogénica y calidad de vida en pacientes con diabetes mellitus 2

Hypoglycemia is a common side effect of treatment of diabetes and is the main limiting factor in achieving glycemic control in patients with type 1 and type 2 diabetes. It is defined as a glucose concentration <70 mg/dl (3.9 mmol/L) by a consensus group in the United States and accompanied by acute symptoms such as dizziness, sweating, tremors, and palpitations. In type 2 DM, hypoglycemia is more prevalent in patients treated with insulin and insulin secretagogues. The primary cause of hypoglycemia is due to intensification of therapy to achieve a lower HbA1C target. In the UKPDS, ACCORD, and ADVANCE studies, the rate of severe hypoglycemia was two to three times higher in the intensively treated patients compared to standard therapy group. The risk of hypoglycemia is greater in older patients, those with longer DM duration, kidney failure, and those with lesser insulin reserve. Dementia is another important risk factor for hypoglycemia, and conversely, recurrent hypoglycemia appears to increase the risk of dementia.

Iatrogenic hypoglycemia represents a significant cause of morbidity and mortality in patients with type 1 and type 2 diabetes. In ADVANCE and ACCORD studies, severe hypoglycemia was associated with significant risk increases for cardiovascular events and mortality. A recent meta-analysis of prospective and retrospective clinical trials demonstrated that severe hypoglycemia doubled the risk of cardiovascular events. In addition, recurrent hypoglycemia can lead to long-term complications such as hypoglycemia associated autonomic neuropathy and cognitive dysfunction, leading to a cycle of recurrent hypoglycemia and hypoglycemia unawareness.

There is a growing body of literature addressing the problem of fear of hypoglycemia, social anxiety and quality of life in young patients with type 1 diabetes, but few studies have addressed the relationship between hypoglycemia and quality of life in type 2 diabetes. These studies have suggested that hypoglycemia can impact on quality of life, productivity and increased worry for patients, poor medication adherence and increased healthcare costs. The cross-sectional study conducted in Spain by Jodar-Gimeno et al. adds and supports existing literature regarding decreased quality of life in patients with diabetes who experience hypoglycemia. They conducted quality of life measures using the Audit of Diabetes-Dependent Quality-of-Life (ADDQoL) and the Worry Subscale of the Hypoglycemic Fear Survey-II (HFS-II) in a large cohort of patients (n=3812) with type 2 diabetes. They then compared the ADDQoL and HFS-II score between patients who experienced hypoglycemia to those who did not experience hypoglycemia in the 6 months prior to inclusion in the study. The study found that 45% of the patients with type 2 DM (n=1711) experienced hypoglycemia in the 6 months prior to inclusion in the study. While the general quality of life measure did not differ between the groups, there was a significant difference in the specific questions in the ADDQoL measures, with patients with hypoglycemia having a worse quality of life than those who did not experience hypoglycemia. Additionally, patients with hypoglycemia also experienced more worry as assessed by HFS-II compared to patients who did not experience hypoglycemia and higher degree of worry was associated with a lower quality of life. The results of this study are similar to others that assessed quality of life in patients with type 2 diabetes and hypoglycemia.

An interesting aspect of this study is that patients with hypoglycemia had more microvascular and macrovascular complications of diabetes. It brings up the question whether they had higher complications due to poor glycemic control from fear of hypoglycemia or whether increased complications, especially microvascular complications such as neuropathy made them more prone to hypoglycemia. It has been hypothesized that the increased worry accompanied by hypoglycemia may in turn have implications for
glycemic control. In the Global Attitude of Patients and Physicians 2 (GAPP2) survey, results from Canada\textsuperscript{19} and the United Kingdom\textsuperscript{22} showed that patients intentionally missed or changed the dose of basal insulin if they experienced a hypoglycemic episode. In another survey performed by Lopez et al.\textsuperscript{16} as part of the United States National Health and Wellness Survey, patients who experienced hypoglycemia had higher HbA1c levels compared to those who did not experience hypoglycemia. While the study by Jodar-Gimeno et al.\textsuperscript{22} does not report specifically on medication adherence or glycemic control, there was a higher prevalence of microvascular and macrovascular complications in the patients who experienced hypoglycemia. These results support the findings from the RECAP-DM study,\textsuperscript{24} where patients with hypoglycemia had higher odds ratio of having macrovascular complications. This may be an indirect indication that poor glycemic control, possibly due to decreased medication adherence from fear of hypoglycemia, may play a role in the development of chronic complications of diabetes in Spain.

Another important aspect of the study by Jodar-Gimeno et al.\textsuperscript{22} was that it assessed health care provider knowledge and attitudes towards hypoglycemia. The study revealed that, while healthcare providers are aware of the risks of hypoglycemia, many of them do not assess quality of life associated with hypoglycemia in these patients and only occasionally changed medication in response to hypoglycemia. This is in contrast to the results from the GAPP2 survey by Leiter et al.\textsuperscript{19} in Canada, where 57% of the people with insulin-treated type 2 diabetes modified their insulin dose after an episode of severe hypoglycemia and 43% modified their dose after experiencing mild or moderate hypoglycemia. However, results from the GAPP2 survey from the United Kingdom\textsuperscript{23} show that only 37% of the healthcare providers discussed insulin dosing with their patients. While the results of these GAPP2 surveys are different to those reported by Jodar-Gimeno et al.,\textsuperscript{22} these studies highlight the importance of the health care providers’ role in the management of hypoglycemia.

Future research studies should explore the potential impact of hypoglycemia on an individual and his/her family members on both cognitive and physical functioning, as well as lifestyle and daily activities, which may have significant negative consequences for quality of life. Activities as disparate as exercise, driving, meals, domestic and social life, recreation activities, holidays, travel and employment may all be affected adversely by hypoglycemia.\textsuperscript{19,25} In addition, the development and/or fear of hypoglycemia requires the need to frequently adjust insulin dosage, or less commonly oral medication, may contribute to ‘diabetes burnout’.\textsuperscript{26} While the symptoms and cognitive consequences of hypoglycemia often resolve rapidly after glucose levels have been normalized, solid evidence in patients with type 1 and type 2 diabetes indicates long-term mood changes, depression, phobia, and permanent cognitive dysfunction in subjects with recurrent severe hypoglycemia.\textsuperscript{26–28}

In summary, hypoglycemia is an important side effect of diabetes treatment and can significantly affect quality of life. The study by Jodar-Gimeno et al.\textsuperscript{22} highlights that in Spain, similar to other parts of the world, hypoglycemia is associated with decreased quality of life. Moreover, it also highlights that health care providers need to be more systematic in assessing how hypoglycemia can affect quality of life and perhaps overall glycemic control and development of long-term complications of diabetes.

References

18. Lopez JM, Annunziata K, Bailey RA, Rupnow MF, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes


P. Vellanki, G.E. Umpierrez*  
Department of Medicine, Division of Endocrinology, Diabetes and Lipids, Emory University School of Medicine, Atlanta, GA, United States

*Corresponding author.

E-mail address: geumpie@emory.edu (G.E. Umpierrez).