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Implication of Findings from International Studies on Hypoglycemia for Management of Diabetes in Insulin-treated Patients in Turkey

Hipoglisemi ile İlgili Uluslararası Çalışmalardaki Bulguların Türkiye'de Insülin Tedavisi Gören Hastalarda Diyabet Yönetimine Etkileri

Rıfat Emral, Ramazan Sarı*, Serdar Güler**,***

Ankara University Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, Ankara, Turkey
*Akdeniz University Faculty od Medicine, Department of Endocrinology and Metabolism, Antalya, Turkey
**Ankara Numune Training Research Hospital, Clinic of Endocrinology, Ankara, Turkey
***Hitit University Faculty of Medicine, Çorum, Turkey

Abstract

Recent estimates indicate that diabetes occurs in 16.5% of the Turkish population, which is in keeping with the increasing global prevalence of diabetes. Following rapid economic growth, increase in life expectancy and changes in lifestyle over the past decade have resulted in the placement of a tremendous cost burden on the Turkish economy by diabetes and associated co-morbidities, representing 20% of overall spending on healthcare.

Maintaining good glycemic control is vital for effective diabetes management. Long-term studies have demonstrated the ability of intensive glucose-lowering strategies to prevent or delay co-morbidities associated with diabetes. However, insulin intensification is commonly associated with hypoglycemia, which is regarded as the most significant barrier to attaining and maintaining good glycemic control. Patients are often unaware of the potential negative impact of hypoglycemia on their long-term health, as well as on daily functions. In addition, hypoglycemia and its associated symptoms or co-morbidities greatly influence adherence and dosing behavior, patients' quality of life (QoL), and significantly affect economic productivity.

The aim of this study is to review the impact of hypoglycemia in patients with diabetes, focusing on the implications of findings from international and Turkish studies for the management of hypoglycemia in Turkish patients.

Keywords: Hypoglycemia; nocturnal hypoglycemia; Turkish diabetic patients; insulin analog; pre-mixed insulin; co-morbidity; quality of life; glucose monitoring

Özet

Son yapılan çalışmalar, Türkiye nüfusunun %16,5'inde diyabet olduğunu göstermektedir ki bu diyabetin artan küresel prevalansı ile uyumludur. Hızlı ekonomik büyümenin ardından, geçtiğimiz on yılda yaşam beklentisinin artması ve yaşam tarzındaki değişiklikler, diyabet ve buna eşlik eden komorbiditelerin Türkiye ekonomisine muazzam bir maliyet yükü getirmesiyle ve toplam sağlık harcamalarının %20'sini oluşturmasıyla sonuçlanmıştır.

İyi glisemik kontrol etkili diyabet yönetimi için hayati öneme sahiptir. Uzun süreli çalışmalar, yoğun glukoz düşürücü stratejilerin diyabetle ilişkili komorbiditelerin önlenmesi veya geciktirilmesinde etkin olduğunu göstermiştir. Bununla birlikte, yoğun insülin tedavisi genellikle hipoglisemi ile ilişkilidir ve bu durum iyi glisemik kontrol elde etmenin ve sürdürmenin önündeki en önemli engel olarak görülmektedir. Hastalar genellikle hipogliseminin günlük faaliyetlerinin ve uzun vadede sağlıklarının üzerindeki potansiyel olumsuz etkilerinin farkında değildirler. Ayrıca, hipoglisemi ve bununla ilişkili semptomlar veya komorbiditeler tedaviye uyumu, dozlama davranışını, hastaların yaşam kalitesini (QoL) ve ekonomik verimliliğini önemli ölçüde etkiler. Bu çalışmanın amacı, hipoglisemi yönetimine dair uluslararası ve Türk çalışmaların bulgularının Türk hastalardaki etkilerine odaklanılarak, diyabetli hastalarda hipogliseminin etkisini değerlendirmektir.

Anahtar kelimeler: Hipoglisemi; gece hipoglisemisi; Türk diyabetik hastalar; insülin analoğu; premiks insülin; komorbidite; yaşam kalitesi; glukoz takibi

Address for Correspondence: Rıfat Emral, Ankara University Faculty of Medicine, Department of Endocrinology and Metabolic Diseases, Ankara, Turkey
Phone: +90 312 508 21 10 **E-mail:** rifatemral@gmail.com **Received:** 24/07/2017 **Accepted:** 18/08/2017

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Introduction

The prevalence of diabetes is increasing worldwide and according to recent global estimates, there will be approximately 642 million adults with diabetes by 2040 (1). The age-standardized prevalence of diabetes in Turkey ranges from 13.7% to 17.0%, with diabetes being more common among women than men (17.2% vs. 16.0%, p=0.008) (2). Recent figures indicate that over 6.5 million adults in Turkey have been diagnosed with diabetes, which represents an increase of 90% over the past 12 years (2). The International Diabetes Federation predicts that the prevalence will rise to nearly 12 million by 2035 (3).

Following rapid economic growth in the past decade, the increase in the life expectancy and changes in lifestyle (2) has resulted in diabetes placing an enormous cost burden on the Turkish economy, accounting for ~1% of the national gross domestic product and approximately 20% of the overall spending on healthcare (4). Therefore, maintenance of good glycemic control by keeping glycosylated hemoglobin levels and pre- and post-prandial blood glucose levels within recommended limits are vital in the management of diabetes (5, 6). However, the management of diabetes cannot follow a 'one size fits all' approach. Rather, treatment customization by balancing the benefits of glycemic control with its potential risks such as the adverse effects of glucose-lowering medications (particularly hypoglycemia), as well as the patient's age and health status among other concerns, is a more viable option (6).

Long-term studies have demonstrated that intensive glucose-lowering strategies (e.g., insulin-based treatment regimens) can prevent or delay co-morbidities such as long-term vascular complications which are commonly associated with diabetes (7-10). However, the most common adverse condition associated with insulin therapy for the management of type 1 and type 2 diabetes mellitus (T1DM or T2DM) is hypoglycemia (11), which is regarded as the most significant barrier preventing patients from attaining and maintaining good glycemic control (12).

Hypoglycemic episodes are usually defined as either asymptomatic, wherein patients are unaware of a current episode, or symptomatic, wherein the hypoglycemia ranges from mild to moderate (non-severe) which patients can self-treat, to severe episodes requiring third-party assistance and which can potentially be life-threatening (13). The aim of this article is to review the impact of hypoglycemia in patients with diabetes, focusing on the implications of data from international and Turkish studies for the management of hypoglycemia in Turkish patients.

Incidence of Hypoglycemia

The development of hypoglycemia, although sometimes asymptomatic, is often initiated by a combination of neurogenic or autonomous (including palpitations, sweating, shaking, hunger) and neurological symptoms (behavioral changes, inability to concentrate, confusion, seizures) (13). The patterns of symptoms vary with individuals and patients can learn to recognize their own pattern of hypoglycemic symptoms (13). Discussing these patterns with a healthcare professional can help in prediction or early recognition of hypoglycemic episodes before they become severe. However, patients often do not report non-severe hypoglycemia, which leads to lack of practical data on the incidence of hypoglycemia and its impact on the management of diabetes in Europe in general, and specifically in Turkey, the Middle East, and North African regions.

The difficulty in estimating the incidence of hypoglycemia is complicated by a high proportion of patients with unrecognized mild to moderate hypoglycemic episodes. Several studies have assessed the incidence of hypoglycemia, including the PREDICTIVE study (14), two European online surveys (15, 16), and two Danish surveys (17, 18). The baseline data from the PREDICTIVE study, which was a large, prospective, international observational study of >19,000 adults with uncontrolled T1DM or T2DM on current treatment and initiating basal insulin, showed an overall incidence of 47.5 episodes and 9.2 episodes of hypoglycemia per patient-year among patients with T1DM and T2DM, respectively. The incidence rates for severe hypoglycemia and nocturnal hypoglycemia were reported as 3.0 and 13.8 episodes, respectively, in patients with T1DM, and 0.8 and 3.4, respectively, in patients with T2DM (14). The baseline frequency of hypoglycemia in insulin-treated patients in the PREDICTIVE study increased with the duration of diabetes, a number of daily injections, and variation in fasting glucose. A similar trend was observed in the Turkish cohort of the study, which included 613 patients with T1DM and 2092 patients with T2DM (14). Another survey recently assessed the self-reported, non-severe hypo-

glycemic episodes in Europe, by recruiting patients via consumer panels, nurses, telephone recruitment, and family referrals to complete four online questionnaires. This survey reported an annual hypoglycemic incidence of 94 episodes per year in T1DM and 21 to 36 episodes per year (depending on regimen) in insulin-treated patients with T2DM (15). A single-center, cross-sectional survey in Denmark, which had recruited successive patients with T2DM with a previously arranged outpatient appointment, assessed patients based on a questionnaire seeking information on the number of hypoglycemic episodes experienced in the past, status of awareness regarding hypoglycemia, and socio-demographic information. This study reported an incidence of <0.5 episodes per patient-year (16). Another survey conducted in Germany, France, and the UK assessed patients via 11 key questions, including their understanding, perceptions, and daily experiences of hypoglycemia, during a 10-min online questionnaire. Also, a cross-sectional questionnaire survey including patients with T1DM from six Danish healthcare institutions evaluated severe hypoglycemic episodes reported during the preceding year, and mild hypoglycemia during the preceding week. Both these studies reported an incidence of severe hypoglycemic episodes of ~1.0-2.4 episodes per patient-year among patients with T1DM (17, 18).

Patients with diabetes regularly experience non-severe hypoglycemic episodes (19), with daytime episodes being more common than nocturnal episodes. Patients are often unaware of non-severe hypoglycemic episodes, and often do not report their self-managed mild to moderate hypoglycemic episodes to their primary care team (15). This makes it difficult to estimate the true incidence of non-severe hypoglycemic episodes. In addition, surveys have shown that nocturnal episodes cause anxiety or worry and concern about the potential negative impact on long-term health (19-21). Furthermore, nocturnal episodes appear to have a greater impact on patients' daily functioning, and the discomfort experienced during a nocturnal episode can carry over to the next day, causing tiredness, irritability, lack of concentration, and fluctuating blood sugar levels (21).

Risk Factors for Hypoglycemia

Risk factors for hypoglycemia are individual-specific and include endogenous insulin deficiency, duration of diabetes, history of hypoglycemia, misinformation or complete lack of awareness on symptoms of hypoglycemia, intensive insulin regimens or stringent glycemic targets, recent moderate or intensive exercise, disrupted sleep patterns, and renal failure (13). Among the risk factors, a high proportion of patients with diabetes reports unawareness or altered awareness about symptoms of hypoglycemia (15) as one factor affecting detection of mild hypoglycemic episodes. In patients with the lack of awareness about hypoglycemia, the risk of severe hypoglycemia increases threefold (16), as mild hypoglycemia, which often precedes severe episodes, is not recognized (13).

Insulin regimens, particularly those with a high number of injections, have also been associated with an increased risk of hypoglycemia (14). In the multicenter, international prospective observational TREAT study containing a Turkish cohort of patients, the incidence of hypoglycemia was higher in patients treated with a basal-bolus regimen compared with a basal-only regimen at six months of treatment (22). The trend remained unchanged over the 2-year study period, with 75% of patients on basal-bolus regimens being injected four times per day (22). Similar long-term findings in the UK cohort were reported by the GAPP2 survey (20). One or more hypoglycemic episodes were reported during the previous month by 29% of patients on basal insulin and 46% on basal-bolus insulin, while 11% and 14% of patients, respectively, reported hypoglycemia during the past year (20).

Impact of Hypoglycemia

Hypoglycemia and associated symptoms or comorbidities greatly impact adherence and dosing behaviors (23), the patients' quality of life (QoL) (19, 21), and significantly affect economic productivity (24-26).

Dosing irregularities

A high proportion of patients with diabetes report being worried about hypoglycemia. Nocturnal episodes cause patients more concern than daytime episodes (19), as they can remain undetected during the night. Many physicians have indicated that they would prescribe intensive insulin therapy more frequently if it were not for concerns over hypoglycemia (23). In addition, there is a high level of fear of hypoglycemia among patients who have previously experienced a severe hypoglycemic episode (27). This fear often results in missed injections and non-

adherence to treatment, as patients attempt to take corrective action to avoid recurrent hypoglycemic episodes (23, 28). A recent single-center survey (n=345) in Turkey showed that patients with T1DM, who had experienced severe hypoglycemia, not only had greater levels of fear and anxiety over recurrent hypoglycemia but also displayed higher treatment adherence behavior than patients with T2DM (29). This behavior may be partially attributed to the fact that patients with T1DM acknowledge that insulin treatment is indispensable for their well-being, resulting in higher levels of treatment control and self-efficacy to avoid potentially life-threatening hypoglycemic episodes than patients with T2DM.

Another study assessing dosing irregularities in response to self-treated hypoglycemic episodes was the GAPP2- a multinational, cross-sectional survey (19). In the UK cohort of the GAPP2 survey, 15-25% of patients either reduced, missed, or mistimed at least one dose of insulin during the month prior to assessment. In the majority of cases, this action was intentional, due to concerns over hypoglycemia (20). Similar results were observed in the Canadian cohort of GAPP2, wherein 23%, 26%, and 13% of patients reported missed, mistimed, or reduced doses of insulin during the month before assessment (28). These patients also cited concern over the risk of hypoglycemia as the most common reason for intentional dose irregularity (28). Many patients have also been reported to intentionally maintain a state of hyperglycemia to give themselves a 'safety margin' to avoid hypoglycemia (17), and to adopt other behaviors associated with avoidance of hypoglycemia.

Health-related quality of life

It has been demonstrated that self-reported hypoglycemic episodes have a strongly negative impact on the QoL of patients with T2DM (30). Patients with symptoms of hypoglycemia have reported significantly higher rates of shakiness, sweating, excessive fatigue, drowsiness, impaired concentration, dizziness, hunger, asthenia, and headache, compared with patients without hypoglycemia (31). The increase in frequency and severity of hypoglycemic symptoms not only had a detrimental effect on patients' rating of their QoL (30-32), but the mere experience of hypoglycemia was also associated with a higher likelihood of developing depression (30).

Economic impact of hypoglycemia

In addition to the impact on patients' QoL and treatment efficacy, the economic impact of hypoglycemia can be categorized into direct costs to treat severe hypoglycemic episodes, and indirect costs that arise due to lost work productivity following severe or non-severe episodes (26). Almost half of the Turkish patients with diabetes are aged between 40 and 64 years (2), and good glycemic control to reduce the risk of hypoglycemia is essential for the economic well-being of patients and their families.

In 2010, it was estimated that the direct cost of managing major hypoglycemia in Turkey was 87 Turkish lira per acute episode (33). Patients have been demonstrated to increase blood glucose monitoring in response to hypoglycemic episodes (19), which may also increase costs associated with the management of hypoglycemia (26).

However, the wider economic impact of severe and non-severe episodes (e.g., absence from work, impacts on QoL and on careers) is largely unknown, as few studies based in Turkey have analyzed this parameter till date. Data from other studies in Europe or the US provide a clear indication of the impact. A recent report of two surveys assessing daytime and nocturnal hypoglycemia in 300 patients with T1DM and T2DM highlighted that daytime and nocturnal hypoglycemic episodes negatively affected patients' sleep and work productivity (26). Nocturnal episodes appeared to have the highest impact on patients, with 29% of respondents going to work late, 16% leaving work early, and 12% missing at least one day of work due to a nocturnal episode (26). Nocturnal episodes, in particular, have been shown to not only affect the individual experiencing hypoglycemia, but also their bed partner (26).

A large UK survey on 861 patients with T1DM and T2DM reported that health-related QoL and work-related productivity decreased with increase in the frequency and severity of hypoglycemia (25). Each episode of nocturnal non-severe hypoglycemia was reported to be responsible for the loss of productivity corresponding to 3.3-7.5 h (24). A European study reported that 10% of patients surveyed had taken time off work due to severe hypoglycemia in the past 12 months (17), while severe hypoglycemia resulted in 34 emergency room visits per 1000 patients with diabetes in the US (34).

Reducing the Risk of Hypoglycemia

More than half of all hypoglycemic episodes can be predicted by regular self-monitoring of blood glucose levels (35). Hence, self-monitoring of blood glucose levels by patients, supported by appropriate training on the signs and symptoms of hypoglycemia, is an important strategy in raising awareness on hypoglycemia and reducing the risk of future severe hypoglycemic episodes. However, a recent single-center, questionnaire-based Turkish study (n=380) showed that patients with T1DM, particularly those with chronic disease, often did not achieve optimal glycemic outcomes and adopted fewer self-management behaviors (36), emphasizing the need for an integrated approach toward monitoring diabetes and patient support. Another study suggested that patients' levels of anxiety and fear of hypoglycemia should be assessed regularly by the primary care team and that patients should be encouraged to record their concerns or hypoglycemic experiences in a diary (29).

Modern long-acting basal insulin analogs such as insulin glargine (IGlar), insulin detemir (IDet), and the ultra-long-acting insulin degludec (IDeg), may reduce the risk of hypoglycemia associated with diabetes. Published clinical evidence has reported that IGlar and IDet have similar, low-risk rates of hypoglycemia. Differences in efficacy among modern basal insulin analogs were demonstrated in 2886 patients of the Turkish cohort in the multinational observational SOLVE study, wherein IDet was associated with a lower risk of minor hypoglycemia than IGlar (37). The findings highlighted the need to customize treatment of individual patients to match their clinical requirements in an environment, which is slow to intensify diabetes treatment to include insulin therapy (13). However, a pre-planned meta-analysis of seven phase III clinical trials comparing IDeg with IGlar on patients with T1DM or T2DM, reported a significantly lower risk of hypoglycemia associated with IDeg compared to IGlar, in the overall pooled population. The reduction in risk of hypoglycemia associated with IDeg was more evident after stabilization of the dose of insulin (>16 weeks) (38), indicating that intensive blood glucose monitoring may be required shortly after initiation of insulin therapy, and also that treatment with insulin analogs was generally a viable option for treatment intensification.

Premixed insulins containing bolus injections of short-acting insulin (basal-bolus) are an easier alternative to the intensification of basal insulin, for patients unable to achieve glycemic targets on basal insulin alone. However, premixed insulin formulations have been associated with a slightly higher degree of hypoglycemia and weight gain than basal regimens (5). This view was recently challenged, when it was demonstrated that switching from a biphasic human insulin premix to a premixed insulin analog could reduce the incidence of hypoglycemia (39). The results from a subgroup analysis showed that such a switch decreased the rates of severe as well as overall hypoglycemia, and improved glycemic control (40). Several patients preferred premixed insulin analogs over premixed human insulin, owing to their more favorable pharmacokinetic profiles, which allowed dosing immediately before or after a meal and helped avoid late postprandial hypoglycemia (41). However, despite premixed insulins offering better glycemic control and improved convenience than basal-bolus regimens, studies still reported varied effects on the incidence of hypoglycemia. PREFER, a study comparing premixed insulin and basal-bolus regimens, demonstrated a lower incidence of severe hypoglycemia for premixed therapy, compared with the basal-bolus regimen, while the rates of non-severe hypoglycemia, weight gain, and nocturnal hypoglycemia were similar (42). In contrast, comparison of premixed insulins and basal insulin therapy demonstrated a higher overall risk of hypoglycemia with premixed insulin analogs (4, 43).

Guidelines on the Management of Hypoglycemia

The treatment and management of T1DM, T2DM, and diabetes-related complications are governed by international guidelines, which are regularly updated (5, 6). In addition, several countries have developed local guidelines to allow for a more tailored and relevant treatment approach. Turkish guidelines for the management of diabetes and its complications are published and regularly updated by the Society for Endocrinology and Metabolism of Turkey (44). These guidelines include specific recommendations for the prevention and management of hypoglycemia (Table 1). One key element highlighted in the Turkish guidelines was the recommendation for increased awareness of, and adherence to, international and local guidelines on the prevention and management of hypoglycemia, in order to minimize the risk of severe and nocturnal hypoglycemia. However, despite the existence of national guidelines (5, 45) and high

Table 1. Turkish (SEMT) recommendations for hypoglycemia management (44).

SEMT Approaches and Recommendations
Hypoglycemia prevention
Education
• After treatment for any hypoglycemic episode, the causes must be reviewed and training should be repeated where necessary
• Training must be provided to individuals with diabetes and family members in a timely fashion to increase knowledge and skills in diabetes self-management
• Individuals with T2DM who use insulin or insulin secretagogues must be assessed for the risk of hypoglycemia
Monitoring
• All individuals with diabetes and family members must be trained in PG measurement to enable them to adjust therapy on the basis of the results
• Individuals with T2DM, especially elderly patients identified with hypoglycemia associated with sulfonylurea use must be monitored for 24-48 h
• In T1DM SMPG must be an integral part of treatment
Treatments and glycemic targets
• Since the risk of symptomatic hypoglycemia and nocturnal hypoglycemia is lower in individuals receiving basal insulin, long-term acting insulin analogs are preferable to NPH in patients at high hypoglycemic risk
• Glycemic targets must be established for pre-pubertal children to minimize hypoglycemia (especially nocturnal):
o Age <6 years: FPG, 100-180 mg/dL; NPG, 110-200 mg/dL; HbA1c, 7.5-8.5%
o Age 8-12 years: FPG fast, 100-180 mg/dL; NPG, 100-180 mg/dL; HbA1c <8.0%
o Age 13-18 near-adult glycemic targets must be achieved: FPG: 80-120 mg/dL; NPG, 90-130 mg/dL; HbA1c, 6.5-7.0%, 48-53 mmol/mol
Nutrition and rescue treatment
• In the individuals with T2DM, the absorption of proteins may increase insulin response without increasing blood glucose concentration. Consequently, proteins must not be used in acute hypoglycemia or nocturnal hypoglycemia
• To avoid recurrent hypoglycemia, after the hypoglycemia has resolved, main meals and snacks must be given at planned intervals. If there is a period of more than one hour between one meal and the next, a snack consisting of 15 g carbohydrate and protein must be given.
• It is preferable that individuals with diabetes do not take alcohol. Consumption of alcohol may cause various health problems in individuals with diabetes with impaired glycemic control, individuals at high risk of hypoglycemia or with uncontrolled hyperlipidemia
• Individuals with T1DM must be warned of increased risk of late hypoglycemia if they take alcohol. To reduce hypoglycemic risk, reduction of alcohol must be exercised and measures such additional carbohydrate consumption, reduction of insulin dose and more frequent SMBG may be applied
Hypoglycemia management
Treatment
• Any carbohydrate source containing glucose may be used in case of hypoglycemia, through ingestion of 15-20 g glucose is preferred
• Fat-containing products (e.g., chocolate or wafer) should not be used
• Response to treatment of hypoglycemia must be obtained within 10-20 min
o Mild hypoglycemia must be treated with 15g oral carbohydrates (4 sugar cubes, or 150 mL fruit juice or lemonade). PG must be measured after 15 min, if <80 mg/dL an additional 15g of carbohydrates must be given
o Moderate hypoglycemia must be treated with 20 g carbohydrates (5 sugar cubes, or 200 mL fruit juice or lemonade). PG must be measured after 15 min, if <80 mg/dL an additional 15 g of carbohydrates must be given
o Severe hypoglycemia must be treated with s.c. or i.m. glucagon injection and emergency medical assistance must be summoned
• The relatives of patients with high risk of hypoglycemia should be taught how to administer a glucagon injection
• An unconscious patient with severe hypoglycemia, which does not resolve with glucagon should receive 10-25 g i.v. glucose (20-50 mL 50% dextrose within 1-3 min or 50-150 mL 20% dextrose within 5-10 min)
Monitoring
• PG levels must be measured one hour after the hypoglycemic event and if necessary additional treatment must be given.

FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; i.m.: Intramuscular; i.v.: Intravenous; NPG: Nocturnal plasma glucose; OAD: Oral antidiabetic drug; PG: Plasma glucose; s.c.: Subcutaneous; SEMT: Society of Endocrinology and Metabolism of Turkey; SMPG: Self-monitored plasma glucose; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

levels of input from primary care and specialist teams, optimal outcomes are often not seen in clinical practice (36). To allow patients and physicians make informed treatment decisions, and to encourage improved monitoring and prevention of hypoglycemia, country-specific data on rates of hypoglycemia and QoL/health-economics impacts are required. Therefore, patients identified to be at s risk of hypoglycemia or those having high levels of fear or anxiety of hypoglycemia should be monitored closely and offered specialist counseling support.

Conclusions and Strategies for the Future

As the prevalence of diabetes increases in Turkey, the Middle East, and North African regions, treatment of diabetes and ultimately treatment intensification with insulin is inevitable. Intensive blood glucose-lowering strategies to attain glycemic control are closely associated with the risk of hypoglycemia, which has a strong negative impact on patient QoL, as well as important health-economic consequences. Altered awareness of hypoglycemia, coupled with a lack of communication or under-reporting of hypoglycemia between patients and physicians has created lack of real-world data on the actual incidence of non-severe and severe hypoglycemic episodes in insulin-treated patients with diabetes and the scale of the burden of hypoglycemia, in clinical practice in Turkey.

A multinational study monitoring the symptoms, management, and prevention of hypoglycemia is required. One such study, the IO-HAT (International Operations Hypoglycemia Assessment Tool) (46), which enhanced the hitherto limited information on the prevalence of hypoglycemia in countries such as Turkey, has recently been completed. The IO-HAT study consisted of two parts that retrospectively and prospectively assessed severe and non-severe hypoglycemia using patient-led self-assessment questionnaires, and explored associations between hypoglycemia, patient co-morbidities, treatment regimen, and QoL. In addition to the IO-HAT study results, which included a large Turkish cohort (>2000 patients), regular patient self-monitoring of blood glucose levels, improved patient awareness regarding symptoms of hypoglycemia, and integrated communication between patients and primary care teams will help in the improvement of hypoglycemia awareness, and reduction in the burden of overall and particularly severe hypoglycemia in insulin-treated patients with diabetes.

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Rifat Emral, Ramazan Sari and Serdar Güler have critically reviewed and contributed to every stage of the manuscript development.

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