Hypoglycemia and its management in primary care setting

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Abstract

Hypoglycemia is common in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) and constitutes a major limiting factor in achieving glycemic control among people with diabetes. While hypoglycemia is defined as a blood glucose level under 70 mg/dL (3.9 mmol/L), symptoms may occur at higher blood glucose levels in individuals with poor glycemic control. Severe hypoglycemia is defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions to assure neurologic recovery. Hypoglycemia is the most important safety outcome in clinical studies of glucose lowering agents. The ADA Standards of Medical Care recommends that a management protocol for hypoglycemia should be designed and implemented by every hospital, along with a clear prevention and treatment plan. A tailored approach, using clinical and pathophysiologic disease

stratification, can help individualize glycemic goals and promote new therapies to improve quality of life of patients. Data from recent large clinical trials reported low risk of hypoglycemic events with the use of newer antidiabetic drugs. Increased hypoglycemia risk is observed with the use of insulin and/or sulfonylureas. Vulnerable patients with T2D at dual risk of severe hypoglycemia and Cardiovascular (CV) outcomes show features of "frailty". Many of such patients may be better treated by the use of GLP-1 receptor agonists or SGLT2 inhibitors rather than insulin. CGM should be considered for all individuals with increased risk for hypoglycemia, impaired hypoglycemia awareness, frequent nocturnal hypoglycemia and with history of severe hypoglycemia. Patients with impaired awareness of hypoglycemia (IAH) benefit from real-time continuous glucose monitoring (CGM). The diabetes educator is an invaluable resource and can devote the time needed to thoroughly educate the individual to reduce the risk of hypoglycemia and integrate the information within the entire construct of diabetes self-management. Conversations about hypoglycemia facilitated by a healthcare professional may reduce the burden and fear of hypoglycemia among patients with diabetes and their family members. Optimizing insulin doses and carbohydrate intake, in addition to a short warm up before or after the physical activity sessions may help avoiding hypoglycemia. Several therapeutic considerations are important to reduce hypoglycemia risk during pregnancy including administration of rapid-acting insulin analogs rather than human insulin, pre-conception initiation of insulin analogs, and immediate postpartum insulin dose reduction.

Keywords: Diabetes, Diabetes Self-management Education, Hypoglycemia, hypoglycemia unawareness Pregnancy, Continuous glucose monitoring (CGM), Technology

Contents

Hypoglycemia is common in patients with type 1 (T1D) and type 2 diabetes (T2D) and constitutes a major limiting factor in achieving glycemic control among people with diabetes.[1]

1. Defining hypoglycemia for clinical practice and clinical trials

The American Diabetes Association (ADA) defined hypoglycemia in diabetes as any episode of an abnormally low plasma glucose concentration that exposes the individual to potential harm. [2] This non-numerical definition was based on the facts that glycemic thresholds for responses to hypoglycemia vary among individuals and within the same individual. Also, there is no specific glucose concentration that defines hypoglycemia in diabetes.

Hypoglycemia is an important safety outcome in clinical studies of glucose lowering agents. It is also frequently defined as a secondary outcome in treat-to-target studies comparing different insulins – whereas the same glycemic target is striven for in all arms, and the hypoglycemia rates are compared.

It is difficult to compare the frequency of hypoglycemic events in different clinical trials due to differences in interventions and methods of data collection, as well differences in definition for hypoglycemia. Additionally, there are limited data regarding background risk of hypoglycemia, and patients with repeated episodes of hypoglycemia are often excluded from clinical trials.

The ADA aimed to provide uniform definitions of glucose levels to be reported in clinical trials. In a recent publication they proposed three levels of definition for hypoglycemia in clinical trials.[1]

Level 1 - A glucose alert value of 3.9 mmol/L (70 mg/dL) or less. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study.

Level 2 - A glucose level of <3.0 mmol/L (<54 mg/dL) is sufficiently low to indicate potentially serious, clinically important hypoglycemia.

Level 3 - Severe hypoglycemia, as defined by the ADA, denotes severe cognitive impairment requiring external assistance for recovery.

A questionnaire may be used by the primary care provider to grade hypoglycemia (Appendix I).

Despite the ADA effort, there are currently no approved guidelines for how hypoglycemia should be captured in clinical trials. Common existing measures to capture hypoglycemia include the use of patient diaries; with some trials mandating self-monitoring of blood glucose (SMBG). Some studies incorporate the use of continuous glucose monitoring (CGM) where only glucose levels under a predefined threshold for >20 minutes are considered. Larger studies, particularly cardiovascular outcome trials (CVOT), in which hypoglycemia is merely a safety concern, have limited event collection to patients' recall once every 3-6 months. Clearly, this level of heterogeneity alters the rate of episodes captured – as can be seen in the table.

Severe hypoglycemia is defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions to assure neurologic recovery.[3] Although this seems quite undisputable, unfortunately this is not always the case. For example, in the DEVOTE (Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) clinical study, only events of major hypoglycemia were adjudicated.[4] Events that may be proposed as major hypoglycemia by study investigators, but are not confirmed as such, may include cases in which the person experiencing hypoglycemia was offered help due to politeness without actual neurological deterioration, or events of very low glucose which are erroneously reported as hypoglycemia.

In spite of the aforementioned limitations, in-depth analysis of the baseline characteristics of patients experiencing hypoglycemia in clinical trials, as well an analysis of the precipitating

factors for the events may improve our understanding of the predictors of hypoglycemia and means to prevent it.

The major predictors of hypoglycemia emerging from clinical trials are insulin use, particularly short acting insulin, and the use of insulin secretagogues such as sulfonylurea. Additional risk factors include impaired kidney function with low glomerular filtration rate (eGFR) due to reduced renal gluconeogenesis and reduced insulin clearance, and long-standing diabetes – which is associated with more severe endogenous insulin deficiency.[5,6] A previous history of hypoglycemia is recognized as risk factor for future episodes of severe hypoglycemia and recurrent events.[7] Body mass index (BMI) and baseline HbA1c have not been consistently shown to be associated with either increased or decreased risk of hypoglycemia.[6]

2. Signs and symptoms of hypoglycemia

According to the ADA Standards of Medical Care, symptoms of hypoglycemia may include, but are not limited to: confusion, hunger, irritability, shakiness, and tachycardia. It is critical to understand that while hypoglycemia is initially defined as a blood glucose level under 70 mg/dL (3.9 mmol/L), symptoms may occur at higher blood glucose levels in individuals with poor blood glucose control. [1]

In individuals with long standing diabetes or widely fluctuating blood glucose levels, there may be no hypoglycemia symptoms, even with much lower blood glucose levels, a condition known as impaired awareness of hypoglycemia.[8]

3. Cognitive effects of Hypoglycemia

The association between hypoglycemia and cognitive dysfunction and/or dementia among people with diabetes has been examined in clinical studies. Several studies have examined if there was a correlation between the effects of repeated hypoglycemic episodes and

acceleration of cognitive dysfunction in patients with diabetes. A recent prospective long-term study in 11,495 individuals with T2DM found that neither severe nor non-severe hypoglycemia were associated with an increased risk for cognitive dysfunction.[9] These findings were similar to those from the ACCORD MIND trial (Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes) and the ADVANCE study (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation).[10,11] In those two large trials there was no direct correlation between severe hypoglycemia and cognitive dysfunction.[10,11]

Cognitive decline has been associated with an increased risk of subsequent hypoglycemic events in T2DM patients regardless of their assignments to standard of care or intensive glycemic control. [11] In addition, some cross-sectional population-based studies in older patients with T2DM have demonstrated an association between a previous history of severe hypoglycemia and poor cognitive function later in life.[12,13] Furthermore, a recent study looked at the effects of severe hypoglycemia on cognitive function. In this cohort of patients followed between 2011 and 2013, people with severe hypoglycemia were found to be 1.51 times more likely to have more mild cognitive impairment and almost 2.35 times more dementia compared to those without severe hypoglycemia . The authors indicated that the exact mechanisms were not clear, but reported that predisposing factors included poor medication taking behavior and less blood glucose monitoring. The authors urged primary care providers to consider screening for history of hypoglycemia in patients with diabetes.[14]

practical Implications: The presence of a hypoglycemia risk in a patient should prompt providers to reevaluate their current diabetes medication regimen with the aim to reduce and prevent hypoglycemia, particularly in people with diabetes and cognitive dysfunction.[14.] This also brings to light concerns of a bidirectional relationship between cognitive dysfunction,

possibly increasing hypoglycemic events, and hypoglycemia, possibly increasing cognitive dysfunction.[15]

4. Impaired Awareness of Hypoglycemia

Repeated hypoglycemic events may induce the development of impaired symptomatic warnings and diminished ability to perceive the onset of hypoglycemia, a condition known as "impaired awareness of hypoglycemia" (IAH).[16]

The exact etiology of IAH syndrome remains unknown. However, a proposed mechanism is a decrease in autonomic (sympathetic neural and adrenomedullary) response to hypoglycemia, with resulting loss of neurogenic symptoms such as tremulousness, sweating, palpitations, anxiety, and hunger.[17,18]

The impaired counterregulatory mechanisms of defense against declining plasma glycemia in T1D have been reviewed in detail.[19,20] The blunted epinephrine response, which is a sign of decreased autonomic, sympathetic neural as well as adrenomedullary response, is particularly involved in the clinical syndrome of IAH.[21] Recent hypoglycemia causes a shift towards lower glycemic thresholds for symptomatic autonomic responses to subsequent hypoglycemia [22,23] arising a vicious cycle where hypoglycemic events lead to more episodes of hypoglycemia, which describes the concept of hypoglycemia-associated autonomic failure (HAAF).[20] This mechanism causes a higher recurrence of severe iatrogenic hypoglycemia.[24] Notably, the frequent exposure to hypoglycemia ought to make the health care provider suspect the syndrome of IAH development. This condition affects a significant number of adults with T1D[25], with a large hospital-based clinic population study reporting that 19.5% of patients with T1D have IAH despite advances in insulin delivery.[26] IAH is also associated with a two-fold increase in less severe hypoglycemia events, and in up to six-fold increased incidence of severe hypoglycemia.[27,28] Frier and colleagues compared 19 patients with T1D with normal

hypoglycemia awareness and 19 patients with IAH (matched for glycemic control, duration of diabetes age and sex). The researchers found a seven-fold increased frequency of severe hypoglycemic events and twice all the episodes of hypoglycemia in the IAH group.[29]

Generally, patients with T1DM have approximately ten-fold higher frequency of iatrogenic hypoglycemia compared to patients with T2DM with long-duration and intensive insulin therapy (62 to 170 Vs. 3 to 73 episodes per 100 patient/years, respectively).[30-34] Of interest, in the DCCT 65% of the intensively treated patients with T1DM experienced severe hypoglycemia, whereas severe hypoglycemia occurred in only 11.2% of patients with T2DM treated with insulin in the UKPDS. Nonetheless, the UKPDS data could have underestimated the frequency of iatrogenic hypoglycemia in T2DM because participants were newly diagnosed and glycemic control was not as rigorous as in the DCTT. However, researchers in the UKPDS, similarly to the DDCT, found that hypoglycemia was the main limitation in achieving more aggressive glycemic control over the study interval.[35,36]

Clinical experience suggests that in addition to progressive insulin deficiency, iatrogenic hypoglycemia occurs more frequently in patients with a long duration of diabetes. Indeed, Cryer and collaborators showed that glucose counter regulation (mainly glucagon response) was virtually absent in patients with longstanding insulin-treated T2DM, and those subjects were at risk for developing IAH, similarly to patients with T1DM.[37] These findings support the clinical observation that iatrogenic hypoglycemia becomes a major issue, especially in patients with longstanding insulin-deficient T2DM.[35,38,39]

Using data from insulin-treated 122 patients with median age 67 years and a median duration of diabetes of 15 years, Frier and collaborators have evaluated the prevalence of IAH in T2DM. Using a specific questionnaire, the authors found that the prevalence of IAH was 9.8%, and that the incidence of severe hypoglycemia was 17-fold higher in the subgroup with IAH compared

with those without IAH. The same population prospectively evaluated for one month, patients with IAH showed a fivefold higher incidence of biochemical hypoglycemia compared to those without IAH. Overall, these data suggest that the development of IAH should be evaluated in patients with T2DM treated with insulin .[40]

Several studies have shown that the rigorous avoidance of iatrogenic hypoglycemic events can reverse hypoglycemia unawareness and improve the impaired glucose counter regulation in during a period as short as 2 to 3 weeks, providing robust support to the concept of hypoglycemia-associated autonomic failure (HAAF) in T1D.[41-43] In addition, relaxation of glycemic targets for 2 to 3 weeks, in patients with T1DM may result in improvement of hypoglycemic unawareness[41-43]

Practical Implications: Clinical practice recommendations suggest that patients with IAH may benefit from frequent glucose monitoring, in particular of the use of real-time continuous glucose monitoring (RT-CGM).[44] The use of RT-CGM reduces severe hypoglycemia in patients with T1DM and IAH as well as increases the time in range (time spent in normoglycemia) compared to self-monitoring of capillary blood glucose.[45] RT-CGM in adolescents with T1DM also seems to improve the epinephrine response and induce higher adrenergic symptom scores to induced hypoglycemia when compared to the control group when tested using hyperinsulinaemic hypoglycemic clamps.[46] This data support the use of real-time CGM in patients with impaired awareness of hypoglycemia, although further studies are warranted.
See Appendix I for more about grading and awareness of hypoglycemia.

(5) 9. Disease heterogeneity and severe hypoglycemia risk

Severe hypoglycemia is almost always related to insulin and sulfonylurea therapy, in both T1DM and T2DM.

Clinical Stratification. Hypoglycemia risk is three-times higher in patients on insulin secretagogues (sulfonylurea) and five-times higher for those on insulin.[47]

Risk Stratification by Disease Origins. Genetic mutations can cause neonatal diabetes mellitus (NDM) and Maturity Onset Diabetes of the Young (MODY), and both can be treated by using sulfonylureas, however NDM cases are not prone to severe hypoglycemia despite needing high-dose sulfonylureas.[48] HNF1A/MODY and HNF4A/MODY, are hypersensitive to sulfonylureas [49], although the use of glinides can ameliorate severe hypoglycemia risk[50] Impairment of glucagon secretion in pancreatitis and cystic fibrosis may explain a predisposition to hypoglycemia plus severe hypoglycemia, especially in the former.[51]

Risk Stratification by Clinical Features. Risk factors for severe hypoglycemia in T2D include both insulin deficiency and islet autoantibodies, both potentially related to disease-clusters within T2D as well as the increased risk that such cases are on insulin or sulphonylureas.[52,53] Other contributing factors to severe hypoglycemia include senility, irregular mealtimes, malnutrition, low educational level, ethnicity, polypharmacy, previous hypoglycemia, impaired awareness of hypoglycemia and comorbidities (e.g. impaired renal function, congestive heart failure, cognitive impairment and frailty)[54,55]

Risk Stratification by Hypoglycemia. While severe hypoglycemia is a risk factor for cardiovascular disease, reduced glycemia is protective[56]

Practical Implications: A tailored approach, using clinical and pathophysiologic disease stratification, can help individualize glycemic goals and promote new therapies to improve life quality and survival of patients. [57,58]

5. Association of hypoglycemia and CV outcomes and the role of frailty

Hypoglycemia is associated with adverse cardiovascular (CV) outcomes and all-cause mortality in patients with T1DM and T2DM.[56,59,60] This association is particularly strong in the context of severe hypoglycemic events, while less severe episodes of hypoglycemia seem to contribute rather little to this association. It is typical that following a severe hypoglycemic event, there is an approximate two-fold increased risk for all-cause mortality, heart failure events and major adverse CV event (MACE) including non-fatal myocardial infarction, non-fatal stroke and CV death.

Whether the association between hypoglycemia and poor health outcome represents a causative link or a simple association, is a matter of ongoing debate. [56,59,60] Clearly, a causative connection is suggested in patients with severe hypoglycemia and the acutely related increased risk of cardiac arrhythmias, hypokalemia, hypertensive crisis, increased platelet activation and endothelial dysfunction.[61-64] However, there has been reported a two to threefold excess risk of severe hypoglycemia occurring after a non-fatal myocardial infarction, acute coronary syndrome, stroke, or hospitalization for heart failure . This bidirectional relationship between severe hypoglycemic events and CV outcomes suggests, or is at least compatible with the notion, that there may be a common multimorbid "frail" T2DM phenotype of patients (as *e.g.* defined by a high Charlson Comorbidity Index) who are susceptible to both of these events. Thus, severe hypoglycemia in many, if not most, instances—rather than being causative of CV death, heart failure events, or all cause death events—may simply be indicative of "frail" patients who are at higher risk of both outcomes likely due to a multitude of coexisting risk factors. Indeed, these types of patients more often develop heart failure after a first CV event and are more likely older, have advanced kidney disease a longer duration of diabetes, and very often are treated with insulin and with higher doses of insulin. Notably, use of sulfonylureas is rather infrequent in those patients. Conversely, their multi-morbidity is reflected by much

higher use of CV medications, especially of antiplatelet therapies, beta-blockers, diuretics, and statins. Of note, HbA1c concentrations of these patients do not seem to differ from those without dual risk or even show a trend to higher levels.[59,60]

Practical implications. Avoiding hypoglycemia, especially the severe form is a high priority goal in the treatment of all people with diabetes. It is important to recognize that vulnerable patients at dual risk of severe hypoglycemia and CV outcomes show many features of multimorbidity or "frailty". In many circumstances such patients may be better treated by antidiabetic drugs not associated with hypoglycemia such as DPP4-inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors rather than insulin or insulin secretagogues (sulfonylurea). Adjusted and more relaxed targets for HbA1c lowering should be considered if insulin therapy is needed. [65,66]

(6) Prevention of hypoglycemia

Prevention of hypoglycemia is crucial and should be considered in every diabetes management plan. CGM is a very important tool to assess diabetes therapy and predict incipient hypoglycemia. People with diabetes treated with insulin or sulfonylureas need to obtain proper education allowing them to understand the situations that may increase the risk of hypoglycemia.

(6.1) <u>The role of the diabetes educator in hypoglycemia detection and prevention</u>

It is evident that diabetes self-management education and support (DSMES) is a crucial component of diabetes care. Within the context of DSMES, delivering hypoglycemia prevention and management education to healthcare professionals and individuals with diabetes is

essential to reduce the risks and improve outcomes. It is recommended that individuals with diabetes be referred to an accredited or recognized diabetes education program with the overall objective to aid the individual in creating lasting positive self-care behaviors, increase problem solving, and shared decision making with all health care professionals involved in that patients' care.[67]

The National Standards for Diabetes Self-Management Education and Support are designed to define quality DSMES and assist those who provide DSMES services to implement evidence-based DSMES. Standard 6 focuses on the curriculum required and highlights the key topics that must be in place within all education programs. The following core content areas demonstrate successful outcomes and are required to be reviewed to determine which are pertinent within every education session:

- Diabetes pathophysiology and treatment options
- Healthy eating
- Physical activity
- Monitoring and using patient generated health data
- Preventing, detecting, and treating acute complications including hypoglycemia, hyperglycemia, diabetes ketoacidosis, sick day guidelines, and severe weather or situation crisis and diabetes supplies management and chronic complications including immunizations and preventive eye, foot, dental, and renal examinations as indicated per the individual participant's duration of diabetes and health status
- Healthy coping with psychosocial issues and concerns
- Problem solving[68]

Practical Implications: There are various methods to deliver information regarding hypoglycemia prevention and successful treatment. However, the core components and concepts should include comprehensive information, with the therapeutic objectives aiming to reduce the hypoglycemic episodes including the severity and duration without increasing the

possibility of hyperglycemia and the higher HbA1c levels.[68] See table 2 for the core concepts that include education about hypoglycemia.

The Diabetes Self-management Education and Support in Type 2 Diabetes joint position statement identified four critical times to assess, provide and adjust diabetes self-management education and support (DSMES): 1) when there is a new diagnosis of diabetes; 2) annually for health maintenance and prevention of complications; 3) when new complicating factors influence self-management and 4) when transitions in care occur.[69] Given the details and time required for proper diabetes self-management education and support, the diabetes educator is an invaluable resource and can devote the time needed to thoroughly educate the individual to reduce the risk of hypoglycemia and integrate the information within the entire construct of self-management.

6.2 Meal planning to reduce the risk of hypoglycemia

There is no one meal plan that has been proven to reduce the risk of hypoglycemia. In fact, it is widely accepted that not a single meal plan will fit the needs of all individuals with diabetes. The key components to reducing the risk of hypoglycemia is having a good understanding of carbohydrate and their appropriate portion sizes in the context of each person's daily meal preferences.

Practical Implications: Individualized diabetes-focused medical nutrition therapy provided by a registered dietitian nutritionist (RDN) is recommended for all people with diabetes at least annually. [70]

(7) Hypoglycemia burden on care givers and families:

A report from a survey titled "Home Alone, family caregivers providing complex chronic care" shed light on the heavy involvement of caregivers of patients with chronic disease, including

diabetes in their care. Ninety-one percent of caregivers are directly responsible for ordering, picking up and paying for patients' medication, 83% administer patient medications, 31 % monitor for potential side effects, 78% perform various medical and nursing tasks including injections and 32 % use meters and monitoring. For all these tasks shockingly, 61% of these caregivers were self-taught. Among the qualitative data, caregivers pointed out diabetes, monitoring as difficult and daunting tasks. This study is a real-life example of the scope of involvement of caregivers in diabetes management.[71]

Hypoglycemia burden is not restricted to the patient with diabetes. In a multinational cross-sectional study that surveyed 4300 family members of people with type 1 or type 2 diabetes on insulin and/or secretagogues for more than or equal to 12 months uncovered significant levels of anxiety and burden. Sixty-six percent of family members reported thinking about the hypoglycemia in their family member with diabetes at least monthly, and 64% felt worried or anxious about their relative with diabetes' risk for hypoglycemia.[72]

Practical implications: Conversations about hypoglycemia, facilitated by a healthcare professional, may reduce the burden stemming from the worry about hypoglycemia and hypoglycemia risk in family members of patients with diabetes. While training family members and caregivers on how to use intramuscular and /or subcutaneous glucagon kits may have been a hindrance in the past, the recent introduction of the easier to administer nasal glucagon is likely to improve rates of utilization of this rescue therapy.

(8) Hypoglycemia Treatment

Administration of fast-acting carbohydrates should be the first line of treatment at blood glucose levels of 70 mg/dL (3.9 mmol/L) or less. Primary care providers should always alert people with diabetes about the importance of fast-acting carbohydrates which include pure glucose in the form of tablets or gels or glucose-containing beverages. Importantly, ingested

fats may delay the acute glycemic response and protein may increase insulin more than increasing blood glucose levels (ADD REF). Providers should always keep in mind the recurrence of hypoglycemia especially when using intermediate or long acting insulin or sulphonylureas.

Glucagon may also be used for the treatment of hypoglycemic episodes in case of inability to eat by mouth. However, proper education of people with diabetes and their custodial care is important to assure appropriate use of SC or nasal glucagon.[1]

(9) Technology and Hypoglycemia

In recent years the usage of technology in diabetes is increasing. While in the past, diabetes technology was attributed only to T1D, use in T2DM is increasing. Moreover, in the 2019 ADA Standards of Medical Care, there is a new section on technology for the management of patients with diabetes. In addition, the UK, position statement for the use of technology in T1DM has recently given technology a well-deserved spotlight . The technology is a tool for the health care provider to work towards achieving glycemic control such that hypoglycemia events are reduced or prevented.[73,74]

Continuous subcutaneous insulin infusion/pump therapy (CSII) remains a standard of care in the treatment of T1DM and is able to demonstrate a reduction in hypoglycemia events mostly in patient with frequent hypoglycemia. An important feature of CSII is the basal infusion which, when carefully determined is a minority of the administered insulin and prevents hypoglycemia when food intake is delayed or reduced. The bolus calculator also adds value in providing a better adjustment of insulin dose for correction of hyperglycemia and mealtime carbohydrate intake. In order to achieve its full impact, a structured education should take place alongside with carbohydrate counting.[75-78]

While in T2DM patients there is a steady increase in the use of CSII, most data relate to the improvement of overall glycemic control rather than its effect on hypoglycemia.

Continuous glucose monitoring (CGM) is becoming standard of care in the management of T1DM and helps to unveil episodes of diurnal and nocturnal hypoglycemia. The frequency of CGM detected hypoglycemia events can reach several-fold higher than that of self-reported hypoglycemia by BGM in insulin-treated patients.[79]

Even in T2DM patients, a short period of CGM use (72 hours), there was a two-fold increase in the detection of hypoglycemia events as compared to self-monitored blood glucose (SMBG) .[80]

In T1DM patients using CGM vs. SMBG with two insulin regimens (analogs vs human) over three days also demonstrated the advantage of CGM, here, the ability to detect hypoglycemia 17 times more frequently.[81]

In patients with T1D, extensive data show the benefits of CGM in frequency and in reducing time spent with hypoglycemia.[82] Bolinder et al. showed that in T1D patients well controlled with HbA1c below 7.5% that CGM can reduce the time in hypoglycemia without increasing HbA1c. Interestingly, the reduction of hypoglycemia was in early phase of the trial and was maintained during the whole trial period.[83] When comparing professional continuous glucose monitoring is-CGM) with real-time continuous glucose monitoring (RT-CGM) in a head to head clinical trial there was a greater magnitude of hypoglycemia reduction with RT-CGM, and there was a minor effect of is-CGM on hypoglycemia when compared to baseline.[84]

Data from several RCT of RT-CGM displayed the benefits of CGM and safety regarding hypoglycemia when using either MDI or CSII and even in those with impaired hypoglycemia awareness.[85-90] In Type 2 patients, a reduction of hypoglycemia events while using is-CGM was also seen without increasing HbA1c.[91] Trend arrows on the CGM can trigger an action to prevent a hypoglycemia event and this valuable information needs to be taught to the patients.[92,93]

The international consensus on the use of CGM was able to standardize the way glucose metrics should be presented. The definition and assessment of hypoglycemia in Clinical Studies are well described[94] with recent consensus of "Time in Range" (TIR) and for "Time Below Range" (TBR) are set with a cutoff of 70-54 mg/dl (3.9 – 3 mmol/L) (level 1) and below 54 mg/dl (3 mmol/L) (level 2 hypoglycemia). The percent of time below 70 mg/dl (3.9 mmol/L) recommendation is different for the general population of patients with diabetes and for Type 1 patients during pregnancy (below 4%) versus older/high risk patients (below 1%).[95]

The ability of CGM devices to communicate with insulin pumps has opened the path for closed loop systems. One important milestone is the suspension ability where the CSII is suspended when the glucose is reaching a threshold (that is set by the healthcare provider) and later on the development of the predictive before low suspension.[96] This feature has proven itself also in the real-world environment with the reduction of hypoglycemia events.[97]

With the advancement of technology and closed loop systems many of the glucose metrics are improving including among them the number of hypoglycemic events and their magnitude. Even in people at high risk for hypoglycemia, there is currently only one FDA approved system and the data were consistent with those findings.[98-100]

While the cost and reimbursement issues may prevent the use of CGM, health care providers need to remember that even with more simplified technology hypoglycemic events can be reduced without increasing HbA1c. Rossi et al reported that with a short messaging systems (SMS) communication system (DID-Diabetes interactive Diary), which has a carbohydrate/bolus calculator, patients can be well informed as a substitute for traditional education.[101]

We must remember that technology has limitations (for example, lag time when CGM and blood glucose monitoring). This may be of particular importance during and following physical activity . Accuracy issues of CGM devices remains a concern although newer devices are becoming more accurate. Lack of adherence to CGM can mask its true effect, for example, the results from HypoCOMPaSS study that failed to show a difference between SMBG and CGM; an

outcome that might have been related to the fact that in the CGM group the adherence to wearing CGM was only 57% and in post-hoc analysis there was a trend in the CGM group with better adherence. Finally, the devices are not plug-and-play and require support and education to maximize their abilities.[102-106]

In contrast to the well-regulated devices (CSII, CGM) the field of mobile applications is breached. There are thousands of mobile apps that might put the patient in danger due to a lack of regulation and the lack of availability of well-established outcomes. Many of those apps provide glucose diaries and some can suggest treatment recommendations. Hypomaps, a mobile application developed by Joslin Diabetes Center and powered by the online portal Glooko in a small pilot study showed a reduction in daytime hypoglycemia in a subset of T1D adults with reduced hypoglycemia awareness but non-completers of this study attributed their non-completion to time required and difficulties using the mobile app.[107] However, that same platform was found to increase blood glucose testing with a greater improvement in blood glucose when compared to users who did not use the mobile platform.[108]

Educational applications for diabetes often include hypoglycemia education, but the glucagon application by Eli Lilly is dedicated to the teaching of glucagon use to patients.[109]

Furthermore, Diabetes Digital Media platform launched an online structured education program targeting both patients and health care providers to improve hypoglycemia awareness but no results are available to date about the effectiveness of this program .[110]

Practical implications: CGM should be considered for all individuals with increased risk for hypoglycemia, impaired hypoglycemia awareness, frequent nocturnal hypoglycemia and frequent severe hypoglycemia.[82]

The role and effectiveness of mobile applications and online platforms need larger studies and further investigation.

We expect that with further technology advancement as with the utilization of machine learning and artificial intelligence (AI) capabilities to predict and prevent hypoglycemic events

may minimize hypoglycemia harmful effects. Those tools will surely assume an important place in the world of hypoglycemia assessment and management.[111,112] Technology can be included as an important tool for evaluation of hypoglycemia episodes, the identification of people at risk for hypoglycemia and for prevention of hypoglycemia events without compromising glycemic control.

10. Newer antidiabetic drugs and risk of hypoglycemia.

Two types of antidiabetic agents are associated with hypoglycemia – insulin secretagogues (i.e., sulfonylureas) and insulin. As shown in Table 1, intensive treatment mainly with supplemental treatment with insulin and SU (ACCORD, ADVANCE, and VADT) shows that the risk of hypoglycemic events are about 2-3 fold higher than compared to standard treatment compared to newer glucose-lowering agents.[47,113] Within the last decade newer antidiabetic drugs have been developed and marketed with minimal if any risk of hypoglycemia when used as monotherapy. These newer drugs are GLP-1 RAs (glucagon-like peptide-1 receptor agonists), DPP4 (dipeptidyl peptidase-4)-inhibitors, and SGLT2 (sodium glucose co-transporter-2)-inhibitors.[113]

10.1 DPP-4 inhibitors

DPP inhibitors inhibit DDP-4, the main enzyme that degrades incretin hormones, e.g., GLP-1 and GIP. DPP-4 inhibitors increase the level of endogenous GLP-1 and GIP by 2-3 folds, stimulating insulin secretion from the ß-cell in a glucose-dependent manner, as well as reducing glucagon secretion.[113]

As shown in Table 1 the risk of hypoglycemic events is very low with this class of drugs and the risk only seems to be marginally increased (by 0-15%) as compared to placebo.[113]

10.2 GLP-1 receptor agonists

GLP-1 receptor agonists, protected against DPP-4 degradation, directly stimulate the ß-cell to secrete insulin through binding to the GLP-1 receptor and inhibit glucagon secretion and thereby reduce hyperglycemia. These agonists are administered as subcutaneous injections (daily or weekly). Exenatide and lixixenatide are given twice daily, liraglutide is given by daily injections. Several weekly formulations are available including exenatide extended release formulation, dulaglutide, albiglutide and semaglutide. As shown in Table 1 GLP1-RA have a robust effect in lowering HbA1c with a low risk of hypoglycemia win patients with T2DM. The explanation for the relatively low level of hypoglycemic events relates to the glucose dependent effect of GLP-1 on insulin secretion--the insulin secretory effect is abolished or reduced at lower plasma glucose concentrations.[113,114]

Recently a daily oral treatment with a GLP-1 analogue, semaglutide, has been investigated in a clinical trials.[115] and received FDA approval. The risk of severe hypoglycemia was also low with oral semaglutide, yet it was higher (1.8%) than in the placebo arm (0.8%) (See Table 1).
It was noted that of these hypoglycemic events occurred with the concomitant use of oral semaglutide with insulin and/or sulfonylurea treatment.

10.3 SGLT-2 inhibitors

SGLT-2 inhibitors reduce blood glucose concentration by increasing glucosuria via blocking glucose reabsorption in the proximal tubule of the kidneys (REF). Most of the FDA approved agents are used once daily (canagliflozin, empagliflozin, dapagliflozin and ertugliflozin). Because the glucose lowering effect of SGLT2-inhibitors is independent of insulin secretion, the risk of hypoglycemia is low when used as monotherapy. The clinical trials shown in Table 1 are in accordance with this expectation. For example, the risk of hypoglycemia using canagliflozin is

extremely low and if hypoglycemia occurs, it is most often associated with background use of insulin or sulfonylureas.[116] Moreover, a recent study of dapagliflozin in patients with heart failure (less than 50% with diabetes) showed similar low rate of hypoglycemia in the dapagliflozin group and the placebo group.[117]

Practical implications:

Data from recent large clinical trials clearly show very low risk of hypoglycemic events associated with the use of these newer drugs, and if an increase is observed it is often due to concomitant use of insulin and/or sulfonylureas. From the present analyses, it is not possible to determine whether there are differences in the risk of hypoglycemia between the three different classes of drugs or whether there are differences between drugs within the same class. .[118,119]

Finally, we have to remember that other glucose-lowering drugs such as metformin and thiazolidinediones (e.g., pioglitazone, rosiglitazone) are also associated with low risk of hypoglycemia and significantly lower costs.[119]

11 Hypoglycemia during Pregnancy

Near-normoglycemia is universally recommended in pregnant women with pre-gestational and gestational diabetes to improve obstetrical, fetal and neonatal outcomes. [120.] As expected, striving for optimal glycemic control imposes a major challenge to the diabetes team and the patient. It increases the maternal risk of minor as well as severe hypoglycemia requiring assistance. [121]

Clearly, severe hypoglycemia is unsafe to the mother and represents the main limiting factor for achieving stringent glucose control throughout pregnancy in women with T1D and T2D.

Severe hypoglycemia comprises hazards that include loss of consciousness, seizures, traffic accidents and even death. Patients with severe hypoglycemia during the first trimester had also higher burden of hypoglycemia-related anxiety than women without hypoglycemia.[122.] In addition, recurrent hypoglycemia in T1D is associated with high glucose variability and episodic hyperglycemia. [123.] Despite optimal HbA1c levels during gestation, the hyperglycemic excursions may explain why macrosomia incidence, the most significant obstetric complication, is still increased.

Possible dangers of maternal hypoglycemia for the fetus have been far less investigated. In animal (rodents) studies, there is strong evidence that hypoglycemia arising early in pregnancy was strongly associated with teratogenesis. [124] However, no such correlation was determined in clinical studies involving women with T1D. Yet, this concern has not been completely dispelled.

In early pregnancy, women with T1DM reported a three-fold increase in severe hypoglycemia frequency compared with the pre-gestational period. [122.] Actually, severe hypoglycemia occurs in 19-44% of pregnant women administered intensive insulin treatment. [125] Reported rates of severe hypoglycemia during pregnancy were up to 15 times higher than those in the Diabetes and Complications Trial. [126]

Peak incidence of hypoglycemia occurs during the first trimester, specifically gestational week 8–16, and is lower in the second half of gestation. [127] Contributing factors for severe hypoglycemia in early pregnancy may be related to gestation-induced nausea and vomiting. Conceivably, the latter exacerbate hypoglycemia tendency due to variations in carbohydrate consumption. It is not clear whether the incidence of minor hypoglycemic episodes or the level of hypoglycemia awareness are altered during gestation. [128]

11.2 Risk factors for Hypoglycemia during pregnancy

Prevention of severe hypoglycemia during pregnancy will be most useful overcoming this obstacle. Risk indicators predictive for severe hypoglycemia during the first trimester include a history of previous hypoglycemic events before gestation, hypoglycemia unawareness, longer duration of diabetes, low HbA1c level ≤6.5%, and change in insulin administration, dosing or regimen, and a high total daily insulin dose.[129]

Previous hypoglycemia is well known as a major risk factor for subsequent severe hypoglycemia in T1DM.[130] The underlying mechanism of "hypoglycemia begetting hypoglycemia" means recurrent exposure to lower blood glucose levels. [131] There is a threshold shift for glucose counter-regulation activation toward reduced blood glucose levels. Hence, it is important to prevent a vicious cycle of hypoglycemia and impaired glucose counter-regulation. Thus, low glycemic targets such as <3.3 mmol/l (60 mg/dL) before and during pregnancy should be avoided.

11.3 Treatment considerations for reducing hypoglycemia rates during pregnancy

As discussed, tight glycemic control with intensive insulin therapy is associated with elevated hypoglycemia rates. Several therapeutic considerations are important to lower hypoglycemia risk during pregnancy.

First, it is crucial to recommend the clinical targets for glucose control. Considering hypoglycemia prevention during pregnancy, the practical and recommended treatment target, by self-monitored blood glucose, is to avoid blood glucose level <3.9 mmol/l (<70 mg/dL). [89] In recent years, continuous glucose monitoring has been used more extensively as sensors became more accurate, convenient and easy to use without the need of calibration. In the recent "Recommendations from the International Consensus on Time in Range (TIR)", the lower glucose target threshold suggested during pregnancy is 3.5 mmol/l (63 mg/dL).[95] Based on data

from Sweden and the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT), the "Time Below Range" (TBR) <3.5 mmol/l (<63 mg/dL) recommended is <4% of readings.[132,133] However, the evidence on CGM metrics and targets, including TBR, for women with T2DM and gestational diabetes mellitus, is lacking.

Second, the preferred insulin type during pregnancy can modify the hypoglycemia hazard. Clinical trials support the administration of rapid-acting insulin analogs during pregnancy, as in non-pregnant subjects, rather than human insulin.[134]

Third, the timing of insulin analog initiation in women with T1DM is also important. Indeed, administration pre-conception may result in a reduced risk of severe hypoglycemia compared with women assigned post-conception. [135] This observation may have several explanations. Women with T1D who initiate insulin analogs pre-conception are more motivated and experienced in diabetes self-management than subjects with post-conception administration. Instead, optimized insulin treatment and a reduced hypoglycemia risk are related to the extra multidisciplinary diabetes teamwork in the pre-conception period.

In the immediate postpartum period, the risk of severe hypoglycemia is considerably higher than that in the second half of gestation and in non-pregnant subjects with diabetes. Consistently, women with T1D should be advised to reduce their insulin dose after delivery and to set pre-conception glycemic control targets.[96]

Practical implications

Several therapeutic considerations are important to lower hypoglycemia risk during pregnancy, including determination of clinical targets for glucose control, administration of rapid-acting insulin analogs, rather than human insulin, pre-conception initiation of insulin analogs, and immediate postpartum insulin dose reduction.

12. Hypoglycemia in Children Vs. Adults

While hypoglycemia can be a significant issue for people of all ages who live with diabetes, there are distinct differences in cause, pathophysiology, symptoms, and treatment between adults and children.

The development and growing availability of improved insulin analogs, insulin pump therapy, and glucose sensors have helped to reduce rates of severe hypoglycemia at all ages, but has not eliminated it.[136] Hypoglycemia continues to be a formidable barrier against optimal diabetes control in children and young adults . The DCCT reported a higher rate of severe hypoglycemia in adolescents as compared to the adults; 86 vs 57 events requiring assistance per 100 patient years. The Juvenile Diabetes Research Foundation (JDRF) CGM study group described bouts of nocturnal hypoglycemia which were frequent (8.5% of nights) and protracted (mean time in hypoglycemia of 81 minutes) both in children and adults, but more prolonged in children. [136] This is significant as prolonged nocturnal hypoglycemia for 2 to 4 hours has been associated with seizures. Studies suggest that younger age, lower HbA1c levels, antecedent exercise and hypoglycemia are associated with a greater frequency of hypoglycemia. [136]

Caregivers of young children with T1D continue to have significant fear of hypoglycemia, in particular of nocturnal hypoglycemia. Such fear may lead caregivers and even healthcare providers to accept higher glucose levels , which can lead to suboptimal glycemic control. Behavioral interventions (cognitive behavioral therapy) and psychoeducation have shown to reduce this fear in adults, although limited data exist on children and adolescents. Similarly, real-time CGM systems and insulin pumps designed with automated insulin suspension in the setting of hypoglycemia have the potential to lessen this fear although related studies are limited.[136] The use of CGM reduces time spent in hypoglycemia with a concomitant decrease in

HbA1c in both children and adults. Although the use of CGM is associated with reduced severe hypoglycemia in adults this is not yet demonstrated in children and young adults. In part, this may be attributed to adolescents who have a high acoustic arousal threshold from sleep, and who sleep through 71% of alarms and therefore can have a severe hypoglycemic event despite wearing a glucose sensor. [136]

There are important differences in the pathophysiology of hypoglycemia between newborns, children and adults. This is in part because the adult brain accounts for greater than one-half of total body glucose consumption. Due of their disproportionately larger brain size relative to their body mass, there is a 2-3 fold higher glucose utilization rate (4-6 mg/kg/min) per kilogram of body weight in infants and young children compared with adults which contribute to a higher risk for hypoglycemia.[137]

In newborns, persistent hypoglycemia results from a congenital or genetic defect in regulating the secretion of insulin, deficiency of cortisol and/or growth hormone, or defects in the metabolism of glucose, glycogen, and fatty acids.[138] During the first 48 hours of life, it may be difficult to assess persistent hypoglycemia disorder from those with transitional hypoglycemia. The mean plasma glucose threshold for suppression of insulin secretion is between 55 and 65 mg/dL (3.0-3.6 mmol/L) shortly after birth, compared with 80-85 mg/dL (4.4-4.7 mmol/L) in older infants, children, and adults.[137] As the glucose stimulated-insulin secretion mechanism matures, mean PG concentration in normal newborns increases and by 72 hours of age is similar to those in older infants and children.

Severe and recurrent hypoglycemia in the first few months of life can lead to significant disability; thus, early recognition and treatment are essential Of concern, plasma ketone levels are suppressed during hypoglycemia in neonates, which results in a greater risk for hypoglycemia-induced brain damage. Additionally, there is limited evidence that the plasma lactate level will be high enough to compensate for low glucose.[138] When hypoglycemia is

recurrent, it is important to exclude insulin associated hypoglycemia (IAH) and rule out coexisting autoimmune disorders such as hypothyroidism, celiac disease, and Addison's disease.[136]

Whipple's triad is useful in confirming hypoglycemia: symptoms and/or signs consistent with hypoglycemia, a documented low glucose concentration, and relief of signs/symptoms when plasma glucose concentration is restored to normal. However, young infants and children often cannot dependably recognize or communicate their symptoms, thus recognition of hypoglycemia in this group may require confirmation by repeated glucose measurements and formal testing.[139]

It is essential that education on hypoglycemia symptoms and treatment be given to children, parents, schoolteachers and other care-givers so they may recognize the early warning signs of hypoglycemia and treat low blood glucose immediately and appropriately.[136]

Symptoms of hypoglycemia result from adrenergic activation (e.g., shakiness, pounding heart), cholinergic (sweating) and neuroglycopenia (e.g., headache, drowsiness, difficulty in concentrating). Behavioral changes in preschool children often result from a combination of both autonomic and neuroglycopenic responses, including tantrums, irritability, stubbornness, agitation and even quietness. Notably, the dominant symptoms of hypoglycemia tend to differ depending on age, with neuroglycopenia more common than autonomic symptoms in the young. See Table 3 for symptoms based on age group. [136]

Hypoglycemia has both acute and long-term consequences. Infants and children with asymptomatic hypoglycemia have been shown to have acute neurocognitive defects during episodes of hypoglycemia, including impaired sensory and auditory-evoked responses and impaired test performance. Long-term consequences of hypoglycemia include decreased head size, lower intelligence quotient (IQ), and brain abnormalities on MRI. Furthermore, as many as 50% of patients who survive hyperinsulinemic hypoglycemia of infancy have long-term

neurologic complications, which emphasizes the need for early recognition and treatment of these children.[136]

Severe hypoglycemia demands urgent treatment. In a hospital or other healthcare setting, this may include intravenous glucose. Glucagon (intramuscular (IM), subcutaneous (SC), or nasal) can also be live-saving, and may be administered anywhere including at home. The recommended glucagon SC dosing is weight based: 1 mg for adults and children >25 kg and 0.5 mg for children <25 kg (according to Novo Nordisk manufacturer guidelines, Eli Lilly uses a weight cut-off of 20 kg). The evidence for these recommendations is unclear.[136]

7. Hypoglycemia in the hospital setting

Hypoglycemia among hospitalized patients is common, occurring in up to one-third of patients treated with insulin in medical and surgical wards. Hypoglycemia in the hospital setting has been associated with increased morbidity and mortality.[140]

A prospective observational study reported that almost 45% of insulin-treated patients whose blood glucose was <70 mg/dL suffered from asymptomatic hypoglycemia.[60] It was also found that older males had a higher risk of asymptomatic hypoglycemia.

The study results supported the recommendations on the need for frequent blood glucose measurements in those treated with insulin in general wards. Health care providers should be aware of the problem of hypoglycemia in the hospital setting.[140]

In the inpatient setting, data from a feasibility study utilizing a computerized system for workflow and decision support for diabetes management have reported lower hypoglycemia rates (1.3% of blood glucose (BG) measurements were <70 mg/dl and 2.6% were >300 mg/dl) as compared to paper charting.[141]

Practical Implications: The ADA Standards of Medical Care recommends that a management protocol for hypoglycemia should be designed and implemented by every hospital, along with a clear prevention and treatment plan. Hypoglycemic episodes should also be documented in the medical record. The ADA also **u**rged for reviewing the treatment regimen to make changes when necessary, aiming for prevention of further hypoglycemic episodes especially if the blood glucose value is <70 mg/dL (3.9 mmol/L). Ideally, an inpatient diabetes management team can facilitate the management of patients with diabetes being treated with insulin or insulin secretagogues.

Iatrogenic hypoglycemia may be related to specific triggers including decrease in oral intake, vomiting, improper timing of insulin injections (either short- or rapid-acting) in relation to meal times, decreasing the infusion rate of IV dextrose, interrupting the oral, enteral, or parenteral feedings, and sudden reduction of the doses of corticosteroid.[1]

13. Hypoglycemia in Particular situations:

13.1 Hypoglycemia & religious duties:

Muslim fasting

According to a recent study done in the Pew Research Institute in 2015, Muslims are the second largest religious community worldwide, a total 1.8 billion Muslims, constituting 24.1% of the global population.[142] Coupling this number with the overall prevalence of diabetes (8.8%), we estimate there are more than 100 million Muslims with diabetes; some of the Islamic traditions not practiced in the proper way could put Muslims with diabetes at risk of hypoglycemia. Ramadan is a holy lunar-based month, the duration of Ramadan could be 29 or 30 days. Every Muslim who chooses to fast should abstain from food, drinks, and any oral medication, from

dawn until sunset; Muslims in Ramadan can consume food or fluid between sunset and dawn. Most Muslims typically eat two meals every day during Ramadan, first at sunset and the second before dawn. [143]

The landmark Ramadan study EPIDIAR, showed that fasting during Ramadan increased the risk of severe hypoglycemia 4.7-fold in Muslims with T1D and 7.5-fold in Muslims with T2DM. In this study, severe hypoglycemia was thought to be underestimated since events requiring assistance from a third party without the need for hospitalization were not included. Citing the high risk of severe hypoglycemia, severe hyperglycemia and diabetic ketoacidosis reported in Muslim patients during fasting.[144]

The latest Ramadan statement published in 2015 paid good attention to the frequency of hypoglycemia during Ramadan and drew attention to some issues related to hypoglycemia. Maximum caution should be practiced with the use of Insulin and/or sulfonylureas during Ramadan. The statement also highlighted the importance of some religious practices during Ramadan (Tarawih prayers) with more physical exertion increasing the risk of hypoglycemia. Lastly the statement recommended a strategy for preventing hypoglycemia (Table 4) and how to manage hypoglycemia during Ramadan (Table 5). [145]

Jewish fasting (Yom Kippur and other fast days)

Yom Kippur (day of atonement) fast is a 24 hour fast where abstinence from food and drink is practiced once annually on the 10th day of the Jewish month of Tishre. Five additional similar fasts are also practiced, including Ninth of Av, a day lasting 25 hours and 4 other days from sunrise to sunset. Although fasting those days are a part of the Jewish faith for many, the Torah states that fasting is not required if it poses a health risk for the individual.

A study conducted to assess the frequency of ER visits 48 hours before and 48 hours after Yom Kippur showed no difference in visits frequency in 3441 orthodox fasting patients with diabetes. There was also no demonstrated increase in frequency between orthodox fasting Jewish and secular patients with diabetes.[146] According to Grajower et al, patients with T1DM

with inadequate control (i.e. blood glucose > 250 mg/dl), physical trauma, sign of infection or fever should not be permitted to fast.[147]

Practical Implications:

Various papers serve as expert opinion pieces on the management of diabetes and avoidance of hypoglycemia during religious fasting.

Hajj. Hajj is an obligatory duty for every Muslim. Hajj, a Muslim pilgrimage should be done in Mecca including a visit to the sacred house of Allah (Kaaba). The risk of hypoglycemia is much higher when performing Hajj. This is a consequence of excessive physical activity and a change in the frequency and amount of food ingested. Moreover, Hajj may be performed during very hot weather, and in addition to very long walking distances there is often prolonged periods awaiting food. [148]

Table 7 and table 8 include some precautions to prevent and treat hypoglycemia during Ramadan and Hajj.

13.2 Physical Activity

Physical activity plays an important role in glycemic management in T1D, T2D, and patients with prediabetes. Increased physical activity and fitness have a positive impact on overall health.[149] Physical activity can improve glycemia in patients with T2D, minimize their cardiovascular risk factors, may contribute to weight control, and improving the sense of well-being.[150] Furthermore, regular exercise may have a role in preventing or delaying the onset of T2D.[151,152] Daily physical activity may also offer glycemic benefits in people with T1D by improving cardiovascular fitness, and insulin sensitivity.[150] However, physical activity may increase the risk of hypoglycemia more commonly in people with T1D and T2D who on insulin and/or insulin secretagogues.

Practical Implications: Optimizing insulin doses and carbohydrate intake, in addition to a short warm-up before or after the physical activity sessions may help avoid hypoglycemia.[153] The practice of high-intensity exercise sessions intermittently while having moderate physical activity may also help in slowing the declines in blood glucose.[154]

Hypoglycemic episodes typically occur within 6−15 hours following increased physical activity sessions, in some cases the risk may extend out to 48 hours.[155] Physical activity may also cause nocturnal hypoglycemia, which poses major clinical concerns. This nocturnal hypoglycemia risk could be reduced by a ~20% decrease of the total basal insulin doses with a reduction of prandial bolus insulin and also consuming low glycemic index carbohydrate after the evening physical activity.[156] For CSII users, reduction of basal rate by almost 20% at bedtime for six hours after the evening physical activity can minimize the possibility of nocturnal hypoglycemia. In addition, a bedtime snack, measuring the blood glucose values overnight, and/or the use of CGM equipped with alarm and automated pump suspension may be useful.

14. Hypoglycemia and Endocrine Disorders

Although much more uncommon than hypoglycemia in diabetes, endocrine disorders can cause hypoglycemia.

Hypopituitarism from almost any cause can lead to hypoglycemia due to secondary adrenal insufficiency, growth hormone deficiency or both. This includes tumors (pituitary, parasellar and metastatic), mechanical or compressive lesions (cysts, spinal fluid as in empty sella syndrome, trauma, aneurysms), infiltrative processes (histiocytosis X, sarcoidosis, hemochromatosis), infections (tuberculosis, syphilis, meningitis), autoimmunity, pituitary infarction (postpartum infarction and apoplexy of any etiology), radiation, neurotoxins, and medications like tyrosine kinase inhibitors.

Hypoglycemia from primary adrenal insufficiency is most commonly autoimmune (Addison's disease) and frequently associated with polyendocrine deficiency syndromes.[157] Though rare now, tuberculosis was formerly a common cause of primary adrenal insufficiency. Fungal infections, infiltrative processes (sarcoidosis, amyloidosis, and metastatic neoplasia), adrenal hemorrhage, demyelinating disorders and congenital adrenal hypoplasia are rare causes.

There has been a disagreement about the correlation of hypothyroidism and hypoglycemia.[158,159] Hypothyroidism is thought to cause hypoglycemia through the reduction of gluconeogenesis in skeletal muscle and in adipose tissue and impairment of glycogenolysis.[160,161]

Pancreatic islet cell tumors or insulinomas are rare but still the most common tumors to cause hypoglycemia. Multiple Endocrine Neoplasia 1 (MEN1) is associated with hypoglycemia through pancreatic insulinomas. Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) with islet hypertrophy or neisidioblastosis is a rising cause of hypoglycemia, particularly with its association with gastric bypass surgery.

Non islet cell tumors can induce hypoglycemia through overproduction of insulin-like growth factors, usually IGF-II. This has been seen in several tumors including poorly differentiated thyroid cancer, adrenocortical, mesenchymal (sarcomas, mesotheliomas, neurofibromas), gastrointestinal, lymphoma, hepatoma, teratomas and genitourinary tumors. These tumors tend to be large (>500 gm and >5 cm), localized to the abdomen and thorax, and in adults.[162]

Lastly, autoimmune hypoglycemia has been seen with antibodies causing activation of the insulin receptor and anti -insulin antibodies with erratic insulin levels.[155,163]

15. Summary of hypoglycemia causes and treatments

In the primary care setting a diabetes team comprising physicians, nurses and diabetes educators is needed for all aspects of care, including hypoglycemia recognition and prevention.

Several efforts to recognize and prevent hypoglycemia start with the empowerment of patients to prevent hypoglycemia and to know what to do if it happens. The key issue is good communication and easy access to primary health facilities in cases of hypoglycemia. The right choice of glucose-lowering drug is essential. Modern developments in glucose monitoring and drug development have provided new approaches that can be used to reduce the risk of hypoglycemia, but their application in primary care is delayed mainly due to cost issues , table 6 summarizes the common causes and treatments of hypoglycemia

16. Discussion/Plans for Action

- Hypoglycemia, being a significant limiting factor in the management of T1DM and T2DM should always be a concern and considered when choosing medications to treat people with diabetes.
- While hypoglycemia is defined as a blood glucose level under 70 mg/dL (3.9 mmol/L), symptoms may occur at higher blood glucose levels in individuals with much higher overall blood glucose control. The diagnosis of hypoglycemia should be based on actual glucose levels with or without the related symptoms and signs.
- Severe hypoglycemia is defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions to assure neurologic recovery.
- Many vulnerable patients at dual risk of severe hypoglycemia and CV outcomes show many features of “frailty.” Those patients may benefit if treated by using GLP-1 receptor agonists or SGLT2 inhibitors with or without metformin rather than using insulin or sulfonylureas.
- The role of the diabetes educator in the detection, prevention and treatment of hypoglycemia is of utmost importance. Ongoing programs for continued healthcare education addressing the issue of hypoglycemia are needed. These programs should also target health care providers in hospital settings as recommended by the ADA Standards of Medical Care urging every hospital to have a prevention and treatment plan.
- Based on the data from recent large clinical trials clearly showing the very low risk of hypoglycemic events associated with the use of the newer antidiabetic drugs, the use of these

agents, with or without metformin, may be considered whenever possible in high CV risk populations.

- Physical activity is the cornerstone in the management of diabetes. There may be a need to adjust insulin doses and carbohydrate intake before and after exercise to reduce the risk of hypoglycemia.
- Special programs and actions are needed aiming to avoid hypoglycemia in special situations like religious fasting and pilgrimage
- The role of family involvement and conversations about hypoglycemia, facilitated by a healthcare professional, may reduce the burden stemming from the worry about hypoglycemia and hypoglycemia risk in family members of patients with diabetes.
- The use of real-time continuous glucose monitoring (CGM) should be encouraged whenever possible, it is of significant benefit in patients with Impaired Awareness of Hypoglycemia.
- CGM should be considered for all individuals with increased risk for hypoglycemia, impaired hypoglycemia awareness, frequent nocturnal hypoglycemia and frequent severe hypoglycemia.
- There are many barriers for the use of CGM, including but not limited to cost, lack of education of proper use and barriers to insurance coverage.

Appendix I

Hypoglycemia grading questionnaire

1. To what extent can you tell by your symptoms that your blood sugar is low?

   Never / Rarely / Sometimes / Often / Always

2. At what glucose level do you begin to experience symptoms? _____
3. Describe your symptoms:
4. Headache, lightheadedness, sweating, weakness, intense hunger, other _____In the last 6 months have you experienced symptomatic episodes of low glucose? YES/NO

   If yes – how often? _____ / month

5. Was hypoglycemia confirmed by SMBG? YES / NO

   If yes – what was the lowest glucose value measured? _____

6. Are there identifiable causes for hypoglycemia?

   If yes – specify _____

7. How do treat hypoglycemia?
   a. Food
   b. Table sugar or sweet beverage
   c. Glucose tablets, gel or syrup
8. Do you check blood sugar before driving? YES / NO

   At what glucose level will you not start driving? _____

9. In the last year, have you had a severe hypoglycemic episode when you were unable to treat yourself and needed someone's help? YES / NO
10. What is hypoglycemia for you? _____

Tables

Table 1 : Prevalence of Hypoglycemia in recent large clinical trials in individuals with T2DM

Name of the study	Interventional drug tested	N	Trial median duration (years)	Baseline HbA1c	% individuals with hypoglycemia*	
					Intervention	Control
ACCORD	Intensive vs standard	10251	3.4	8.1	16.2	5.1
ADVANCE	Intensive vs standard	11140	5.0	7.2	2.7	1.5
VADT	Intensive vs standard	1791	5.6	9.4	8.5	3.1
ORIGIN	Insulin/Glargine	12537	6.2	6.4	5.7	1.8

DPP-4 inhibitors						
SAVOR	Saxagliptin	16492	2.1	8.0	2.1	1.8
EXAMINE	Alogliptin	5380	1.5	8.0	0.7	0.6
CARMELINA	Linagliptin	6991	2.2	7.9	15.9	16.4
CAROLINA	Linagliptin					
TECOS	Sitagliptin	14671	3.0	7.0 – 7.4	0.78	0.70
GLP-1 analogues						
LEADER	Liraglutide	9340	3.8	8.7	3.3	2.4
REWIND	Dulaglutide	9901	5.4	7.2	1.3	1.5
SUSTAIN 6	Semaglutide	3297	2.0	8.7	21.7	21
Pioneer6	Oral Semaglutide	3183	2.3	8.2	1.4	0.8
SGLT-2 inhibitors						
EMPA-REG	Empagliflozin	7020	2.6	8.1	1.5	1.3
CANVAS	Canagliflozin	10142	3.6	7.0-10.5	-	-
CREDENCE	Canagliflozin	4401	2.6	8.3	10.2	10.9
DECLARE	Dapagliflozin	17160	4.2	8.3	0.7	0.9
DAPA-HF	Dapagliflozin		4744	1.5	-	0.2

* Hypoglycemia was defined differently in the different studies and it is, therefore, not possible to perform comparisons between the studies, but only comparison within each study. However, in most of the studies the prevalence is estimated as pct of individuals with at least one major hypoglycemic event.

Table 2: Diabetes Self-management Education for Hypoglycemia Prevention

- For group or individual education:
  - Diabetes basics, glycemic goals, complications
    - Effect of medications on risk of hypoglycemia, especially insulin or secretagogues
    - Insulin clearance is decreased with renal failure, hepatic failure, hypothyroidism, or, rarely, high levels of insulin-binding antobodies
  - Self-Monitoring of Blood Glucose (SMBG), insulin use
    - Impact of insulin on hypoglycemia:
      - If doses are excessive, ill-timed or of the wrong type
  - Understanding and detecting hypoglycemia, treatment using carbohydrate
  - Meal planning for diabetes
    - Exogenous glucose delivery is decreased after a missed or low-carbohydrate meal and during an overnight fast
    - Exogenous insulin production is decreased after alcohol ingestion
    - Adjusting carbohydrate surrounding physical activity to reduce risk of hypoglycemia
  - Physical activity and foot care
    - Effect of exercise on hypoglycemia risk especially immediately or several hours later
      - Glucose utilization is increased during and shortly after exercise
      - Sensitivity to insulin is increased in the middle of the night, late after exercise and after weight loss or improved fitness
  - Stress management
- Intensive individualized education for hypoglycemia:
  - Understanding hypoglycemia

- Detection of hypoglycemia symptoms
  - Severe hypoglycemia
  - Documented symptomatic hypoglycemia
  - Documented asymptomatic hypoglycemia
- Corrective management using carbohydrate and re-testing blood glucose within 15-30 minutes after treatment
  - 15-20 grams of glucose or any form of carbohydrate that contains glucose and minimal if no fat or protein such as the following:
    - 3 to 4 glucose tablets (follow package instructions)
    - glucose gel
    - 8 to 10 hard candies
    - 2 tablespoons of raisins
    - 1 tablespoon of sugar, honey or corn syrup
    - 4 to 6 ounces non-diet soft drink
    - 4 to 6 ounces of juice
    - 1 piece of fruit
    - 1 cup low-fat or non-fat milk
- General guidelines for treating hypoglycemia:
  - Only consume the specific required carbohydrate intake ; wait 15 to 30 minutes, then test blood glucose to identify if additional carbohydrate is needed
  - It will take up to 15-30 minutes for symptoms to disappear; continuing to eat until symptoms disappear will lead to much higher blood glucose levels
  - Do not use high-fat foods for treatment since they will not aid in increasing glucose levels quickly
  - Always carry some type of carbohydrate
  - Keep carbohydrate at your bedside to treat overnight hypoglycemia

▪ Always wear diabetes medical identification o Assessment of possible causes o Dose adjustment of medication schedule

- References for table 2: (International Hypoglycemia Study Group. Minimizing hypoglycemia in diabetes. Diabetes Care. 2015; 38:1583-1591

  Lifestyle Management: Standards of Medical Care in Diabetes – 2018. Diabetes Care. 2018; 41(suppl 1): S38-S50.
- Yong Y-M, Shin K-M, Lee K-M et al. Intensive individualized reinforcement education is important for the prevention of hypoglycemia in patients with type 2 diabetes. Diabetes Metab J. 2015;39: 154-163

  The Art and Science of Diabetes Self-Management Education Desk Reference. Fourth Edition.. Chapter 18. Pharmacotherapy for Glucose Management. 2017, American Association of Diabetes Educators, Chicago, IL.
    - Silbert R, Salisido-Montenegro A, Rodriguez-Gutierrez R et al. Hypoglycemia among patients with type 2 diabetes: epidemiology, risk factors and prevention strategies. Current Diabetes Reports. 2018;18: 53. https://doi.org/10.1007/s11892-018-1018-0)

Table 3: Symptoms of hypoglycemia by age group

Symptoms of hypoglycemia by age group	Neonates	Older children
	Tremulousness Brisk Moro reflex Lethargy Poor feeding Irritability Hypothermia Respiratory distress Apnea Bradycardia Seizure Coma Sudden death	Dizziness Sweating Hunger Anxiousness Confusion Lethargy Poor feeding Irritability Seizure Coma Sudden death

Table 4 Guide for preventing hypoglycemia during Ramadan and Hajj

▸ Frequent monitoring of blood glucose levels, especially for those on insulin and/or Sulphonylureas , monitor 4 – 6 times daily

▸ seek the help of your healthcare provider if there is a need for adjusting your medication aiming to avoid hypoglycemia

- at least 1 month prior to Ramadan and Hajj. Avoid or reduce sulfonylureas and/or insulin daily dosage after consulting your health care provider

▸ Avoid skipping predrawn meals in Ramadan and early morning breakfast during the Hajj

▸ Avoid strenuous physical activity during fasting period

▸ Adjust medication dose and eat a snack in the presence of hypoglycemia (see Table ***). Consider breaking the fast if there is severe or recurrent hypoglycemia and get immediate rest during the Hajj

▸ Record blood glucose measures to determine patterns contributing to hypoglycemia

Table5 : Recommendations for treatment of hypoglycemia during Ramadan and Hajj

Examples of 15 g of carbohydrate to be used when getting hypoglycemia :

- Four ounces (1/2 cup) of apple or orange juice
- Four ounces (1/2 cup) of regular sweetened soda
- Three or four glucose tablets
- One serving of glucose gel—the amount equal to 15 g of carbohydrate
- Eight ounces (1 cup) of milk
- Five or six pieces of hard candy
- One tablespoon of sugar or honey

Table 6 : Hypoglycemia Causes and Treatments

Causes	Treatments
Physical activity	Medication adjustment or addition of carbohydrate
Skipped or irregular meals	Maintain consistent carbohydrate at meals or medication adjustment
Erratic schedule	Medication adjustment, use of CGM or increased SMBG to identify patterns
Stress	Medication adjustment
Diminished cognitive status	Use of CGM with alerts or increased SMBG

History of hypoglycemia unawareness	Use of CGM with alerts or increased SMBG, medication adjustment
Duration of diabetes	Use of CGM
Comorbidities	Medication adjustment

References for table 6:

1. Kedia N. *Diabetes Metab Syndrome Obes: Targets Ther.* 2011;4:337-346.

2. Geller AI et al. *JAMA Intern Med*. 2014;174(5):678-686.

3. ADA. *Diabetes Care*. 2020;43(Suppl. 1). https://care.diabetesjournals.org/content/43/Supplement_1

4. Frier BM. *Nat Rev Endocrinol. 2014;*10:711–722.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

References

1) Glycemic Targets: Standards of Medical Care in Diabetes2019. Diabetes Care 2019;42(Suppl. 1):S61–S70 | https://doi.org/10.2337/dc19-S006

2) International Hypoglycemia Study Group* Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–157.

3) Seaquist ER, Anderson J, Childs B et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384–95.

4) Marso SP, McGuire DK, Zinman B et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. DEVOTE Study Group. N Engl J Med. 2017 Aug 24;377(8):723-732). doi: 10.1056/NEJMoa1615692. Epub 2017 Jun 12.

5) Alsahli M, Gerich JE. Renal glucose metabolism in normal physiological conditions and in diabetes. Diabetes Res Clin Pract. 2017 Nov; 133: 1-9. doi: 10.1016/j.diabres.2017.07.033. Epub 2017 Aug.

6) Cahn A, Raz I, Mosenzon O. Predisposing Factors for Any and Major Hypoglycemia With Saxagliptin Versus Placebo and Overall: Analysis From the SAVOR-TIMI 53 Trial. Diabetes Care. 2016;39(8):1329-1337.

7) Cahn A, Mosenzon A, Bhatt DL et al. Hypoglycemia manifestations and recurrent events: Lessons from the SAVOR-TIMI 53 outcome study. Diabetes Obes Metab. 2017 Jul;19(7):1045-1050).

8) Oyer DS. Curr Diabetes Rev. The science of hypoglycemia in patients with diabetes. 2013 May;9(3):195-208.

9) Cukierman-Yaffe T, Bosch, J, Jung H et al. Hypoglycemia and Incident Cognitive Dysfunction: A Post Hoc Analysis From the ORIGIN Trial. Diabetes Care 2019 Jan; 42 (1): 142-147. https://doi.org/10.2337/dc18-0690

10) Jacobson AM, Ryan CM, Cleary PA, et al.; Diabetes Control and Complications Trial/EDIC Research Group. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. Diabetologia 2011;54:245–255pmid:20803190.

11) Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787–793pmid:22374637

12) Aung PP, Strachan MW, Frier BM, et al. Edinburgh Type 2 Diabetes Study Investigators. Severe hypoglycemia and late-life cognitive ability in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabet Med 2012;29:328–336pmid:22023662

13) Whitmer RA, Karter AJ, Yaffe K, et al. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572pmid:19366776

14) Selvin E. Epidemiologic Evidence Linking Hypoglycemia to the Heart and Brain. Presented at: Heart in Diabetes CME Conference; July 12-14, 2019 Philadelphia.

15) Medha N. Munshi, Cognitive Dysfunction in Older Adults With Diabetes: What a Clinician Needs to Know. Diabetes Care 2017 Apr; 40(4): 461-467. https://doi.org/10.2337/dc16-1229

16) Frier B.M. Impaired Awareness of Hypoglycemia. In: Frier B.M., Fisher B.M., eds. Hypoglycemia in Clinical Diabetes. Chichester,U.K.: John Wiley and Sons, 2007; 14.

17) Cryer, PE Hypoglycemia: The limiting factor in the glycaemic management of Type I and Type II Diabetes Diabetologia. 2002; 45:937–948.

18) Seaquist, ER. Beyond the brain: do peripheral mechanisms develop impaired awareness of hypoglycemia? J Clin Invest. 2018 Aug 31; 128(9): 3739–3741. Published online 2018 Aug 6. doi: 10.1172/JCI122449.

19) Cryer PE. Hypoglycemia. Pathophysiology, Diagnosis and Treatment. 1997. Oxford University Press: New York

20) Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol 2001; 281:E1115–E1121.

21) P. E. Cryer et al.: Hypoglycemia: The limiting factor in the glycaemic management 939, Diabetologia. 2002;45:937–948.

22) Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia associated autonomic failure in insulin dependent diabetes mellitus. J Clin Invest 1993;91:819–828,

23) Fanelli CG, Paramore DS, Hershey T et al. Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes mellitus. Diabetes 1998;47:1920–1927..

24) White NH, Skor D, Cryer PE, et al. Identification of type 1 diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 1983;308:485–491.

25) Geddes J., Schopman J.E., Zammitt N.N., Frier B.M. Prevalence of impaired awareness of hypoglycemia in adults with type 1 diabetes. Diabet Med 2008; 25:501-504 .

26) Diabetic Medicine 2008; 25(4): 501-504.

27) Geddes J., Schopman J.E., Zammitt N.N., Frier B.M. Prevalence of impaired awareness of hypoglycemia in adults with type 1 diabetes. Diabet Med 2008; 25:501-504 .

28) Gold A.E., MacLeod K.M., Frier B.M. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994; 17:697-703.

29) JE Schopman, J Geddes, BM Frier. Frequency of symptomatic and asymptomatic hypoglycemia in type 1 diabetes: effect of impaired awareness of hypoglycemia. Diabetic Medicine 2011; 28:352-355.

30) The Diabetes Control and Complications Trial Research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–986.

31) MacLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycemia in insulin-treated diabetic patients. Diabet Med. 1993; 10:238–245.

32) Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): The Stockholm Diabetes Intervention Study (SDIS) after 5 years. J Intern Med 1991;230:101–108.

33) Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. Diabetes Care. 1995;Aug;18(8):1113-23.

34) Saudek CD, Duckworth WC, Giobbie-Hurder A, et al. Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent diabetes mellitus: a randomized clinical trial. Department of Veterans Affairs Implantable Insulin Pump Study Group. JAMA. 1996 ;276(16):1322-7.

35) U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes. 1995;44(11):1249-58.

36) United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, 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 Feb 1;128(3):165-75.

37) Segel SA, Paramore DS, Cryer PE. Hypoglycemia associated autonomic failure in advanced type 2 diabetes. Diabetes .2002;51:724–733.

38) United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, 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 Feb 1;128(3):165-75.

39) Hepburn DA, MacLeod KM, Pell ACH, et al. Frequency and symptoms of hypoglycemia experienced by patients with type 2 diabetes treated with insulin. Diabet Med. 1993;10:231–237.

40) Schopman JE, Geddes J, Frier BM. Prevalence of impaired awareness of hypoglycemia and frequency of hypoglycemia in insulin-treated Type 2 diabetes. Diabetes Research and Clinical Practice, 2010; 87(1): 64-68.

41) Fanelli CG, Pampanelli S, Epifano L et al. Longterm recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycemia following institution of rational intensive therapy in IDDM. Diabetologia 1994;37:1265–1276.

42) Cranston I, Lomas J, Maran A, Macdonald I, Amiel S. Restoration of hypoglycemia unawareness in patients with long duration insulin-dependent diabetes mellitus. Lancet. 1994;344:283–287 33.

43) Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 1994;43:1426–1434.

44) Glycemic Targets. American Diabetes Association Standards of Medical Care. Diabetes Care 2019;42(1):S61-S70.

45) van Beers CA, DeVries JH, Kleijer SJ et al., Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycemia (IN CONTROL): a randomised, open-label, crossover trial, Lancet Diabetes Endocrinol. 2016;4(11):893-9029.

46) Ly TT, Hewitt J, Davey RJ, et al. Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes, Diabetes Care. 2011;34(1):50-52.

47) Dunkley AJ ,Fitzpatrick C, Gray LJ et al. Incidence and severity of hypoglycemia in type 2 diabetes by treatment regimen: A UK multisite 12-month prospective observational study. Diabetes Obes Metab. 2019. 21:1585–1595. DOI: 10.1111/dom.13690.

48) Bowman P, Sulen A, Barbetti F et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. Lancet Diabetes Endocrinol.,2018;6(8):637-646. doi: 10.1016/S2213-8587(18)30106-2. Epub 2018 Jun 4.

49) Shepherd MH, Shields BM, Hudson M. A UK nationwide prospective study of treatment change in MODY: genetic subtype and clinical characteristics predict optimal glycaemic control after discontinuing insulin and metformin. Diabetologia, 2018; 61(12):2520-2527. doi: 10.1007/s00125-018-4728-6. Epub 2018 Sep 18.

50) Tuomi T, Honkanen EH, Isomaa B, et al. Improved prandial glucose control with lower risk of hypoglycemia with nateglinide than with glibenclamide in patients with maturity-onset diabetes of the young type 3. Diabetes Care, 2006. 29(2):189-94

51) Ballmann M, Hubert D, Assael BM et al. Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol., 2018. 6(2):114-121. doi: 10.1016/S2213-8587(17)30400-X. Epub 2017 Dec 5.

52) Dennis JM, Shields BM, Henley WE, et al. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. Lancet Diabetes Endocrinol., 2019. 7: 442–51http://dx.doi.org/10.1016/S2213-8587(19)30087-7.

53) Chow LS, Chen H,Miller ME et al. Biomarkers related to severe hypoglycemia and lack of good glycaemic control in ACCORD. Diabetologia, 2015. 58(6):1160-6. doi: 10.1007/s00125-015-3512-0. Epub 2015 Feb 5.

54) Nicolucci A, Prosperini G, Buzzetti R et al. A multistep approach for the stratification of the risk of severe hypoglycemia in patients with type 2 diabetes. Minerva Endocrinol., 2018. 43(4):501-510. doi: 10.23736/S0391-1977.18.02850-X.

55) Misra-Hebert AD, Pantalone KM, Ji X et al. Patient characteristics associated with severe hypoglycemia in a type 2 diabetes cohort in a large, integrated health care system from 2006 to 2015. Diabetes Care. 2018. 41(6): 1164-1171. https://doi.org/10.2337/dc17-1834

56) Standl E, Stevens SS, Lokhnygina Y, et al Confirming the Bidirectional Nature of the Association Between Severe Hypoglycemic and Cardiovascular Events in Type 2 Diabetes: Insights From EXSCEL. Diabetes Care 2019 Dec; dc191079, https://doi.org/10.2337/dc19-1079, Published online 27 December 2019

57) Home P. Controversies for Glucose Control Targets in Type 2 Diabetes: Exposing the Common Ground. Diabetes Care. 2019;42(9):1615-1623. doi: 10.2337/dci19-0002. Epub 2019 Jun 8.

58) Leslie RD, Palmer J, Schloot NC, Lernmark A. Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment. Diabetologia. 2016;59(1):13-20. doi: 10.1007/s00125-015-3789-z.

59) International Hypoglycemia Study Group. Hypoglycemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. Lancet Diabetes Endocrinol 2019;7:385-396.

60) Standl E, Stevens SR, Armstrong PW, et al. TECOS Study Group. Increased risk of severe hypoglycemic events before and after cardiovascular outcomes in TECOS suggests an at risk type 2 diabetes frail patient phenotype. Diabetes Care 2018;41:596-603,

61) Desouza C, Salazar H, Cheong B, et al. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care 2003;26:1485–1489.

62) Tsujimoto T, Yamamoto-Honda R, Kajio H, et al. Vital signs, QT prolongation, and newly diagnosed cardiovascular disease during severe hypoglycemia in type 1 and type 2 diabetic patients. Diabetes Care 2014;37:217–225.

63) Stahn A, Pistrosch F, Ganz X, et al. Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: silent hypoglycemias and silent arrhythmias. Diabetes Care 2014;37:516–520.

64) Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010;33:1389–1394.

65) Zoungas S, Arima H, Gerstein HC, et al. Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431–437.

66) Munshi MN, Slyne C, Segal AR, et al. Liberating A1C goals in older adults may not protect against the risk of hypoglycemia. J Diabetes Complications 2017;31:1197–1199.

67) Hypoglycemia Quality Collaborative Strategic Blueprint: A Resource to Increase Awareness of Hypoglycemia and Promote Activities to Reduce its Incidence. Report and Strategic Recommendations. Endocrine Society. 2016. https://endocrinenews.endocrine.org/wp-content/uploads/HQC_Strategic_Blueprint_VIEW.pdf.

68) Beck J, Greenwood DA, Blanton L et al. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care. 2017; 40(10): 1409-1419.

69) Powers MA, Bardsley J, Cypress M et al. Diabetes Self-management education and support in type 2 diabetes: a joint position statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. The Diabetes Educator. 2017;43(1): 40-53.

70) Evert AB, Dennison M, Gardner CD et al. Nutrition Therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care. 2019. Published online ahead of print April, 18, 2019. https://doi.org/10.2337/dci19-0014.

71) https://www.aarp.org/content/dam/aarp/research/public_policy_institute/health/home-alone-family-caregivers-providing-complex-chronic-care-rev-AARP-ppi-health.pdf Accessed October 22, 2019.

72) Ratzki-Leewing, A . Rizi, EP, Harris SB .Family Members: The Forgotten Players in the Diabetes Care Team (The TALK-HYPO Study) Diabetes Ther. Published online 9 Sept 2019. https://doi.org/10.1007/s13300-019-00687-y.

73) Diabetes Technology: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019 Jan;42(Suppl 1):S71-S80.

74) Choudhary et al. A Type 1 diabetes technology pathway: consensus statement for the use of technology in Type 1 diabetes. Diabet Med. 2019 May;36(5):531-538

75) Beato-Vibora P, Yeoh E, Rogers H, Hopkins D, Amiel SA, Choudhary P (2015) Sustained benefit of continuous subcutaneous insulin infusion on glycaemic control and hypoglycemia in adults with type 1 diabetes. Diabet Med 32:1453–1459.

76) Quiros C, Gimenez M, Rios P et al (2016) Long-term outcome of insulin pump therapy: reduction of hypoglycemia and impact on glycaemic control. Diabet Med 33:1422–1426.

77) Ramotowska A, Golicki D, Dzygalo K, Szypowska A (2013) The effect of using the insulin pump bolus calculator compared to standard insulin dosage calculations in patients with type 1 diabetes mellitus – systematic review. Exp Clin Endocrinol Diabetes 121: 248–254.

78) Barnard K, Parkin C, Young A, Ashraf M (2012) Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. J Diabetes Sci Technol 6:144–149.

79) Levy, Davies, Holman for the 4-T Study Group. Continuous glucose monitoring detected hypoglycemia in the Treating to Target in Type 2 Diabetes Trial (4-T). Diabetes Res Clin Pract. 2017 Sep;131:161-168.

80) ZICK et al. Comparison of Continuous Blood Glucose Measurement with Conventional Documentation of Hypoglycemia in Patients with Type 2 Diabetes on Multiple Daily Insulin Injection Therapy. Diabetes Technol Ther. 2007 Dec;9(6):483-92

81) Agesen et al. Effect of Insulin Analogs on Frequency of Non–Severe Hypoglycemia in Patients with Type 1 Diabetes Prone to Severe Hypoglycemia: Much Higher Rates Detected by Continuous Glucose Monitoring than by Self-Monitoring of Blood Glucose—The HypoAna Trial. Diabetes Technol Ther. 2018 Mar;20(3):247-256.

82) Edelman et al. Clinical Implications of Real-time and Intermittently Scanned Continuous Glucose Monitoring. Diabetes Care 2018;41:2265–2274.

83) Bolinder , Antuna , Geelhoed-Duijvestijn , et al.. Novel glucose-sensing technology and hypoglycemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016; 388: 2254–2263.

84) Reddy et al. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycemia. Diabet Med. 2018 Apr; 35(4): 483–490.

85) O´lafsdo'ttir et al. A Randomized Clinical Trial of the Effect of Continuous Glucose Monitoring on Nocturnal Hypoglycemia, Daytime Hypoglycemia, Glycemic Variability, and Hypoglycemia Confidence in Persons with Type 1 Diabetes Treated with Multiple Daily Insulin Injections (GOLD-3). Diabetes Technol Ther. 2018 Apr;20(4):274-284.

86) Beck RW, Riddlesworth T, Ruedy K, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 2017; 317: 371–378.

87) Lind M, Polonsky W, Hirsch IB, et al. Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA 2017; 317: 379–387.

88) Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycemia awareness or severe hypoglycemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018; 391: 1367–1377.

89) van Beers CA, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycemia (IN CONTROL): a randomised, open-label, crossover trial. Lancet Diabetes Endocrinol 2016; 4: 893–902.

90) Battelino T, Phillip M, Bratina N, et al. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011;34:795-800.

91) Haak T, Hanaire H, Ajjan R, et al. Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes Ther 2017; 8: 573–586

92) Leelarathna L, Wilmot EG. Flash forward: a review of flash glucose monitoring. Diabet Med 2018; 35: 472–482.

93) Laffel LM, Aleppo G, Buckingham BA, et al. A practical approach to using trend arrows on the Dexcom G5 CGM system to manage children and adolescents with diabetes. J Endocr Soc 2017;1:1461–1476.

94) Danne et al. international consensus on use of continuous glucose monitoring. Diabetes Care 2017 Dec; 40(12): 1631-1640.

95) Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019 Jun 8. pii: dci190028. doi: 10.2337/dci19-0028. [Epub ahead of print].

96) Bosi, Choudhary, de Valk, et al. SMILE Study Group. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycemia-proneadults with type 1 diabetes (SMILE): an open-label randomised controlled trial. Lancet Diabetes Endocrinol. 2019 Jun;7(6):462-472.

97) Choudhary et al. Use of sensor integrated pump therapy to reduce hypoglycemia in people with Type 1 diabetes: a real-world study in the UK. Diabet Med. 2019 May 27. doi: 10.1111/dme.14043. [Epub ahead of print].

98) Weisman A, Bai JW, Cardinez M, et al. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomized controlled trials. Lancet Diabetes Endocrinol. 2017;5:501–12.

99) Anderson, Buckingham, Breton, et al. Hybrid Closed -Loop Control Is Safe and Effective for People with Type 1 Diabetes Who Are at Moderate to High Risk for Hypoglycemia. Diabetes Technol Ther. 2019 Jun;21(6):356-363.

100) Garg, Weinzimer, Tamborlane, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2017;19:155–63.

101) Rossi et al. Impact of the "Diabetes Interactive Diary" telemedicine system on metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes Diabetes Technol Ther. 2013 Aug;15(8):670-9.

102) Biagi L, Bertachi A, Quiro´s C, et al. Accuracy of continuous glucose monitoring before, during, and after aerobic and anaerobic exercise in patients with type 1 diabetes mellitus. Biosensors 2018;8:E22.

103) Dessi et al. Lag Time Remains with Newer Real-Time Continuous Glucose Monitoring Technology During Aerobic Exercise in Adults Living with Type 1 Diabetes. Diabetes Technol Ther. 2019 Jun;21(6):313-321.

104) Bailey. Clinical Implications of Accuracy Measurements of Continuous Glucose Sensors. Diabetes Technol Ther. 2017 May;19(S2):S51-S54.

105) Little el al. Recovery of Hypoglycemia Awareness in Long-standing Type 1 Diabetes: A Multicenter 2 X 2 Factorial Randomized Controlled Trial Comparing Insulin Pump With Multiple Daily Injections and Continuous With Conventional Glucose Self-monitoring (HypoCOMPaSS) Diabetes Care 2014;37:2114–2122.

106) International Hypoglycemia Study Group. Minimizing Hypoglycemia in Diabetes. Diabetes Care 2015;38:1583–1591.

107) Feuerstein-Simon C , Bzdick S , Padmanabhuni A , et al. Use of a Smartphone Application to Reduce Hypoglycemia in Type 1 Diabetes: A Pilot Study.J Diabetes Sci Technol. 2018 Nov;12(6):1192-1199. doi: 10.1177/1932296817749859. Epub 2018 Jan 1.

108) Offringa R, Sheng T, Parks L et al. Digital Diabetes Management Application Improves Glycemic Outcomes in People With Type 1 and Type 2 Diabetes. Journal of Diabetes Science and Technology 2018, Vol. 12(3) 701 –708.

109) https://apps.apple.com/us/app/glucagon/id553314007. Accessed December 3, 2019.

110) https://www.hypoprogram.com/. Accessed December 3, 2019.

111) Contreras I, Vehi J. Artificial Intelligence for Diabetes Management and Decision Support: Literature Review J Med Internet Res. 2018;20(5):e10775.

112) Vehí J, Contreras I, Oviedo S, et al. Prediction and prevention of hypoglycaemic events in type-1 diabetic patients using machine learning. Health Informatics J. 2019;13:1460458219850682.

113) Farngrem, Ahrén B. Incretin-based medications (GLP-1 receptor agonists, DPP-4 inhibitors) as a means to avoid hypoglycaemic episodes.Metabolism 2019;99:25-31.

114) Nauck MA, Heimesaat MM, Behle K et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab 2001;87: 1239-46

115) Husain M, Birkenfeld AL, Donsmark M et al Pioneer 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2019;29;381(9):841-851. DOI:10.1056/NEJMoa190118.

116) Rosenthal N, Meininger G, Ways K et Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes Mellitus. Ann NY Acad Sci 2015;1358:28-43.

117) McMurray JJV, Solomon SD, Inzucchi SE et al. et al for the DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019.. doi: 10.1056/NEJMoa1911303.

118) TODAY Study Group. A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes. N Engl J Med 2012;366:2247-56.

119) Davies MJ, D'Alessio DA, Fradkin J et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018; 61:2461-98.

120) Ringholm L, Damm P, Mathiesen ER. Improving pregnancy outcomes in women with diabetes mellitus: modern management. Nat Rev Endocrinol. 2019;15(7):406-416. doi: 10.1038/s41574-019-0197-3.

121) Rosenn B, Siddiqi TA, Miodovnik M. Normalization of blood glucose in insulin-dependent diabetic pregnancies and the risks of hypoglycemia: a therapeutic dilemma. Obstet Gynecol Surv 50:56–61, 1995.

122) Evers IM, ter Braak EW, de Valk HW, et al. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. Diabetes Care. 2002;25(3):554-9.

123) Kyne-Grzebalski D, Wood L, Marshall SM, Taylor R: Episodic hyperglycaemia in pregnant women with well-controlled type 1 diabetes mellitus: a major potential factor underlying macrosomia. Diabet Med 16:702–706, 1999.

124) Smoak IW, Sadler TW. Embryopathic effects of short-term exposure to hypoglycemia in mouse embryos in vitro. Am J Obstet Gynecol 163:619–624, 1990.

125) Persson B, Hansson U. Hypoglycemia in pregnancy. Baillieres Clin Endocrinol Metab 1993;7:731–739.

126) ter Braak EW, Evers IM, Willem Erkelens D, Visser GH. Maternal hypoglycemia during pregnancy in type 1 diabetes: maternal and fetal consequences. Diabetes Metab Res Rev 2002;18:96–105.

127) Rosenn BM, Miodovnik M, Holcberg G, et al. Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. Obstet Gynecol 85:417–422, 1995.

128) Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, et al.. Hypoglycemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. Diabetes Care. 2008 Jan;31(1):9-14.

129) Evers IM, ter Braak EW, de Valk HW, et al. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. Diabetes Care. 2002 Mar;25(3):554-9.

130) DCCT group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial: the DCCT Research Group [see comments]. Am J Med 90:450–459, 1991.

131) Cryer P: Hypoglycemia is the limiting factor in the management of diabetes. Diabet Metab Res Rev 15:42–46, 1999.

132) Kristensen K, Ogge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia. 23 March 2019 [Epub ahead of print]. DOI: 10.1007/s00125-019-4850-0.

133) Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017; 390:2347–2359.

134) Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran S, Bellaire S, Raben A, Insulin Aspart Pregnancy Study Group. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care 2007;30:771–776.

135) Heller S, Damm P, Mersebach H, Skjøth TV, Kaaja R, Hod M, Durán-García S, McCance D, Mathiesen ER. Hypoglycemia in type 1 diabetic pregnancy: role of preconception insulin aspart treatment in a randomized study. Diabetes Care. 2010 Mar;33(3):473-7.

136) Abraham et al. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatric Diabetes October 2018; 19 (Suppl. 27): 178–192.

137) Thornton et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. The Journal of Pediatrics, Vol. 167, No. 2 August 2015.

138) Deeb et al. A phase 3 multicenter, open-label, prospective study designed to evaluate the effectiveness and ease of use of nasal glucagon in the treatment of moderate and severe hypoglycemia in children and adolescents with type 1 diabetes in the home or school setting. Pediatr Diabetes. 2018 Aug;19(5):1007-1013.

139) Gandhi, Kajal. Approach to hypoglycemia in infants and children. Transl Pediatr Oct 2017, 17;6(4):408-420.

140) Cardona S, Gomez PC, Vellanki P, et al. Clinical characteristics and outcomes of symptomatic and asymptomatic hypoglycemia in hospitalized patients with diabetes. BMJ Open Diab Res Care 2018;6:e000607. doi:10.1136/bmjdrc-2018-000607

141) Spat, S, Donsa, K, Beck, P, et al. A Mobile Computerized Decision Support System to Prevent Hypoglycemia in Hospitalized Patients With Type 2 Diabetes Mellitus: Lessons Learned From a Clinical Feasibility Study Journal of Diabetes Science and Technology 2017, Vol. 11(1) 20 –28.

142) https://www.pewresearch.org/fact-tank/2017/04/06/. Accessed august 4th 2019.

143) Al-Arouj M, Assaad-Khalil S, Buse J et al. Recommendations for Management of Diabetes During Ramadan Update 2010.

144) Salti I, Be´nard E, Detournay B, et al. EPIDAR study group. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 2004;27:2306–2311.

145) Ibrahim M, Abu AlMagd M, Annabi FA, et al. Recommendations for management of diabetes during Ramadan: update 2015.BMJ Open Diabetes Research and Care 2015;3:e000108. doi:10.1136/bmjdrc-2015-000108.

146) Maier Beckera ,Tomas Karpatia ,Liora Valinskyab , Anthony Heymann. The impact of the Yom Kippur fast on emergency room visits among people with diabetes. Diabetes Research and Clinical Practice Volume 99, Issue 1, January 2013, Pages e12-e13 https://doi.org/10.1016/j.diabres.2012.10.005.

147) Grajower MM, Zangen D. Expert opinion and clinical experience regarding patients with type 1 diabetes mellitus fasting on Yom Kippur. Pediatr Diabetes 2011:12: 473–477.

148) Ibrahim M, Abdelaziz SI, Abu Almagd M, et al. Recommendations for management of diabetes and its complications during Hajj (Muslim pilgrimage).BMJ Open Diab Res Care2018;6:e000574. doi:10.1136/bmjdrc-2018-000574

149) Warburton DER, Bredin SSD. Curr Opin Cardiol. Health benefits of physical activity: a systematic review of current systematic reviews. 2017;32(5):541-556. doi: 10.1097/HCO.0000000000000437.Review.PMID:28708630.

150) Colberg SR , Sigal, RJ, Yardley, JE et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association . Diabetes Care 2016 Nov; 39(11): 2065-2079.

151) Schellenberg ES, Dryden DM, Vandermeer B,Ha C, Korownyk C . Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:543–551.

152) Ibrahim M, Tuomilehto J, Aschner P, et al. Global status of diabetes prevention and prospects for action: A consensus statement. Diabetes Metab Res Rev.2018;e3021. doi: 10.1002/dmrr.3021. Epub 2018 Jun 8.

153) Bussau VA, Ferreira LD, Jones TW, Fournier PA . A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. Diabetologia 2007;50:1815–1818.

154) Maran A, Pavan P, Bonsembiante B, et al . Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. Diabetes Technol Ther 2010;12:763–768.

155) MacDonald MJ Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care 1987;10:584–588.

156) Campbell MD, Walker M, Bracken RM, et al . Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: a randomized controlled trial. BMJ Open Diabetes Res Care. 2015. 12;3(1):e000085. doi: 10.1136/bmjdrc-2015-000085. eCollection 2015

157) Neufeld M, Blizzzard RM. In: Pinchera, A ed. Autoimmune aspects of endocrine disorders. New York: Academic Press, 1980:357.

158) Samaan NA .Hypoglycemia secondary to endocrine deficiencies. Endocrinol Metab Clin North Am. 1989 Mar; 18(1):145-54.

159) Saleh M, Grunberger G. Hypoglycemia: An excuse for poor glycemic control? Clin Diabetes. 2001;19:161–7.

160) McCulloch AJ, Johnston DG, Baylis PH, et al. Evidence that thyroid hormones regulate gluconeogenesis from glycerol in man. Clin Endocrinol. 1983;19:67–76.

161) McDaniel HG, Pittman CS, Oh SJ, DiMauro S. Carbohydrate metabolism in hypothyroid myopathy. Metabolism. 1977 Aug; 26(8):867-73.

162) Morioka T, Ohba K, Morita H, et al. Non-islet cell tumor-induced hypoglycemia associated with macronodular pulmonary metastases from poorly differentiated thyroid. Thyroid. 2014;24(2):395-9. doi: 10.1089/thy.2013.0141. Epub 2013 Sep 11.

163) Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline.. The Journal of Clinical Endocrinology & Metabolism. 2009. 94;3(1):709–728. https://doi.org/10.1210/jc.2008-1410

"Authors' contributions:
MI determined the manuscript strategy , wrote the first draft , fixed the coauthors comments on each version , JB wrote a section about hypoglycemia in children , AC wrote a section about the definition of hypoglycemia in clinical trials , RHE , PG JT and GEU provided intellectual content in interpreting data and critically reviewed the manuscript , NES shared in the technology section and helped in fixing some coauthors comments , RDL & SP wrote a section Disease heterogeneity and severe hypoglycemia risk , SP, DT & PP wrote a section about hypoglycemia unawareness and contributed substantially to write the manuscript , BR wrote a section about newer antidiabetic drugs and risk of hypoglycemia , ER wrote a section about Technology and Hypoglycemia , ER wrote a section about Association with CV outcomes and the role of frailty , SLW wrote a section about hypoglycemia in Endocrine Disorders , All authors revised and approved the final version of the manuscript."