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Strategies to Avoid Hypoglycemia in Patients with Diabetes Mellitus Receiving Pharmacotherapy – A Review

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Abstract

Diabetes mellitus (DM) is a metabolic disorder presenting with high blood glucose concentrations which exert detrimental damage to structures and functions of multiple organs and tissues due to chemical as well as physical changes in the milieu of long time exposure to hyperglycemia. The frequent co-existence of hypertension, dyslipidemia, and chronic kidney disease as significant cardiovascular disease risk factors may further cause and exaggerate severities of pathophysiological changes in both micro- and macro-vascular systems. To minimize the detrimental impact on health caused by this continuum of cardio-metabolic disorder, it is imperative to bring the above-mentioned disorders back to normal status as early and as much as possible, with hyperglycemia the most fundamental element encountered by health-care givers involved in management of DM. Nevertheless, mostly the stringent goals of glycemia intensely pursued can only be achieved by the use of intensified anti-diabetic pharmacological therapies. And, while doing so patients may frequently be frustrated by facing the opposite side of glycemic spectrum, which is hypoglycemia, an even worse and unwanted impact that may result in deteriorating function in cardiovascular, neurological, and cognitive functions, or even death in vulnerable patient groups. Patients at risk including the elderly, the frail, and those with poor renal function and/or cardiovascular diseases must be identified, anti-diabetic regimen individually tailored, structured diabetes education programs and, when applicable, appropriate modern technologies regarding glycemic monitoring provided, to minimize risk of hypoglycemia while optimal glycemic control is managed in a comprehensive manner. (J Intern Med Taiwan 2022; 33: 16-33)

Key Words: Diabetes Mellitus, Counter-regulatory hormone responses, Hypoglycemia unawareness, Severe hypoglycemia

Introduction

The prominently higher rates of multiple morbidities (cardio-renal and micro-vascular complications) and mortality observed in patients with diabetes mellitus (DM) as compared with the non-

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diabetic population are caused not only by the significantly higher rates of associated cardiovascular (CV) risk factors (e.g. hypertension, dyslipidemia, chronic kidney disease) but also the chronic exposure to hyperglycemia per se [1-3]. In a large cohort of 271,174 patients with T2DM who were recruited in the Swedish National Diabetes Register, among those 96,673 (35.6%) with complete data on all of the five risk factors analyzed (glycated hemoglobin (HbA1c) level ≥ 7.0%, low-density lipoprotein cholesterol (LDL-C) level ≥ 97 mg/dL, presence of micro- or macro-albuminuria, smoking, and high blood pressure (BP) with systolic BP ≥ 140 mmHg or diastolic BP ≥ 80 mmHg) that are considered to be associated with higher risks of acute myocardial infarction (AMI), stroke, hospitalization for heart failure, and death, an HbA1c level above the target range was found to rank first among the various strongest predictive factors for AMI and stroke [4]. In various acute disease states that require hospitalization into general ward or intensive care unit (ICU) for care, the presence of hyperglycemia has been found to be associated with poor clinical outcomes regarding length of stay, rate of infections, morbidity, mortality, and overall complications regardless of existing diagnosis of diabetes[5]. In patients suffering from intracranial hemorrhage, a retrospective study on association between trajectory glycemia over time and patients' outcomes had found that patients with persistent hyperglycemia (defined as > 144 mg/dL) throughout the 72-hour observation period and early hyperglycemia in the first 24 hours after event onset had significantly higher rate of 6-month mortality compared to those with persistently normoglycemia and late hyperglycemia[6]. Though not a universal finding, results from certain studies have shown that the negative impact from in-hospital hyperglycemia could be improved when target-driven control of hyperglycemia is intentionally approached[7,8]. On the other hand, clinical observations and trials have noted there existing a U-shaped effect of glycemia on various outcomes of patients with DM. A meta-analysis derived from published literatures had found that, among the diabetes cohort examined, HbA1c levels ranging between 6 and 8% were associated with the lowest all-cause and CV mortality, as compared to levels above (with the highest when > 9.0%) or below (with significantly higher risk when < 6.0%) this range[9]. In an observational, prospective, and multi-center study with follow-up of over 7.4 years among a cohort of 15,656 Caucasian patients with T2DM, it was found that the mortality risk was not only increased in patients having the highest HbA1c category (> 8.5%) (adjusted hazard ratio:1.34, 95% confidence interval [CI], 1.22-1.47, $p < 0.001$), but also in those having the lowest HbA1c category (< 6.5%) (1.16, CI,1.03-1.29, $p = 0.01$) after adjustment for other risk factors including age, gender, smoking habits, diabetes duration, body mass index (BMI), triglycerides, total and high-density lipoprotein cholesterol, lipid-lowering treatment, systolic and diastolic BP, and anti-hypertensive treatment[10]. Furthermore, stringent glycemic control to near-normal level in patients with diabetes who were to receive percutaneous coronary intervention (PCI) has been found to carry a poor prognosis for clinical outcomes. In a single-center, retrospective observational study carried out in Japan, a consecutive 4,542 patients who underwent PCI between years 2000 and 2016 were followed for a median of 6.2 years to examine the association between HbA1c levels and CV mortality. Among the five HbA1c levels categorized (< 6.5%, 6.5-7.0%, 7.0-7.5%, 7.5-8.5% and ≥ 8.5%), the investigators found that there was a significantly higher cumulative CV death in patients with a pre-procedure HbA1c < 6.5% as compared to those with 7.0-7.5% ($p = 0.042$). A U-shaped relationship between pre-procedural HbA1c level and risk of CV death was revealed, and the lowest risk was seen in those with HbA1c levels of 7.0-7.5%[11]. Although there could be specific causes, such as

frailty and a decline in functional reserve in certain patient groups that may contribute to the association between low HbA1c levels and poorer outcomes, a tight glycemic control may not be applicable to all patients with diabetes. It would be prudent for both health-care providers and patients to find the most appropriate glycemic control strategy based on individual requirement to stand on a firm stage where benefits gained and harms avoided during the management of this chronic disease[12-14].

A walk on a tightrope

Based on results derived from multiple long-term clinical trials and after-trial follow-ups conducted in patients with T1DM or T2DM, optimal control of glucose concentrations to as close to the upper end of the normal ranges as clinically feasible has been advocated to prevent long-term complications from chronic exposure to hyperglycemia[15,16]. However, despite the well-recognized benefits of keeping glycemia to homeostasis, patients with diabetes have to always tread on a tightrope to keep balance between the swings of high and low glucose concentrations, since the occurrence of the latter, when severe enough may acutely precipitate the general health of the patients to critical and hazardous states. Of concern is that a diminution in the symptomatic responses to hypoglycemia has long been observed as patients approach near normo-glycemia while receiving intensified glucose-lowering regimens[17]. Furthermore, the threshold of ambient glucose concentrations required to trigger the reactive symptoms would fall after repetitive episodes of hypoglycemia[18]. An association between subjective unawareness to hypoglycemia happening and a failure in epinephrine secretion has been demonstrated in previous clinical studies. Even a single episode of hypoglycemia is sufficient to partially attenuate epinephrine secretion and the symptoms associated, and repetitive episodes may further lead to an autonomic failure[19]. Human brain has an absolute dependence on glucose utilization as its source of energy, and glycogen as storage form in the brain (primarily in astrocytes) could only fuel brain function for a few minutes in the absence of continuous provision of glucose[20]. When the glucose supply is interrupted, shortage of glucose in the brain (neuroglycopenia) triggers a hierarchy of neuroendocrine responses with the first defense a decrease in insulin secretion, which is followed by increase in the secretion of glucagon for hepatic glycogenolysis and the glucose-raising hormone epinephrine from adreno-medullary activation. Only after prompt and potent counter-regulatory hormone responses (CRHR) are triggered by neuroglycopenia then are blood glucose (BG) levels raised to maintain brain function normal. Reactive symptoms aroused by the sympatho-adrenal system include a sensation of hunger, palpitations, tremulousness, and sweating, whereas those by neuroglycopenia can manifest as difficult concentration, confusion, hallucinations, irritability, bizarre behavior, focal neurological deficits (e.g, hemiplegia), and, in extreme cases, coma or even death. Ambient glucose concentrations in previous time periods can influence the thresholds at which an individual responding to subsequent hypoglycemia episodes. Patients who had experienced repeated hypoglycemia may have blunted or almost no symptoms (impaired awareness or unawareness to hypoglycemia) due to development of autonomic failure[18,21].

Definition of hypoglycemia in patients with DM

A BG concentration of 70 mg/dL has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes. Since patients with diabetes may demonstrate impaired CRHR to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level < 70 mg/dL is considered clinically important independent of the presence or severity of hypoglycemic

symptoms. Furthermore, a fact not to be neglected is the advancing hypoglycemic effects from certain anti-diabetic agents (ADAs) (e.g. exogenous insulin or sulfonylureas (SUs) as insulin-secretagogues) the suffering patients may have received. Hence, the mildest but clinically significant level 1 hypoglycemia is defined as a BG level lower than 70 mg/dL. When BG level drops further down to 54 mg/dL and lower, a more severe level 2 hypoglycemia is reached, the threshold at which neuroglycopenic symptoms are about to occur and immediate action to resolve the event is required. Finally, a level 3 hypoglycemia (severe hypoglycemia, SH) is defined as an event severe enough to require assistance from other persons for recovery due to altered mental and/or physical functioning[22].

Epidemiology of hypoglycemia in patients with DM

Despite the efforts spent for betterment in structured diabetes management, significant advancement in the development of anti-diabetic pharmaco-therapeutics, and applications of multiple cutting-edge monitoring systems in modern era, the improvement anticipated in glycemic control for patients with DM throughout the past 2 to 3 decades has not been consistent in all observational studies[23-27]. During the pursuit of near-normal or even non-diabetic glycemic goals, there comes also an increase in the prevalence of hypoglycemia, which may instead cause an impeding barrier to glycemic control[28-30]. Patients with T1DM are consistently noted to be at higher risk of developing hypoglycemia than patients with T2DM. In a systematic literature review conducted to analyze results of studies carried out in Spain, it was found that the estimated rate of SH events ranged from 0.90 to 1.50 per patient per year (PPPY) in patients with T1DM, while the corresponding figure was from 0.30 to 0.63 PPPY in T2DM counterpart. Furthermore, patients who experienced hypoglycemic events expressed a higher fear and had a poorer quality of life (QoL) than those who did not[31]. In the Diabetes Control and Complications Trial (DCCT), those T1DM subjects assigned to intensive (INT) diabetes therapy who achieved a median HbA1c of 7% was noted to have a 3-fold higher increase in the rate of SH compared to the conventional (CON) therapy group with a mean HbA1c of 9% (61.2 vs. 18.7 per 100 patient-years (PY)). A similar rate was also found in the subset of episodes involving coma or seizure. It was later found that nearly half of the DCCT and the following 18 years of Epidemiology of Diabetes Interventions and Complications (EDIC) trial cohort had reported episodes of SH. During EDIC, the adoption of INT by the original CON group resulted in a narrowing and then disappearance of the differences in HbA1c levels maintained during DCCT. On the other hand, while the rate of SH in the former INT group of DCCT fell, it rose instead in the former CON group, finally equalizing each other (40.8 vs. 36.6 episodes per 100 PY, respectively) with a relative risk of 1.12 (95% CI, 0.91-1.37). It was concluded that SH remains a challenge persistently for T1DM patients across their life span[29]. To find the epidemiology of hypoglycemia in real world scenario, a study carried out in Canada was conducted by distributing questionnaires to adults (≥ 18 year-old) patients with T1DM or T2DM. In the total of 552 subjects (T1DM: 17%; T2DM: 83%) who had completed the questionnaire, up to 65.2% of the total respondents reported experiencing at least one event (severe or not) at an annual crude incidence density of 35.1 events per person-year (PPY). The findings underline an urgent need for improving management strategies aiming at reducing the burden that hypoglycemia could cause[32]. Reported rates of hypoglycemia in T2DM vary widely as there is marked heterogeneity in how hypoglycemia is defined (documented- or patient-reported hypoglycemia) and sources of data obtained (survey or interview in cross-sectional

studies, or the use of administrative or electronic health record data or diagnosis codes retrieved in retrospective studies) in different research works. In randomized controlled trials, rates of SH ranging from 0.7 to 12 per 100 PY have been reported. In observational studies, from 0.2 (patients treated without insulin or SU) to 2.0 per 100 PY (insulin- or SU-users) of the study populations have been found to require emergency department (ED) visits or hospitalization due to hypoglycemia (HH)[33]. Of note, patients receiving insulin therapy had higher self-reported rates of hypoglycemia[34]. A post hoc analysis of data derived from the Veterans Affairs Diabetes Trial (VADT), which included 1,791 T2DM military veterans (age 60.5 ± 9.0 years) with sub-optimal glycemic control (HbA1c 9.4 ± 2.0%), a disease duration of 11.5 ± 7.5 years, with or without known CV disease and additional CV risk factors at study entry, had revealed that the rate of SH in the intensive treatment arm was 10.3 per 100 PY compared with 3.7 per 100 PY in the standard treatment counterpart ($p < 0.001$). Multivariable analysis further identified that insulin use at baseline ($p = 0.02$), presence of proteinuria ($p = 0.009$) and autonomic neuropathy ($p = 0.01$) were independent risk factors for SH. A notable finding in this clinical trial found that, SH within the past 3 months regardless of glycemic treatment group assignment was associated with a significantly higher risk of serious CV events ($p = 0.032$), CV mortality ($p = 0.012$), and total mortality ($p = 0.024$)[28].

The settings where the hypoglycemia is assessed may give different results regarding epidemiology reported. ED in a hospital is usually the site where patients suffering from SH are investigated for cause-finding and immediate management. From a national dataset containing longitudinal medical claims of the insures under universal health insurance coverage in Taiwan, the time trends of hypoglycemia-related ED visits between years 2000 and 2010 with focus on T2DM patients receiving anti-diabetic agents were analyzed. Rates of hypoglycemia-related ED visits increased significantly by a 4.8-fold during this time period examined (adjusted incidence rate ratios (IRR) 4.88, 95% CI, 3.94-6.05, $p < 0.001$). SH requiring ED visits was also noted to prevail in patients older than 65 years[35]. A retrospective, observational study which included patients visiting ED with a measured finger prick BG ≤ 60 mg/dL at the time of arrival retrieved from ED triage register was performed in a tertiary care medical college hospital in South India. Among patients with DM (69.3% of the cohort studied) who were diagnosed to have hypoglycemia (mean random BG measured by glucometer: 39 mg/dL), identifiable causes included medication-related in the majority of cases (intensive control by oral hypoglycemic agents and/or insulin therapy, 59.81%), followed by infections (20.19%) and chronic kidney disease (11.40%)[36]. In a retrospective analysis from an administrative data set of commercially insured and Medicare Advantage beneficiaries across the U.S., the causes of re-admission within 30-days from an index hospitalization among T2DM patients were analyzed, and the results showed that severe dysglycemia, which ranked second to heart failure, accounted for 2.6% of index hospitalizations (50.4% hypoglycemia, 48.1% hyperglycemia, 1.5% unspecified) and 2.5% of readmissions (61.0% hypoglycemia, 38.3% hyperglycemia, 0.7% unspecified), respectively[37].

Complications of hypoglycemia

Mild hypoglycemia may cause generalized discomfort, impairment in carrying out regular daily activities, and a negative impact on QoL. These impacts may be quickly relieved with prompt recognition and self- or assisted management without significant sequelae. However, asymptomatic hypoglycemia as well as BG swings created in laboratories has been found to be associated with systemic inflammation, oxidative stress, impaired nitric

oxide bioavailability, and endothelial dysfunction, the occurrences of which have been considered as risk factors preceding the development of clinical cardiovascular events[38,39]. Although mild or moderate hypoglycemia is not life-threatening, it may still cause cognitive impairment if recurring frequently. In an animal study by using STZ-induced T1DM rat model to assess cognitive function by using Barnes maze and open field tests, recurrent and moderate hypoglycemia was induced by insulin injection. After 6 weeks of experiment, it was found that the hypoglycemia-induced oxidative injury of the hippocampal Cornu Ammonis-1 dendritic region was associated with chronic cognitive impairment in diabetic rats thus treated. The neuronal damage could be reduced by the administration of nicotinamide adenine dinucleotide phosphate oxidase assembly inhibitor, apocynin, providing evidence of oxidative injury as underlying pathology induced by hypoglycemia[40]. Though findings may differ, reported clinical cases using magnetic resonance imaging (MRI) to assess the changes in human brains during hypoglycemia insult had demonstrated lesions identifiable in certain topographic localizations (e.g. the posterior limb of the internal capsule, cerebral cortex, corona radiata, centrum semiovale, hippocampus, and basal ganglia), and notably, reversible changes on follow-up imaging had been observed after correction of hypoglycemia[41,42]. Hypoglycemia has long been known to affect the patterns of electrocardiogram (ECG) recordings, causing ST wave changes with lengthening of the QT interval and cardiac repolarization[43]. There have been cases reported on non-ST segment-elevation or ST segment changes on ECG recordings mimicking patterns of MI during episodes of hypoglycemia, and the electrophysiological changes were reversed to normal on correction of hypoglycemia. Thus, in any patient with diabetes who is noted to have abnormal ECG patterns, hypoglycemia should be enlisted in differential diagnoses[44,45]. In a clinical study conducted in insulin-induced hypoglycemia (a controlled steady fall in BG down to ~31 mg/dL) in patients of T1DM with mean HbA1c 7.4% at study baseline, it was found that, compared to findings during euglycemia time frame, there were hypoglycemia-associated changes in both ECG and electroencephalography (EEG) patterns almost at the same time. Since SH is preceded by changes in both ECG and EEG features in this study, the authors considered, if practically applicable, use of a biosensor that combines information obtained from both EEG and ECG recordings a valuable measure for early detection of hypoglycemia episode for patients at risk[46]. Due to all these notable harms that hypoglycemia could cause to general health, indiscriminate application of intensive glucose-lowering therapy with potential of precipitating diabetic patients to dangerous hypoglycemia, especially in those having risk factors for or history of overt CVD, should be mindfully avoided. Patients with T2DM who had experienced SH have been shown to have an increased risk of mortality. In a retrospective study using nationally representative sample of Taiwanese adults aged 65 years and older who were diagnosed with new-onset diabetes (NOD), data available between years 2001-2011 were analyzed to investigate into the all-cause mortality rates and adverse health outcomes among this cohort. The results regarding impact of hypoglycemia on the outcomes of interest have shown that the rate of mortality in those diabetes patients who had hypoglycemia was significantly higher than the non-hypoglycemia counterpart with adjusted relative risk of 2.33 (95% CI, 1.81-3.01) for men and 2.73 (95% CI, 2.10-3.52) for women after adjustment for other variables[47]. In another nationwide population study conducted in Korea by using the database retrieved from the National Health Insurance System of Korea which covers the entire Korean population, the association between episodes of SH and CVD risk and all-cause mortality in patients with T2DM during the

period between years 2007 and 2009 was investigated. After adjustment for confounding factors, the hazard ratio (HR) of MI was noted to increase significantly with frequency of hypoglycemia episodes in a sequential manner as follows: 0 vs. 1 episode, HR 1.56 (95% CI, 1.46-1.64); 0 vs. 2 episodes, HR 1.86 (95% CI, 1.61-2.15); 0 vs. 3 or more episodes, HR 1.86 (95% CI, 1.48-2.35, p for trend all < 0.001). Similar findings were noted regarding the association of SH episodes with stroke, heart failure, and all-cause mortality. The authors concluded that the possibility of direct causality between SH and CV outcomes and mortality was suggested from these significant results[48]. Furthermore, a bidirectional nature of the association between SH and CV events has been observed in patients with T2DM. In a post hoc analysis of results from 14,752 T2DM patients recruited in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) study, although the SH episodes were not common and not associated with use of this incretin therapy, the investigators had noted that not only SH was significantly associated with high risk for subsequent CV events, but also CV events were significantly associated with high risk for subsequent SH. The occurrence of either SH episodes or CV events can predispose patients with T2DM to a higher hazard of having the other one[49].

Risk factors for hypoglycemia

Multiple risk factors have been identified that may predispose patients of DM who are receiving anti-diabetic medications to the development of hypoglycemia.

Elderly patients of DM- In general, the principles applied to older patients with diabetes are not much different from those for younger patients, including life style modification and adequate use of various kinds of ADAs. However, since the elderly may suffer from a higher risk for hypoglycemia due to altered adaptive physiologic responses to low glucose levels, having comorbidities such as cognitive and functional loss that interfere with prompt identification and/or appropriate treatment of hypoglycemia, special emphasis on avoiding hypoglycemia is highly required in this vulnerable patient group[50]. Using claims data from 1.66 million privately insured and Medicare Advantage patients with T2DM from years 2006 to 2013 in the U.S., the overall age- and sex-standardized rate of SH was 1.3 events per 100 PY in both years 2006 and 2013 (p for trend over time: 0.72). Although SH rate was noted to have modestly decreased over this time period among the older (age 65-74; 1.4 to 1.3 events per 100 PY; $p < 0.001$) and the oldest (age ≥ 75; 2.9 to 2.3 events per 100 PY; $p < 0.001$) populations, it still ranked the highest among patients of the oldest-age, as compared to other younger age groups. Patients with two or more comorbidities had remained a high rate of SH throughout the study period (3.2 to 3.5; $p = 0.36$). In a recent study carried out in old T1DM patients (mean age 67.2 year-old), SH was found to be associated with reduced cognitive function when global and domain-specific cognition (language, executive function, episodic memory, and simple attention) were assessed. The findings deserve clinical attention on considering the increasing life expectancy in people with T1DM[51].

Impaired renal function- Changes in drug pharmacokinetics due to decreased kidney function is important clinical issue, since most ADAs are excreted by the kidneys. Instead of serum creatinine levels, the Cockroft-Gualt and the Modification of Diet in Renal Disease formulas are used to calculate the estimated glomerular filtration rates (eGFR) for adjusting the doses of medications, including ADAs. When the prescription of more recently developed ADAs has been on a steady rise, metformin still ranks first as the most-prescribed first-line agent for T2DM patients[52]. The risk for lactic acidosis in patients with decline in renal function has been a major concern when using metformin, especially in older populations. However, a meta-analy-

sis of studies over the past 2 decades has shown that metformin can be used safely in patients with eGFR up to 45[53]. Insulin and SUs are commonly used ADAs to raise plasma insulin concentrations which are known to cause higher risks for hypoglycemia, especially in patients with impaired renal function[54,55]. A judicious use of these agents is advised during clinical practices when treating patients at risk of hypoglycemia[56].

Near-normal glycemic control goals reached- A common clinical observation is the association between higher risk of hypoglycemia and the achieved HbA1c levels at the lower end, a reversed relationship between the two parameters that could also be drawn from randomized clinical trials designed to compare efficacies and safety issues among various treatment modalities[57]. In the DCCT/EDIC study, it was noted that a preceding episode of SH was the most powerful predictor of subsequent episodes. Rates of SH increased with lower HbA1c levels similarly among participants in both treatment groups (CON or INT)[29]. However, a U-shaped relationship between high- or low- glycemic profile and HH has been found in a nested case-control study (no = 304 in each comparative group) conducted in England. The results indicated that in T2DM patients, a proximal HbA1c level (defined as most proximal to, and within 90 days before the first HH) above or below the reference value of 7.0% increases the risk of a first incidence of HH. The investigators found that when HbA1c level was between 8.0% and 11.5%, even a small increment of 0.5% was associated with a 16% to 34% higher risk of first HH. On the other hand, when HbA1c level was between 4.0% and 6.5%, a 0.5% increment was associated with a 14% to 63% lower risk of first HH, indicating a higher risk of hypoglycemia in the face of lower HbA1c reached. The investigators also found that approximately 78% of current non-insulin non-SU users had received insulin or SUs prior to the index HH, implying an association between the use of regimens comprising insulin suppliers and risk of hypoglycemia. The higher risk of first HH in T2DM patients with poor glycemic control could be driven by a proportion of patients who have persistently high HbA1c levels but are resistant to intensified anti-hyperglycemic treatment with stronger drugs or higher doses, which might impose these patients to a higher risk of hypoglycemia[58]. Similar findings had been reported in an earlier study carried out in T2DM patients among whom a higher risk of SH was associated with either HbA1c level < 6.0% [OR, 1.25; 95% CI, 0.99-1.57)] or > 9.0% [(OR, 1.16; 95% CI, 0.97-1.38)] as compared with levels between 7% and 7.9%[59].

Glycemic variability- While HbA1c remains widely used as a measure of mean glycemia, it may not be the best marker for predicting hypoglycemia[60]. An observational study conducted in Canada among insulin-treated T1DM and T2DM patients had failed to identify HbA1c levels as significant predictive factor for development of hypoglycemia[61]. Instead, glycemic variability (GV), an integral component of glucose homoeostasis, has emerged as a significant parameter to assess both the adequacy of glycemic management and the risk for the development of hypoglycemia[62]. In clinical trials using GV as parameter to assess diabetes-related complications, patients with the highest coefficient of variation (CV) in glucose profiles were found to have an increased risk of insulin initiation, retinopathy, macrovascular complications and mortality independent of mean glycemia represented by HbA1c levels, while the associations were weaker and less consistent when HbA1c was used as comparator[63-66]. In a randomized control trial studying the CV safety of two long-acting insulin preparations (Degludec vs Glargine) in T2DM patients, it was found that the day-to-day GV of self-monitored blood glucose (SMBG) at fasting hours was significantly associated with SH and all-cause mortality, a finding that was maintained even after adjustment

for the most recent HbA1c measurement, or baseline characteristics including investigational medication product, diabetes duration, smoking status, CV risks, and renal function[67]. In a study that performed a re-analysis from data derived from the DCCT trial, the results showed that not only magnitude of HbA1c and mean BG levels, but also GV measurements each has an independent role in determining an individual's risk of hypoglycemia in T1DM[68]. A nested case-control study conducted by Zhong et al.[69] that was designed to find association between HbA1c variability and HH in a cohort of adults with T1DM or T2DM, the HbA1c variability (calculated from standard deviation of ≥ 3 HbA1c measurements) has shown that, in T1DM, every 1.0% increase in its variability was associated with 90% higher first HH risk (95% CI, 1.25-2.89) and 392% higher recurrent HH risk (95% CI, 1.17-20.61), while the corresponding figures for T2DM patients were 556% higher first HH risk (95% CI, 3.88-11.08) and 573% higher recurrent HH risk (95% CI,1.59-28.51), respectively. Accumulating evidence has suggested that wide glycemic swings, represented by either short- (within-day and between-day variability) or long-term GV (visit-to-visit variability), are associated with an increased risk of hypoglycemia, diabetic macrovascular and microvascular complications, mortality rates and other adverse clinical outcomes[66].

Hypoglycemia unawareness- Repeated episodes of hypoglycemia are known to lead to impairment of the counter-regulatory system with the potential for fostering hypoglycemia unawareness. In a study carried out by Henriksen et al.[70] in T1DM patients, 153 unselected subjects had received 6 days of blinded continuous glucose monitoring (CGM) and recorded hypoglycemia symptoms. Patients were grouped by the number of hypoglycemic events during the recording period (group 1: one event; group 2: two to three events; group 3: four to six events; group 4: seven or more events), and fractions of asymptomatic events were calculated. Across the four groups, the fraction of asymptomatic hypoglycemia was found to increase with frequency of hypoglycemia episodes: 57% in group 1, 61% in group 2, 65% in group 3, and 80% in group 4 ($p < 0.001$). Higher fraction of asymptomatic hypoglycemia was positively associated with risk for SH (IRR, 1.3; 95% CI, 1.1-1.5; $p = 0.003$). Group 4 consisted of patients characterized by classic risk factors of SH (longer duration of diabetes, lower HbA1c, and more frequent impaired awareness of hypoglycemia). The authors concluded that such patients deserve particular attention in clinical practice.

In a study in which hyper-insulinemic-euglycemic and -hypoglycemic glucose clamping techniques were applied in non-diabetic, healthy subjects to investigate into the impact of hypoglycemia on magnitude of subsequent CRHR, the results showed that two episodes of short-duration (5 or 30 minutes), moderate hypoglycemia (52.2 ± 1.8 mg/dL) can produce significant blunting of key neuroendocrine (significantly and similarly blunted epinephrine, glucagon, growth hormone, cortisol, and pancreatic polypeptide concentrations, $p < 0.01$) and metabolic response (similarly blunted muscle sympathetic nerve activity and endogenous glucose production, $p < 0.01$). The authors concluded that neuroendocrine, autonomic nervous system, and metabolic responses are sensitive to the blunting effects of prior hypoglycemia, even of short-duration[71]. In another clinical study carried out in health controls (HC, n = 13), T1DM with hypoglycemia awareness (T1DM-Aware, n=16) and T1DM with hypoglycemia unawareness (T1DM-Unaware, n= 13), a 2-step hyper-insulinemic-euglycemic (90 mg/dL)/-hypoglycemic (60 mg/dL) clamping technique was also applied to induce hypoglycemia for the assessment of neural responses to mild hypoglycemia. Despite that both the T1DM-Aware and T1DM-Unaware groups were indistinguishable in HbA1c levels, a significantly higher self-reported

rates of SH episodes in the preceding year ($p = 0.03$) was noted among the T1DM-Unaware individuals. During the hypoglycemia clamping, the researchers found that mild hypoglycemia in HC subjects had altered activity in the caudate, insula, prefrontal cortex, and angular gyrus shown on functional MRI, whereas the altered activation patterns in T1DM-Aware subjects were noted in the prefrontal cortex and angular gyrus, without notable changes in the caudate and insula areas. The most striking finding was that, in direct contrast to HC and T1DM-Aware subjects, the T1DM-Unaware counterpart had failed to show any hypoglycemia-induced changes in brain activities, which were also associated with blunted CRHR (notably plasma glucagon and cortisol levels) as well as hypoglycemia symptom scores during mild hypoglycemia. It was concluded that in T1DM, and particularly in T1DM-Unaware patients, there is a progressive blunting of brain responses in cortico-striatal and fronto-parietal neurocircuits in response to mild-moderate hypoglycemia[72]. Furthermore, evidences derived from animal studies had suggested that neurological dysfunction that occurred after repeated hypoglycemia may be linked to neuronal death, dendritic injury, or cognitive impairment[40]. Although the incident rate of hypoglycemia is noted to be higher in T1DM, repeated hypoglycemia may also happen to patients with T2DM[73,74]. A higher risk exists especially in those with co-morbidities, physical frailty, mental impairment, and being treated with medications that are insulin supplier and/or insulin-secretagogues. Around 25% of people with T2DM taking insulin for > 5 years were found to have SH events, which is comparable to rate in adults with T1DM diagnosed within 5 years[75].

Role of education team providing optimal glycemic control to patients with DM

Diabetes self-management is required in most patients in their daily livings, so the purpose of education is to facilitate the development of knowledge, skills, attitudes and behaviors that enable and empower the patient to perform self-care on a day-to-day basis. Studies have found that, when specialized and skillful diabetes educators are integrated into the process at primary care settings, customized education thus administered can serve to enrich the experiences of patients, provide key education to improve patients' understanding that help meet their individualized needs and goals, and, can also help primary care physicians with key information to improve overall clinical care. The integrated education program has been advocated and endorsed by academic societies[76,77].

Modern technologies to help achieve optimal glycemic control

Patients and physicians in the 21st century require new tools to manage the growing burden of chronic illness, and those for management of DM are not exceptional. For providers responsible for the care of diabetic patients, developments in information management, real-time health education and feedback, and new approaches to self-monitoring and insulin delivery hold great promise to improve the quality and safety of diabetes care. On looking back on the history of development of technology applied in diabetes management, two major categories are notable: the more previously developed tools for insulin administration by syringe, pen, or pump, and BG monitoring as assessed by meter or continuous glucose monitor system (CGMS). More recently, cutting-edge technology has advanced to include hybrid devices that both monitor glucose and deliver insulin, some automatically, as well as software that serves as a medical device, providing patients of diabetes with self-management support[78].The advantage of insulin pumps (continuous subcutaneous insulin infusion, CSII) over multiple daily insulin injection includes more precise and flexible insulin dosing with fewer injections, improved glycemic control, and reduced risk of

hypoglycemia[79]. The application of CGMS has helped identify asymptomatic hypoglycemia in T1DM patients at risk, who deserve particular attention in clinical practice[70]. A more recent technological advance is the introduction of real-time CGM units with hypoglycemia alarm function integrated with sensor-augmented insulin pumps. This cutting-edge technology allows developing algorithms that automatically tune insulin dosing based on CGM measurements in order to mitigate the incidence of critical episodes of alarmingly high or low BG levels[80]. Therefore, these systems are considered valuable to avoid recurrent SH, especially in unaware patients prone to its recurrence. Further testing is ongoing and required before the closed-loop insulin delivery system is ready to take part in diabetes management in a real-world setting. While technology is rapidly evolving and has become an integral component in management of diabetes, concerns are still required to ensure that the applications to be based on the best evidence for safety and efficacy of patients, and also for the personnel who are actively involved in their use for diabetes management[81].

Management of hypoglycemia

Guidelines on hypoglycemia management released by academic societies are essential for the endorsement of pragmatic management for patients living with DM. During a hypoglycemia episode, when the patient is still conscious and could follow order without risk of choking, glucose (15-20 g) is the preferred treatment when BG is < 70 mg/dL (level 1 hypoglycemia), although any form of carbohydrate that contains glucose may be given[82]. However, one pitfall that must be kept in mind is when alpha-glucosidase inhibitors (AGIs) are in use, since the pharmacological character of this category of ADA would prevent the hydrolysis and breakdown of complex carbohydrates in the brush border of the small intestines, hindering the absorption of glucose as monosaccharides into the intestinal mucosa and vasculature, rendering plasma glucose level unable to rise when complex carbohydrates are given as rescue (e.g. table sugar, juice, regular soft drink, candy). Hypoglycemia is unlikely to occur with AGI monotherapy but may occur when used in combination with other ADAs (eg, SUs, insulin). Thus, patients suffering from hypoglycemia in the presence of AGIs must receive monosaccharides (e.g. glucose, dextrose, honey), or milk which mainly contains lactose, as an effective rescue therapy. From previous clinical studies, it has been suggested that 20 g of carbohydrate in the form of glucose tablets raised BG levels by approximately 45-65 mg/dL in adults[83,84]. Fifteen minutes after treatment, if SMBG still shows persistent hypoglycemia, the treatment should be repeated (the “15-15 rule” or “ rule of 15”) until BG is raised to 100 mg/dL or higher, a threshold agreed upon by most academic societies as safe from hypoglycemia insult. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence. Glucagon kits should be prescribed and ready for use for all individuals at increased risk of level 2 (BG < 54 mg/dL) and level 3 (require assistance from other persons for recovery) hypoglycemia. Glucagon administration is not limited to health care professionals, since there are both intra-nasal and soluble forms prepared in auto-injector pens available. Caregivers, school personnel, or family members of these individuals should be aware of its storage site, as well as when and how to administer it in emergency[82] (Table 1).

Prevention of hypoglycemia while providing optimal glycemic control

When risk factors have been identified and verified, they can be used as potential predictors, and certain validated risk assessment tool has thus been developed in hope to practically assess patients at risk of hypoglycemia. The following 6 patient-specific inputs are included in the validation test: 1. total number of prior episodes of hypoglycemia-

Table 1. Categories, Clinical Presentations, and Algorithm of Onsite Rescue for Hypoglycemia Episodes in Patients with Diabetes Mellitus

Level of Hypoglycemia	BG measured	Clinical Presentations	On-site Rescue Strategy (The 15-15 Rule)
Level 1	54 ~ 70 mg/dL	Sensation of hunger, palpitations, tremulousness, sweating**	• 15-20 g of glucose (1 tablespoon table sugar, 3 glucose tablets, or 120 mL juice or regular soda) when patient is conscious enough without risk of choking*** • Measure BG after 15 minutes • Repeat sugar administration till BG is raised to > 100 mg/dL • Consume a meal or snack to prevent recurrence of hypoglycemia after success of the above treatment • ED visit is required if repeated treatment fails
Level 2	< 54 mg/dL	Difficult concentration, confusion, hallucinations, irritability, bizarre behavior, focal neurological deficits (e.g, hemiplegia)**	• As in Level 1 • Glucagon administration if available when unable to swallow safely, disturbed consciousness, having seizure
Level 3	Not applicable*	disturbed consciousness, seizure, comatose state	• Glucagon administration whenever available • ED visit is required

*: Conscious level of the patient prevails BG levels measurable in determining hypoglycemia severity and rescue strategy.
**: The clinical signs and symptoms between levels 1 and 2 hypoglycemia may not present absolute hierarchy of happening as the BG could define.
***: When α-glucosidase inhibitors are in use, simple sugar in forms of monosaccharides should be administered (e.g. glucose, dextrose, honey), or milk that mainly contains lactose.
Abbreviations: BG- Blood glucose; ED- Emergency department.
(Synthesized from ref. 82-84)

related ED or hospital utilization, 2. number of ED encounters for any reason in the prior 12 months, 3. insulin use, 4. SU use, 5. presence of severe or end-stage kidney disease, and 6. age. This hypoglycemia risk stratification tool could facilitate targeted population management interventions, potentially reducing hypoglycemia risk and improving patient safety and QoL[85].

In a study using CGMS to identify potential risk factors in patients with T2DM, patients with low mean blood glucose levels and large fluctuations in BG were more likely to develop hypoglycemia, suggesting that assessment of these two variables is useful for the prediction of hypoglycemia. To achieve optimal glycemic control free of hypoglycemia, approaches that can minimize fluctuations in BG levels are required[86].

Hypoglycemia may result from a mismatch between the pharmacokinetics of exogenously administered insulin and the digestion and absorption of carbohydrate derived from various kinds of food, as well as the effect of exercise. Long-acting insulin analogue has been found to carry less risk of hypoglycemia compared to conventional Neutral Protamine Hagedorn (NPH) insulin preparation[87]. In an observational study, a cohort of 469 T2DM patients who had received NPH as basal insulin regimen but with poor glycemic control was recruited to assess the efficacy and safety of switching to long-acting insulin analogue glargine-300 (Gla-300) during a 6-month study period. At 6 months after the switch, 71.7% of participants had a ≥ 0.5% improvement in HbA1c from baseline. Mean HbA1c decreased at 3 and 6 months by 0.77% (± 0.98) and 1.01% (± 1.12), respectively ($p < 0.00001$ versus baseline), while fasting glycaemia decreased by 32 mg/dL and 37 mg/dL, respectively ($p < 0.00001$ versus baseline). The percentage

of participants with ≥ 1 hypoglycemia event during the preceding 4 weeks decreased significantly from baseline to 3 and 6 months, as did the proportion with symptomatic nocturnal hypoglycemia ($p < 0.00001$ versus baseline). No participants had SH after a switch to Gla-300. This prospective, observational study demonstrated that switching from NPH insulin to Gla-300 not only resulted in a significant improvement in HbA1c but also a concomitant decrease in risk of hypoglycemia[88]. Similar findings were available for insulin detemir, another long-acting insulin analogue, the use of which also showed less hypoglycemia as compared with NPH insulin in young or older T2DM patients[89]. Additionally, a prospective study conducted collaboratively by multiple European countries among patients with T1DM or T2DM who collected hypoglycemia data from dedicated patient diaries was carried out to evaluate the safety and effectiveness of degludec (a more recently developed basal insulin analog with an ultra-long duration of action > 42 hours at steady state and a lower day-to-day variability in BG-lowering effect) that is switched from other basal insulins. In addition to significant reductions in both fasting plasma glucose and HbA1c levels at the end of the 12-month clinical trial, there were also significantly lower rate ratios of overall, non-severe, severe, and nocturnal hypoglycemia recorded by the study subjects, suggesting the significantly lower hypoglycemia rates with this long-acting insulin regimen[90]. More recently, a newly developed long-acting basal insulin analogue, the once-weekly icodec, has been examined in a clinical phase 2 trial for its efficacy in glycemic control and safety concern including rate of hypoglycemia as compared to insulin glargin-U100 in T2DM patients naïve for insulin treatment. Among those 247 patients recruited in the 26-week study, the investigators found that the estimated mean change from baseline of HbA1c level was -1.33 percentage points in the icodec group and -1.15 in the glargine group, to estimated means of 6.69% and 6.87%, respectively, at study end; the estimated between-group difference in the change from baseline was -0.18 percentage points (95% CI, -0.38 to 0.02, $p = 0.08$). For hypoglycemia, the observed rates with severity of level 2 (BG level < 54 mg/dL) or level 3 (severe cognitive impairment) were low (icodec group, 0.53 events PPY; glargine group, 0.46 events PPY; estimated rate ratio, 1.09; 95% CI, 0.45 to 2.65). The mean weekly insulin dose was lower for the icodec group (approximately 33 U per day) than the glargine group (approximately 41 U per day), with an estimated icodec: glargine ratio of 0.81 (0.69 to 0.94). Given the expected equipotency between the two drugs, this finding awaits further clinical trials to determine whether the difference is observed consistently. It was concluded that, this once-weekly basal insulin analogue had glucose-lowering efficacy and a safety profile similar to those of once-daily insulin glargine-U100 in patients with T2DM[91]. Adherence to prescribed medications has impact on the performance of outcomes in patients with diabetes, so does the complexity of prescription. A less complex regimen that is easier to follow by the patients has been found to result in better glycemic control[92]. On considering the evidences derived from multiple head-to-head clinical trials comparing efficacy and safety issues between short- and long-acting glucagon-like peptide-1 receptor agonists administered to patients with DM, a once-weekly insulin regimen may have the potential to improve treatment satisfaction, adherence, and persistence in patients who are going to receive basal insulin therapy[93,94].

Conclusion

In the long spanning time course of management of patients with diabetes, early recognition of hypoglycemia risk factors in vulnerable patient groups, selection of tailored treatment regimens with minimal or no risk of hypoglycemia, appropriate educational programs provided to empower

patients for self-care are the major ways forwards maintaining good glycemic control, minimize the risk of hypoglycemia and thereby prevent both acute and chronic complications[95]. Consequences of hypoglycemia include acute and long-term cognitive function deterioration, cardiac arrhythmia, MI, serious falls, and even death. Hypoglycemia can occur in both T1DM and T2DM patients, especially when insulin or SUs are included in the regimen. Hypoglycemia presents a major physiological and psychological barrier to achieving optimal glycemic control. Self-monitoring of BG is the key to help identifying the causes, establish strategies for prevention and treatment. The threshold of glycemic control should be set to keep BG levels not lower than 70 mg/dL at any time point while maintaining the best possible glycemic profile with minimal GV as well as SH occurrences. In clinical practice, a glucose value ≤ 70 mg/dL is used as the clinical alert or threshold value for initiating treatment for hypoglycemia in diabetes because the potential for blood glucose to fall further may exist, especially when insulin and/or SUs are in use. In case of SH, impaired cognitive function of the patient requires assistance from another person for carbohydrates or glucagon administration, or even a visit to the ED for life-saving management. Thanks to the tremendous computing capacity and algorithm thus derived powered by the thriving artificial intelligence technology, smart wearable devices that integrate real-time CGM units and sensor-augmented insulin pumps hold promise to improve self-care quality for patients of DM and minimize the harm caused by hypoglycemia, particularly in those with hypoglycemia unawareness. When hypoglycemia dose happen, the “15-15 rule” for onsite rescue will practically help to raise BG to a safe level above 100 mg/dL. In the long-term management for patients with DM, stringent glycemic control is highly expected to prevent complications but may also implicate a higher risk of hypoglycemia while doing so. Interventions to reduce hypoglycemia should also set on helping clinicians identify high-risk patients in order to make individualized therapy for the best outcomes. For this desired purpose to accomplish, the delivery of practical and efficient education programs through the active involvement of education teams consisting of specialized and skillful diabetes educators will be helpful for this comprehensive care. Treatment of older adults with T2DM is complex because they represent a heterogeneous group with a broad range of comorbidities and functional abilities. Polypharmacy, a hardly avoidable prescription behavior caused by co-existing multiple chronic comorbidities (especially impaired renal function), can increase the risk of SH in this group of patients, which is especially true when regimens containing insulin or SUs are used. Glycemic goals can be relaxed in the older population as part of individualized care, and physicians must take the patient-centered principle to make the best treatment strategies[96].

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避免糖尿病患因降糖藥物療法產生低血糖風險之策略-文獻回顧

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摘 要

伴隨糖尿病常見之高血壓、血脂異常、慢性腎臟疾病，是導致糖尿病患併發心血管疾病的重要風險因子，長期控制不良的高血糖則可造成各類微小血管病變，包括神經系統，視網膜，及糖尿病腎病變，這些併發症除了導致生理機能異常，病患的生活品質亦受到明顯影響，因此，針對高血糖的治療策略希望是以嚴格控制，可盡量接近正常無糖尿之範疇為方針，以減少高血糖對身體器官機能引起的傷害。然而，在積極追求血糖控制達標的同時，因為患者身體狀況的特殊屬性(高齡，孱弱，腎功能異常)，或者使用的降糖藥物特性(例如胰島素療法，刺激胰島素分泌之硫醯基尿素類)，往往潛藏發生低血糖的風險。反覆發生低血糖之後，內分泌及神經系統的因應保護機制會逐漸遲鈍，產生「低血糖不自覺」現象，無法即時且有效升高體內糖份，可能損及中樞神經系統功能，且進入惡性循環模式。因此，積極預防低血糖的發生乃臨床要務。研究指出：當糖化血色素的達標值越低，低血糖的風險相對提高；另外值得注意的風險因素則是血糖變異度：當自我血糖監測或是連續性血糖監測紀錄顯示較大變異度時(血糖濃度高低震盪幅度越大)，發生低血糖風險的機率明顯增加，因此，除了藉由適當的衛教課程，提供病患提升自我照護的能力之外，能應用各種量測工具，據以針對不穩定的血糖變動進行療法的調整，不但可達到控制高血糖的目的，也可有效地降低發生低血糖的風險。