

## Inpatient Hypoglycemia Management Protocol

### Task force:

Dr. Mohammed Y. Alharbi (1), Dr. Badi Q. Alenazi (2), Dr. Jihad Zahraa (3), Dr. Zohair Aseri (4), Dr. Abdulmajeed Alrashoud (5), Dr. Imad Addin Brima (6), Dr. Saad Alzahrani (6), Ms. Haifa O. Alshehri (7), Ms. Fatmah A. Ghulman (8), Dr. Ibrahim Almutairi (9), Dr. Ahmad Safwat (10), Dr. Ibrahim Sulman Magawry (11).

- (1). Consultant Pediatric Endocrinologist and Diabetes, Deputyship of Curative Services, MOH.
- (2). Consultant Pediatric Endocrinologist and Diabetes, Alyamamah Hospital, MOH.
- (3). Consultant Pediatric Intensivist, KFMC, MOH.
- (4). Associate Professor and consultant ICU and ED, KSU.
- (5). Consultant Pediatrics ED, KSMC, MOH.
- (6). Consultant Endocrinologist, KFMC, MOH.
- (7). General administration of pharmaceutical care, MOH.
- (8). General Directorate of nursing affairs, MOH.
- (9). Director of Diabetes Centers, Deputyship of Curative Services, MOH.
- (10). General Directorate of Quality, MOH.
- (11). General Directorate of blood bank and lab, MOH.

### Introduction and aim:

Hypoglycemia is considered to be one of the causes of mortalities due to tight diabetes management in order to reach optimal diabetes control. From our observation in the emergency departments in ministry of health that we don't agreed upon protocol of hypoglycemia management, our aim is to develop a unified hypoglycemia management protocol to be implemented in ministry of health hospitals.

### Methodology:

Development of hypoglycemia management protocol in adults went through 4 steps as follows:

**Phase 1:** review the literature of Diabetic Ketoacidosis with special attention to the world wide protocols and guidelines in this regard including the existing protocols and their effect in managing patients with diabetic ketoacidosis, this phase has been done by experts in adult Endocrinology and Diabetes. The outcome of this phase is unified DKA management protocol according the best evidence based practice.

**Phase 2:** the panel of experts has been extended to including adult Emergency Medicine and intensive care units whom they reviewed the protocol developed by the endocrinologist and diabetologists and put their input according to their specialty

**Phase 3:** the protocol has been reviewed and amended by another panel of experts from nurses, pharmacists, lab experts as well as quality improvement experts

**Phase 4:** experts from the different specialties including (adult endocrinology and diabetology, adult emergency medicine, and adult intensive care) from the 20 regions of Saudi Arabia whom they reviewed the protocol and shared their opinion.

### Literature Review:

Diabetes Mellitus (DM) is one of most common endocrine disorder in Saudi Arabia which affects both children and adults<sup>1</sup>.

World Health Organization (WHO) in 2014 reported that the diabetes prevalence in Saudi Arabia is very high and it ranked 7th in the world. Out of total population of 33.3million, almost 7 million are having diagnosed diabetes and another 3 million have pre diabetes<sup>2</sup>. A study in 2014 from Riyadh reported that in adults aged 30 and above, 25.4% have diabetes and another 25.5% had pre diabetes<sup>3</sup>. This very high prevalence of diabetes in Saudi Arabia is a major reason for more and more patients visits in ER with diabetes related complications especially hyperglycemia and hypoglycemia, which may be life threatening.

Hypoglycemia represents most serious challenge in patients with diabetes mellitus. Its frequency in patients with diabetes on treatment is very high. Another issue in patients with diabetes and hypoglycemia is that it acts as barrier to achieving good glycemic control<sup>4</sup>.

The hypoglycemia is defined as any blood glucose less than 70mg/dl or 3.9mmol/l<sup>5</sup>. This level of glucose represents a level which can trigger activation of counter regulatory hormones<sup>6</sup>. American Diabetes Association and Endocrine Society USA also endorse same definition<sup>7</sup>.

In hospitals, hypoglycemia patients can present to emergency room or it can occur in those patients already admitted in hospital. The emergency room attendance with hypoglycemia has been reported similar to that of hyperglycemia<sup>8</sup>. And for those patients who are already admitted inside hospitals and receiving subcutaneous insulin treatment for diabetes, the hypoglycemia has very high incidence<sup>8</sup>. In ICU settings the incidence of hypoglycemia is 5-28% and in non-ICU settings like in wards it ranges from 1-33%<sup>9-11</sup>. Studies have also shown that Type 1 DM is associated with more incidence of hypoglycemia than in type 2 DM<sup>11</sup>. For example, In Type 1 DM it ranges between 30-40% and in Type 2 DM its ranges 10-30%<sup>12-14</sup>.

One study from Saudi Arabia reported that out of 1000 patients admitted, 8.7% of patients were admitted with hypoglycemia. Out of these patients, frequency of hypoglycemia in type 1 DM was 30.4%, in non-obese type 2 DM was 6.4% and then obese type 2 DM was 5.6%<sup>15</sup>. Another study from Saudi Arabia reported that prevalence of inpatient hypoglycemia in type 1 DM was 38.5% and in type 2 DM it was 14.1%<sup>16</sup>.

Mild hypoglycemia is defined as any degree of hypoglycemia in which patient can help himself to treat hypoglycemia symptoms. And severe hypoglycemia is where a patient needs third party assistance. As per this definition, one of surveys where patients self-reported that 51% with diabetes (both type 1 and type 2) had mild hypoglycemia in a year time and 28% of type 1 DM and 17% of type 2 DM had severe hypoglycemia<sup>17</sup>. Biochemical definition of severe hypoglycemia is, any glucose levels below 2.2mmol/l (below 40mg/dl)<sup>15</sup>. And one study showed that severe hypoglycemia occurred in up to 5% of all hypoglycemia admissions<sup>18,19</sup>

Hypoglycemia has been associated with high morbidity and mortality<sup>20,21</sup>. Hypoglycemia can cause serious and acute problems like arrhythmias and myocardial infarction and neurological issues like altered mental status, seizure and stroke<sup>22-24</sup>. Another study showed that severe hypoglycemia is associated with elevated blood

pressure, hypokalemia and prolonged QT intervals on ECG<sup>25</sup>. Particularly Nocturnal hypoglycemia is associated with bradycardia, atrial arrhythmia and ventricular premature beats<sup>26</sup>.

Hypoglycemia is one of cause of inability to achieve good glycemic control and it can increase the risk of falls, impaired quality of life, fear of hypoglycemia and reduced work productivity<sup>27,28</sup>. Permanent brain damage and deaths have been reported in cases with prolonged hypoglycemia<sup>29,30</sup>. ACCORD studies showed that recurrent severe hypoglycemia increased chances of cardiovascular disease and death<sup>31,32</sup>. Hypoglycemia is associated with two to three-fold increase in mortality<sup>33</sup>. This is more common in those with past history of severe hypoglycemia and in those with advanced age<sup>34</sup>.

Inpatient mortality from hypoglycemia is divided into two main categories. The one due to medication/ insulin treatment or iatrogenic and another that occurs in non-diabetics called spontaneous hypoglycemia. Iatrogenic hypoglycemia is more common in those with advanced age with co morbidities, long diabetes duration, renal failure, liver failure, tight glycemic control, past history of hypoglycemia, inability to maintain good oral intake and hormonal deficiencies<sup>35,36</sup>. Spontaneous hypoglycemia is mainly observed in critical ill patients with sepsis and organ failure especially liver failure and end stage renal disease, cancer patients and dementia patients. In some studies mortality is reported more in those with spontaneous hypoglycemia than iatrogenic hypoglycemia due to severity of illness<sup>37-40</sup>.

One Study from UK reported that a total number of 97000 patients visit ER per year for hypoglycemia and out of these patients one third require inpatient admissions especially those with advanced age using sulfonylureas and or insulin<sup>41</sup>.

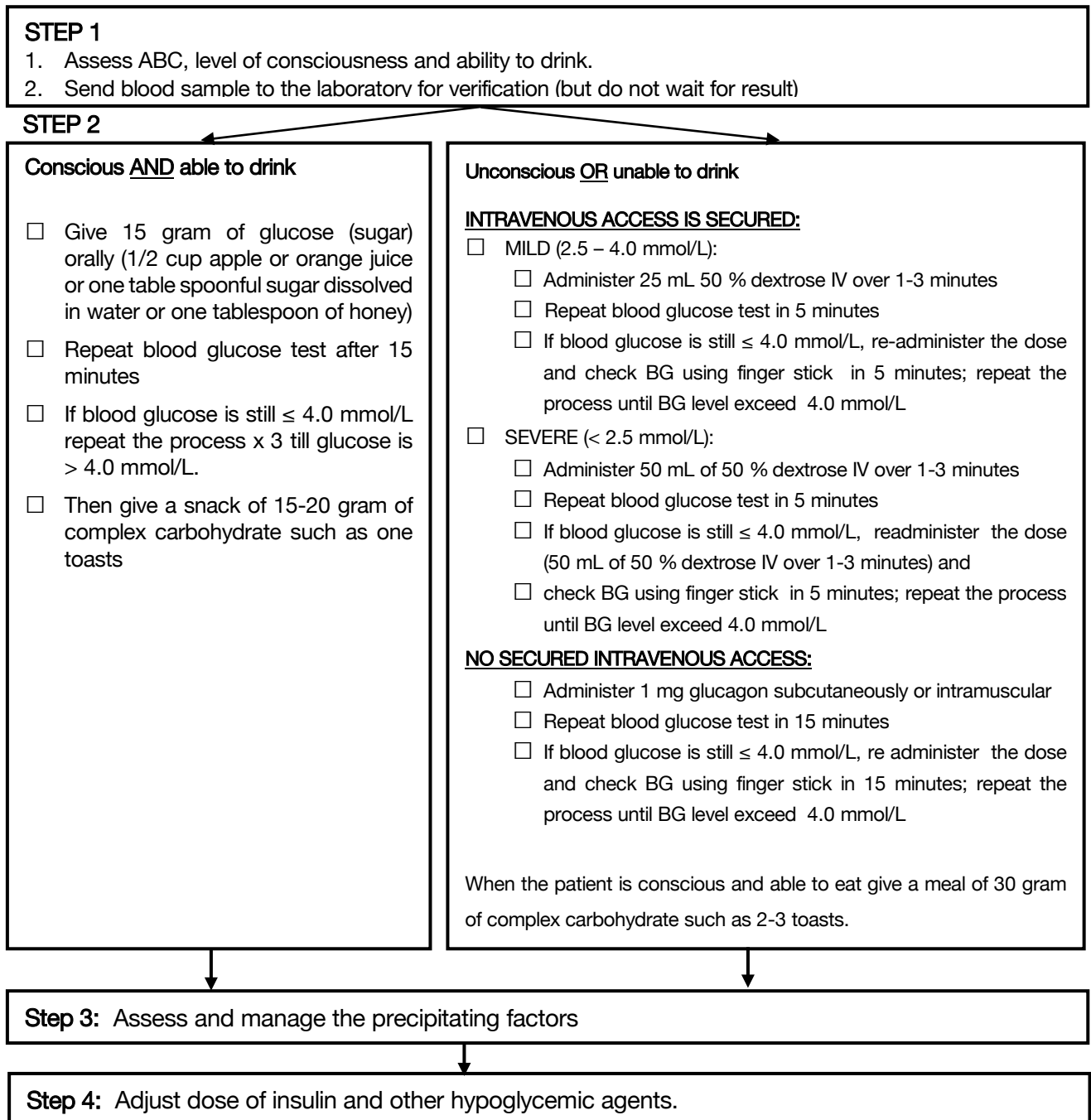
Diabetes and Hypoglycemia increases the cost of care as well<sup>42</sup>. In Saudi Arabia, people with diabetes spend 10 time more on their health than non-diabetics (3686 US\$ vs 380 US\$)<sup>43</sup>. And over 1.3 billion US\$ is spent on diabetes related services per year<sup>44</sup>. The cost of managing hypoglycemia in ER and inpatient is very high<sup>41</sup>. One of study from USA reported that the cost of hypoglycemia was estimated as \$3.49 billion in 2005 and it decreased gradually to \$1.84 billion in 2009. Which is still very high<sup>45</sup>.

Its standard practice worldwide to have standard hospital protocol for inpatient hypoglycemia management. The implementation of such standard protocols improves quality of care, reduce length of stay, reduce morbidity and reduce mortality.

There have been many studies to prevent hypoglycemia both inpatient and outpatients worldwide<sup>46-47</sup>. These studies have shown clearly that there exit many successful strategies for prevention of inpatient hypoglycemia<sup>46-48</sup>. But Currently, there is no much available data from Saudi Arabia except about hypoglycemia prevention in Ramadan and there is no any unified protocol for management of hypoglycemia in adults.

So, keeping in view high incidence of inpatient hypoglycemia which can lead to high morbidity, high mortality and very high cost of management of inpatient hypoglycemia, the aim of our hypoglycemia management protocol as per vision 2030 is to unify the management throughout the Kingdom of Saudi Arabia and to reduce morbidity and mortality.

**MANAGEMENT OF HYPOGLYCEMIA IN SUBJECTS WITH DIABETES MELLITUS PATHWAY  
(ADULTS) (Blood Glucose <4.0 mmol/L)**



**Call MD if any of the following:**

- Patient is put NPO, tube feeding or TPN initiated or stopped
- Persistent nausea/vomiting
- Deterioration of the level of consciousness or seizure
- For patients who presented with hypoglycaemia secondary to long acting sulphonylurea (e.g. Gliclazide MR or Glibenclamide) there might be a need for prolonged observation.

### References:

- 1- Forouhi NG, Wareham NJ. Epidemiology of diabetes. *Medicine* [Abingdon]. 2014; 42: 698-702.
- 2- World Health Organization 2014.
- 3- Al-Rubeaan K, Al-Manaa HA, Khoja TA, et al. Epidemiology of abnormal glucose metabolism in a country facing its epidemic: SAUDI-DM study. *J Diabetes*. 2014 Sep 30.
- 4- Cryer, P. E. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. *Diabetes* 63, 2188–2195 (2014).
- 5- Seaquist, E. R. et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J. Clin. Endocrinol. Metab.* 98, 1845–1859 (2013).
- 6- Cryer, P. E., Davis, S. N. & Shamon, H. Hypoglycemia in diabetes. *Diabetes Care* 26, 1902–1912 (2003).
- 7- Seaquist, E. R. et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 36, 1384–1395 (2013).
- 8- Geller, A. I. et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Int. Med.* 174, 678–686 (2014).
- 9- Umpierrez, G. E. et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 30, 2181–2186 (2007).
- 10- Krikorian, A., Ismail-Beigi, F. & Moghissi, E. S. Comparisons of different insulin infusion protocols: a review of recent literature. *Curr. Opin. Clin. Nutr. Metab. Care* 13, 198–204 (2010).
- 11- Umpierrez, E. et al. Randomized study of basal bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 34, 256–261 (2011).
- 12- Miller, C. D. et al. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch. Intern. Med.* 161, 1653–1659 (2001).
- 13- Weinstock, R. S. et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. *J. Clin. Endocrinol. Metab.* 98, 3411–3419 (2013).
- 14- Cryer, P. E. Hypoglycemia-associated autonomic failure in diabetes: maladaptive, adaptive, or both? *Diabetes* 64, 2322–2323 (2015).
- 15- Famuyiwa OO, Sulimani RA, Laajam MA, Al-Jasser SJ, Mekki MO. Diabetes mellitus in Saudi Arabia: The clinical pattern and complications in 1,000 patients. *Ann Saudi Med.* 1992 Mar;12(2):140-51.
- 16- Khalid Z. Alshali et al. Prevalence of Hyperglycemia and Hypoglycemia among Adult Inpatients at a University Hospital in Saudi Arabia. *JKAU: Med. Sci.*, Vol. 21 No. 4, pp: 25-37.
- 17- McCoy, R. G. et al. Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. *Endocr. Pract.* 19, 792–799 (2013).
- 18- Umpierrez, G. E. et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 30, 2181–2186 (2007).
- 19- Umpierrez, G. E. et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. *Diabetes Care* 36, 2169–2174 (2013)
- 20- Turchin, A. et al. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care* 32, 1153–1157 (2009).
- 21- Carey, M., Boucai, L. & Zonszein, J. Impact of hypoglycemia in hospitalized patients. *Curr. Diabetes Rep.* 13, 107–113 (2013).



## وزارة الصحة Ministry of Health

- 22- Goto, A., Arah, O. A., Goto, M., Terauchi, Y. & Noda, M. Severe hypoglycemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* 347, f4533 (2013).
- 23- Hsu, P. F. et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population- based study. *Diabetes Care* 36, 894–900 (2013).
- 24- Chow, E. et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes* 63, 1738–1747 (2014).
- 25- Tsujimoto, T. et al. Vital signs, QT prolongation, and newly diagnosed cardiovascular disease during severe hypoglycemia in type 1 and type 2 diabetic patients. *Diabetes Care* 37, 217–225 (2014).
- 26- Chow, E. et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes* 63, 1738–1747 (2014).
- 27- Feinkohl, I. et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care* 37, 507–515 (2014).
- 28- Amiel, S. A., Dixon, T., Mann, R. & Jameson, K. Hypoglycemia in type 2 diabetes. *Diabet. Med.* 25, 245–254 (2008).
- 29- Reno, C. M. et al. Severe hypoglycemia-induced lethal cardiac arrhythmias are mediated by sympathoadrenal activation. *Diabetes* 62, 3570–3581 (2013).
- 30- Tanenberg, R. J., Newton, C. A. & Drake, A. J. Confirmation of hypoglycemia in the 'dead-in-bed' syndrome, as captured by a retrospective continuous glucose monitoring system. *Endocr. Pract.* 16, 244–248 (2010).
- 31- Seaquist, E. R. et al. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. *Diabetes Care* 35, 409–414 (2012).
- 32- The Accord Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N. Engl. J. Med.* 364, 818–828 (2011).
- 33- McCoy, R. G. et al. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 35, 1897–1901 (2012).
- 34- McCoy, R. G. et al. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 35, 1897–1901 (2012).
- 35- Leese, G. P. et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 26, 1176–1180 (2003).
- 36- Rhoads, G. G. et al. Contribution of hypoglycemia to medical care expenditures and short-term disability in employees with diabetes. *J. Occup. Environ. Med.* 47, 447–452 (2005).
- 37- Kosiborod, M. et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA* 301, 1556–1564 (2009).
- 38- Boucai, L., Southern, W. N. & Zonszein, J. Hypoglycemia- associated mortality is not drug-associated but linked to comorbidities. *Am. J. Med.* 124, 1028–1035 (2011).
- 39- Finfer, S. et al. Hypoglycemia and risk of death in critically ill patients. *N. Engl. J. Med.* 367, 1108–1118 (2012).
- 40- Garg, R., Hurwitz, S., Turchin, A. & Trivedi, A. Hypoglycemia, with or without insulin therapy, is associated with increased mortality among hospitalized patients. *Diabetes Care* 36, 1107–1110 (2013).
- 41- Geller, A. I. et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Int. Med.* 174, 678–686 (2014).



## وزارة الصحة Ministry of Health

- 42- Rhoads, G. G. et al. Contribution of hypoglycemia to medical care expenditures and short-term disability in employees with diabetes. *J. Occup. Environ. Med.* 47, 447–452 (2005).
- 43- Alhawaish KA (2013). Economic costs of diabetes in Saudi Arabia. *Fam community Med.* 20(1):1 – 7.
- 44- Al Rubeaan K (2010). Diabetes tsunami in the Gulf states: why, what to do. In: Presented at International Diabetes Summit. Dubai.
- 45- Zhao Y, Shi Q, Wang Y, Fonseca V, Shi L. Economic burden of hypoglycemia: Utilization of emergency department and outpatient services in the United States (2005-2009). *J Med Econ.* 2016 Sep;19(9):852-7.
- 46- Samann, A., Muhlhauser, I., Bender, R., Kloos, C. & Muller, U. A. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. *Diabetologia* 48, 1965–1970 (2005).
- 47- Korytkowski, M. T. Diabetes and aging. *Diabetes Spectrum.* 26, 3–4 (2013).
- 48- Little, S. A. et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPASS). *Diabetes Care* 37, 2114–2122 (2014).