Consensus of Experts on Physician-Pharmacist Co-management of Perioperative Blood Glucose

Perioperative dysglycemia includes hyperglycemia, hypoglycemia and blood glucose fluctuation. On the one hand, perioperative dysglycemia leads to increased mortality, the incidence of postoperative infection, nonhealing wounds and the duration of hospital stay [1-3]. On the other hand, surgical anesthesia, trauma and other stress can increase the secretion of insulin antagonist hormones (such as catecholamines, cortisol, etc.), causing elevation in blood glucose levels. In addition, a complex interplay between perioperative and other factors（such as sepsis, starvation, high nutritional support, and vomiting） aggravate glucose metabolism disorders [4-5].

Diabetes patients were confirmed as high-risk group for perioperative dysglycemia as compared to non-diabetic patients [6]. With the increase incidence and prevalence of diabetes mellitus, the number of people required surgical treatment with diabetes is also increasing in our country. Therefore, the management of perioperative blood glucose is receiving increasing attention. The Expert Consensus on blood glucose Management for Chinese inpatients and the American diabetes association (ADA) recommend that physicians, nurses, pharmacists and other disciplines jointly manage diabetic patients to promote blood glucose control. Therefore, this expert consensus intends to summarize the blood glucose management of perioperative patients in the hospital through the joint discussion of physicians and pharmacists, so as to provide reference for non-endocrinologists and clinical pharmacists to manage blood glucose, and provide a reference physician-pharmacist co-management model for perioperative blood glucose management.

➢ Physician-Pharmacist co-management for perioperative blood glucose

Hospital inpatients with dysglycemia are mainly diagnosed and treated by endocrinologist. Surgeons often ignore important issues beyond their professional focus, such as perioperative hyperglycemia. Most surgeons have insufficient experience in the use of hypoglycemic drugs (especially insulin), which may lead to untimely or inadequate diagnosis and treatment in patients with perioperative hyperglycemia. Due to the shortage of medical resources, it is impossible for endocrinologists to be involved in the management of dysglycemia in each perioperative patient. The blood glucose management of patients were completed by the medical staff in their departments. The guidance by specialist doctors was limited.

There were studies shown that physician-pharmacist co-management has a positive impact on glycemic control and diabetes-related disease maintenance [7,8]. Therefore, the relevant treatment standards have included pharmacists in the comprehensive treatment of diabetes team. As the American Diabetes Association (ADA) “the management of diabetic patients” point out: People with diabetes should receive health care from a team that may include physicians, nurse practitioners, physician assistants, pharmacists, nurses, exercise specialists, dietitians, dentists, podiatrists, and mental health professionals. Pharmacists are important members of this multidisciplinary clinic team [9].

With the gradual advancement of clinical pharmacy work in China, clinical pharmacists in many hospitals in China have successively carried out pharmaceutical services for diabetic patients, and the benefits for patients have been gradually confirmed [10,11]. Therefore, the hyperglycemia management model for inpatients recommended in the 2017 edition of the

"Expert Consensus on Blood Glucose Management for Chinese inpatients" includes the consultation professional management model, also known as the diabetes team model, in which doctors, nurses, pharmacists, nutritionists, etc. are all members of the team. The role of pharmacists is gradually being concerned and emphasized in China.

The pharmaceutical care services previously provided by pharmacist is in blood glucose management focus more on the endocrinology department, not widely the surgical field. At present，the clinical pharmacists working mode of perioperative blood glucose management has not well formed around China, and the whole process medication management needs to be improved. Therefore, this consensus intends to establish a physician-pharmacist co-management model for Perioperative patients with dysglycemia and provide clinical reference. The specific process is shown in Figure 1.

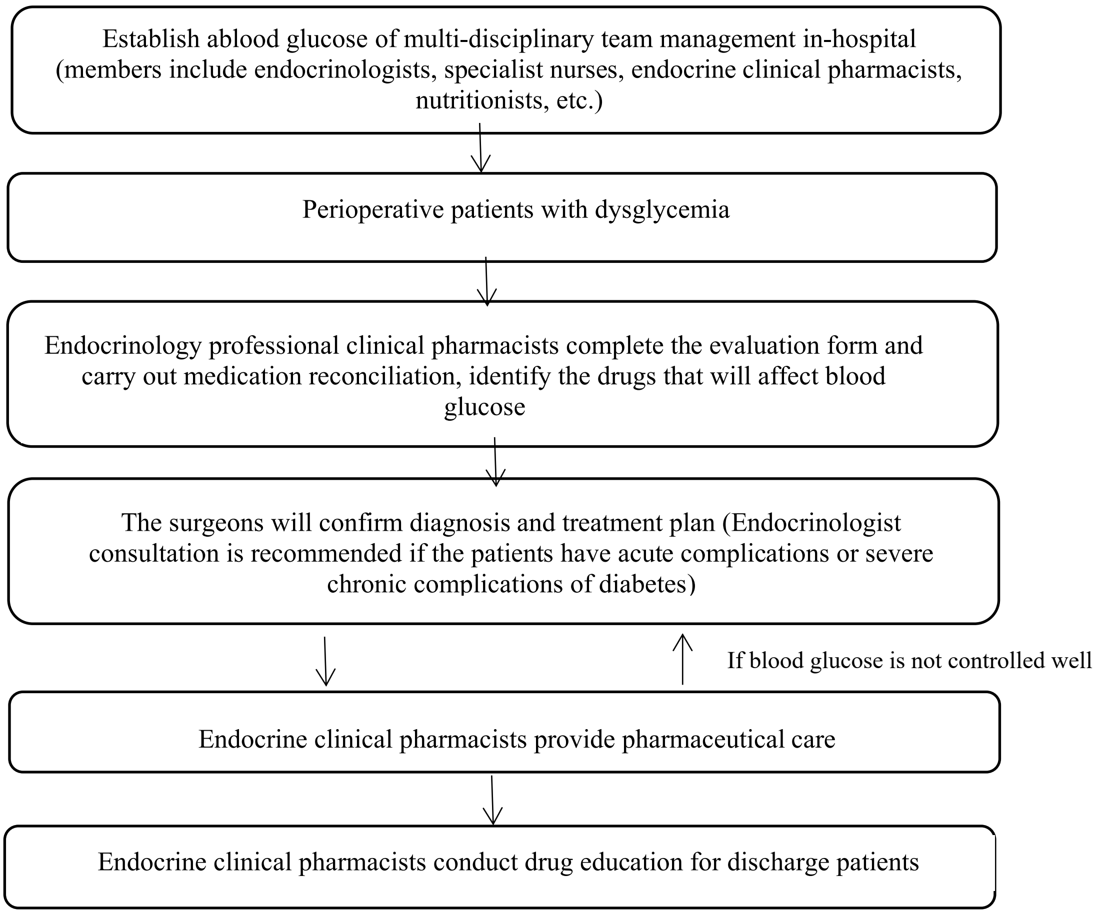

Figure 1. Flow chart of the physician-pharmacist co-management mode of perioperative blood glucose management

To establish a physician-pharmacist co-management model for perioperative blood glucose management, a blood glucose of multi-disciplinary team management in-hospital should be established first, and its members should include endocrinologists, specialist nurses, endocrine clinical pharmacists, nutritionists. Clinical pharmacists should pay close attention to medication-related problems， including drug-drug interactions， medication effects（ side effects and concerns over lack of effectiveness）, medication overuse or omission ， medication errors ， etc. (Appendix 1). Clinical pharmacists can serve as a bridge between non-endocrinologists, endocrinologists, nurses, and patients in the team.

For patients with dysglycemia during the perioperative period, endocrine clinical pharmacists can fill in the Evaluation Form firstly (Appendix 3), carry out medication reconciliation and identify the drugs that will affect blood glucose. Then, surgeons determine the treatment plan (Endocrinologist consultation is recommended if the patient is having acute or severe chronic complications of diabetes), and fill in the Blood Glucose Control Method Table (Appendix 4). Clinical pharmacists conduct pharmaceutical care in patients with dysglycemia (including tracking blood glucose monitoring results (Appendix 5), adverse reactions etc.). In case of poor blood glucose control or condition changes during the treatment, the clinical pharmacist will feedback the results to the physician and make adjustment in time. For discharged patients, clinical pharmacists should provide drug education to improve their medication compliance (including the use and preservation of insulin and oral hypoglycemic agents, the prevention of hypoglycemia, etc.).

➢ Management of perioperative blood glucose

1.Preoperative evaluation

Hyperglycemia was the main dysglycemia in perioperative period. A random blood glucose concentration of more than 7.8 mmol/L has been regarded as a threshold to consider the diagnosis of perioperative hyperglycaemia. [12] If the blood glucose level continues to be significantly higher than this level, it indicates that the risk of perioperative hyperglycemia is increased. Perioperative hyperglycemia patients mainly include known diabetes patients, undiagnosed diabetes patients and patients with "stress hyperglycemia". Therefore, it is recommended to carry out multi-point blood glucose monitoring before and after the operation for all patients, so as to timely find patients with abnormal blood glucose during the perioperative period. If conditions permit, the glycosylated hemoglobin level (HbA1c) can be measured, and the risk factors of abnormal blood glucose management can be evaluated.

1.1 evaluation of blood glucose level: blood glucose monitoring: routine monitoring of fasting blood glucose before operation, monitoring of postprandial and random blood glucose when necessary (when blood glucose ≥ 16.7 mmol/L, further detection of blood ketone or urine ketone, blood gas, blood lactic acid, etc.) [12]; Detection of HbA1c: for patients without previous history of diabetes, if HbA1c ≥ 6.5% is being increasingly applied in the diagnosis of diabetes, it indicates that the risk of dysglycemia during perioperative period is high. However, for patients with diabetes who have been clearly diagnosed in the past, if HbA1c ≤ 7%, it indicates that the blood glucose control in the last three months is good, and the risk of abnormal blood glucose in the perioperative period is low [13].

1.2 assessment of risk factors for dysglycemia**:** for perioperative patients, poor preoperative blood glucose control, course of diabetes > 5 years, previous history of frequent hypoglycemia, old age (or life expectancy < 5 years), combined cardiovascular and cerebrovascular diseases、 liver and kidney dysfunction, malignant tumor, severe infection, etc. are important risk factors for dysglycemia. In addition, the larger the operation, the longer the fasting time before the operation, and the stronger the stress, the higher the risk of dysglycemia in the perioperative period. And the risk of dysglycemia in patients with general anesthesia is higher than that in patients with local anesthesia or epidural anesthesia [14,15].

2. Perioperative blood glucose control objectives

After the above evaluation, patients are managed hierarchically and different blood glucose control goals are set to achieve individualized management. Perioperative blood glucose management should try to avoid hypoglycemia and large fluctuations of blood glucose, but it should not increase the risk of infection and hyperglycemia crisis due to inappropriate and loose blood glucose management. For the patients with diabetes hyperglycemia crisis (such as diabetes ketoacidosis, hyperglycemia and hypertonic syndrome), the elective surgery should be postponed. According to different blood glucose control levels, blood glucose control objectives can be divided into strict control, general control and loose control [16]. See Table 1 for details. Among them, the target for general control is 6.1-7.8 mmol / /L for fasting blood glucose or premeal blood glucose, and 7.8-10.0 mmol / /L for 2 hours postprandial glucose or random blood glucose when unable to eat.

Table 1. Blood glucose control objectives of each operation during perioperative period

		Blood glucose control Target layering	Fasting or Premeal blood glucose (mmol/L)	2 hours postprandial blood glucose or random blood glucose when unable to eat (mmol/L)
Elective operation (Preoperative, Intraoperative and Postoperative)	Major and minor operations	general control	6.1～7.8	7.8～10.0
	Organ transplantation	general control	6.1～7.8	7.8～10.0
	Fine surgery (such as plastic surgery)	Strict control	4.4～6.1	6.1～7.8
Emergency surgery (intraoperative and postoperative)	Major and minor operations	Loose control	7.8～10.0	7.8～13.9
	Organ transplantation	general control	6.1～7.8	7.8～10.0
	Fine surgery (such as plastic surgery)	Strict control	4.4～6.1	6.1～7.8
Special groups	patient in severe condition	general control	6.1～7.8	7.8～10.0
	Elderly over 75 years old, life expectancy < 5 years (such as cancer), complicated with cardiovascular and cerebrovascular diseases, moderate and severe liver and kidney dysfunction, high-risk group of hypoglycemia, people with mental or intellectual disabilities, and parenteral nutrition	Loose control	7.8～10.0	7.8～13.9

Note: perioperative period: refers to the period from the time when the surgical treatment is decided to the end of the treatment related to this operation. Including three stages preoperative, intraoperative and postoperative. Elective surgery: surgery that can be performed at an appropriate time after adequate preoperative preparation. Emergency operation: perform the operation immediately after necessary preparation in the shortest time, otherwise the patient's life will be endangered. Minor surgery [17]: that is, surgery with operation time ≤ 1h, local anesthesia and no fasting. Major surgery [17]: that is, operations with operation time> 1h, spinal anesthesia or general anesthesia, fasting, such as thoracic and abdominal surgery, craniotomy, amputation, etc.

2.1 blood glucose control objectives of patients undergoing elective surgery

Patients undergoing elective surgery have different goals for blood glucose control due to different types of surgery. The general control standard was adopted for the patients who underwent minor, major operations and organ transplantation. For patients undergoing fine surgery (such as plastic surgery), blood glucose should be strictly controlled.

2.2 blood glucose control objectives of emergency surgical patients

Because of the emergency situation, it is difficult to intervene the blood glucose level before emergency surgery, regardless of whether diabetes has been diagnosed or not. However, the intraoperative and postoperative hyperglycemia should be controlled. For patients undergoing major and minor emergency operations, the blood glucose control goal should be loosely.

2.3 blood glucose control objectives of severe patients

A large number of evidence-based medical evidence showed that intensive blood glucose control during perioperative period did not reduce the total mortality and complication rate of severe patients, but significantly increased the risk of hypoglycemia in severe patients [18-20]. In 2009the findings of a landmark trial(NICE-SUGAR) showed that intensive glucose control increased mortality, a blood glucose target of ≦10 mmol/L resulted in lower mortality than did a blood glucose target of 4.5-6.0 mmol/L among adults in the ICU. [19]. Both American Association of Clinical Endocrinologists (AACE) and ADA recommended the target of blood glucose control for the majority of critically ill patients with hyperglycaemia is 7.8-10.0 mmol/L. [21]. Therefore, for severe patients (patients requiring intensive care or mechanical ventilation), blood glucose control should not be too strict. For young patients without cardiovascular and cerebrovascular diseases or liver and kidney dysfunction, the goal of blood glucose control is general control.

In addition to considering the type of surgery, the age, complications and condition of patients should be considered comprehensively. For example, for the elderly over 75 years old, patients with other complications (such as cardiovascular and cerebrovascular diseases, liver and kidney dysfunction, mental or intellectual disability), or patients at high risk of hypoglycemia and patients requiring parenteral nutrition, the target value of blood glucose can be appropriately relaxed.

3. Approaches of glycemic control in the perioperative period

People with diabetes should be scheduled for surgery as early as possible in the morning to minimize the impact of blood glucose on patients and surgery [22]. Insulin is the mainstay of treatment for perioperative dysglycemia, the specific management approaches is shown in Figure 2.

3.1 Elective surgery

3.1.1 Major surgery

Both the ADA and SAMBA suggest the use of subcutaneous insulin for non-critical patients who require major surgery [23]. The more commonly used insulin regimens include the "basal-bolus" regimen (medium-acting/long-acting insulin before bed combined with short-acting/rapid-acting insulin before each of the 3 main meals in the day), pre-mixed insulin or continuous subcutaneous insulin infusion. During fasting, prandial insulin should be discontinued, while the basal insulin still be in the regimen.

Patients should be treated with a continuous intravenous insulin infusion during the perioperative period. On the morning of surgery, the morning dose of insulin should be omitted. An insulin infusion should be commenced prior to the induction of anaesthesia. At present, the continuous intravenous insulin infusion mostly adopts the dual-channel administration method, which meaned normal saline + short-acting insulin continuous intravenous infusion in one channel while glucose (such as 5% glucose solution 100-125 ml/h) is given in another channel. The advantage with this regimen is its safety、stability and easy dose adjustment[24]. Blood glucose level (BGL) should be closely monitored in intraoperative period, and the speed of intravenous insulin administration should be dynamically adjusted according to BGL. Intravenous insulin may promote potassium from entering cells，which can contributes to hypokalemia that might lead to intraoperative arrhythmia and even cardiac arrest. Therefore, attention should be paid to monitoring the serum potassium, and preventive potassium supplementation can be provided if necessary.

The insulin infusion should be continued for at least 24hrs postoperatively and until the patients have returned to normal diet [25]. When the patient returns to a normal diet, we recommend that the insulin administration transitioning from IV to subcutaneous

3.1.2 Minorsurgery

For patients whose blood glucose are well controlled (HbA1c<7.0%), the original glycemic control regimen can be maintained when normal diet is possible after minor surgery. Oral anti-hyperglycaemic medications (AHG) and short-acting/rapid-acting insulin before breakfast are discontinued the day of surgery, and give half of NPH dose or 60-80% doses of a long-acting insulin. Patients who use an insulin pump before surgery should receive continuous subcutaneous insulin infusion at the basal infusion rate during surgery. If stress hyperglycemia occurs during surgery, subcutaneous rapid-acting insulin should be given (up to a maximum of 6 IU) [26]. When the patient returns to a normal diet, the original glycemic control regimen can be reinstituted if available and not contraindicated.

If patients have poorly controlled diabetes or have unstable BGLs during the preoperative period, insulin should be used preoperatively even for minor operations.

3.2 Critically ill patient

Insulin infusion is the first choice for glucose control in critically ill patients [27,28]. As critically ill patients are in stable condition postoperatively，transitioning from intravenous to subcutaneous insulin will be needed when patients returns to a normal diet.

3.3 Emergency surgery

For patients undergoing emergency surgery, blood glucose and ketone bodies should be tested. Patients with acute complications of diabetes such as ketoacidosis or hyperosmolar hyperglycemic state are unable to undergo surgery unless their blood glucose under controlled. Management goals include restoration of circulatory volume and tissue perfusion, resolution of hyperglycemia, and correction of electrolyte imbalance and ketosis. For patients with ketoacidosis or hyperosmolar hyperglycemic state, continuous intravenous insulin is the standard of care. The recommended starting dose of insulin is 0.1 U·kg-1·h-1. Blood glucose levels should be monitored every hour during this time. If the blood glucose level does not reduce obviously within the first hour and dehydration has been substantially corrected, the insulin dose may be doubled. when the blood glucose level drops below 13.9 mmol/L，the insulin dose is reduced to 0.05-0.1 U·kg-1·h-1 to maintain glucose concentrations between 8.0 and13.9 mmol/L. The intraoperative and postoperative treatment principles of patients undergoing emergency surgery are basically the same as those of patients undergoing major surgery，but more close observation is in need.

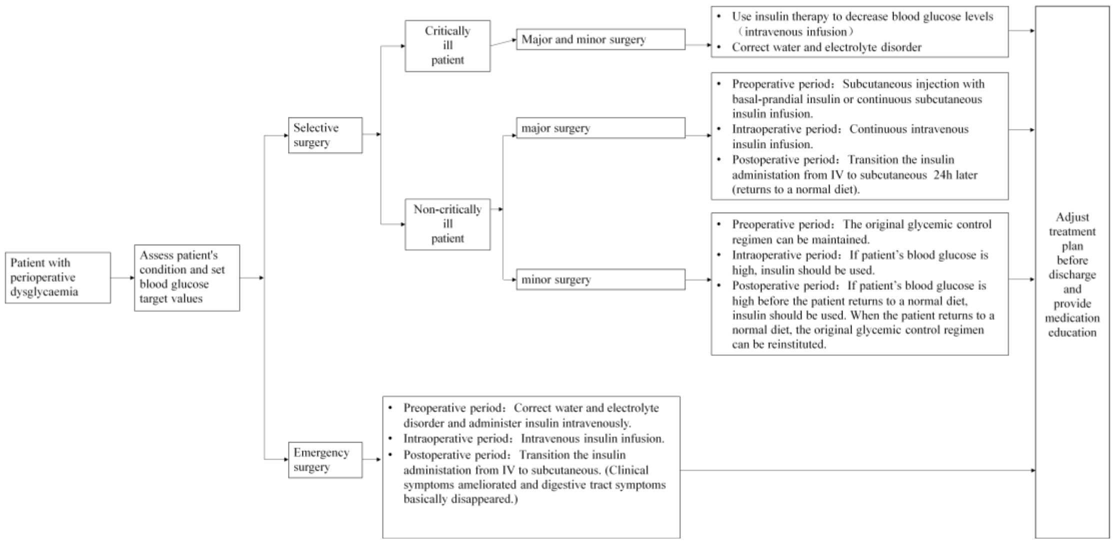

Figure 2 The perioperative glycemic control method

4. Methods of insulin administration

Insulin therapy is the preferred treatment of perioperative hyperglycemic control, and the classifications and characteristics of commonly used insulin are shown in appendix 2. The administration routes of insulin mainly include subcutaneous injection and intravenous infusion, and subcutaneous injection includes multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII).

4.1 Multiple daily injections (MDI) [27,29]

Choice of injection: Perioperative patients with hyperglycemia are recommended with MDI, a method often adopts the mode that meal-time insulin plus basic insulin ("three-short-one-long" insulin therapy), and premixed insulin subcutaneous injection. The combination of mealtime insulin with basic insulin can better control blood glucose and help to shorten the preparation time before operation and the hospitalization time.

Choice of insulin: the basic insulin includes medium-acting insulin (neutral protamine Hagedorn (NPH) insulin) and long-acting insulin analogs (e.g., insulin detemir, insulin glargine, insulin degludec). Mealtime insulin includes short-acting human insulin and quick-acting insulin (e.g., insulin aspart, insulin lispro). At present, the three-short-one-long program usually uses the combination of quick-acting insulin with long-acting insulin.

Time of subcutaneous injection: Due to late-onset, short-acting human insulin must be injected subcutaneously about 30 minutes before a meal in order to make the peak of insulin and the postprandial blood glucose coincide. Quick-acting insulin can be injected immediately before or even after the meal. And long-acting insulin usually can be injected subcutaneously once a day before bedtime.

Determination of initial dose: Patients who cannot eat normally may be given basic insulin only. While patients on a normal diet should be given basic and mealtime insulin. The dose of insulin can refer to the patient's insulin dose out-of-hospital, for patients who do not use insulin outside the hospital, the total amount of initial insulin can be estimated according to 0.4-0.5 u/kg ·d, of which 50 percent is basic insulin, the other 50 percent is mealtime insulin. For patients who cannot eat or who eat less than 25g of staple food, only basic insulin is recommended.

4.2 Continuous subcutaneous insulin infusion (CSII)

Pharmacokinetics of the insulin pumped into the body is closer to the physiological pattern of insulin secretion. The blood glucose control time of patients treated with insulin pump is short, which treatment can shorten the perioperative time of diabetic patients and promote wound recovery.

Choice of insulin: Only short-acting human insulin or quick-acting insulin can be used in the insulin pump. And quick-acting insulin is lower-risk to cause catheter occlusion and more suitable for insulin pump therapy.

Determination of initial dose: Patients who have received insulin treatment can calculate the dosage based on the insulin amount before treatment with insulin pump. The total daily dose (U) = pre-pump insulin dose (U) × (70%-100%) . The initial dose of insulin can be calculated as 0.4-0.5 u/kg·d for the patients who have not received insulin therapy. The daily basic insulin infusion and three pre-meal insulin doses both accounted for 50%. The specific dose may depend on the control of patient's blood glucose.

4.3 Intravenous infusion of insulin

The intravenous use of insulin takes effect quickly, and is convenient to titrate the dose, which is beneficial to reduce the fluctuation of blood glucose. At present, CSII with micro-pump is widely used in clinical practice.

Choice of insulin: The intravenous use of insulin can choose short-acting insulin or quick-acting insulin. Short-acting human insulin is generally preferred because it is easier to dispense.

Preparation of insulin with micro-pump: 50U short-acting insulin injects into 49.5 ml normal saline to the concentration of 1 U/ml.

Preparation of insulin in common intravenous infusion set: 25U short-acting insulin injects into 250 ml normal saline to the concentration of 0.1 U/ml.

Determination of initial infusion rate: if the patient has used insulin < 24 U/d, the initial rate of insulin with pump should be 0.5 ~ 1 U/h, if the patient has used insulin > 24 U/d, the initial rate of insulin with pump should be 1 ~ 2 U/h, and the rate of insulin infusion should be adjusted according to the monitoring of blood glucose during the period [31].Details about the rate of insulin infusion in patients with ketoacidosis are included in the emergency operation part of the method of perioperative blood glucose control.

4.4 How to switch from intravenous use of insulin to subcutaneous use of insulin

When switching from continuous intravenous infusion to intermittent subcutaneous injection after surgery, subcutaneous insulin doses are determined based on the rate of the most recent stable insulin infusion and the state of dietary condition at that time. For example, the average infusion rate of insulin in the recent 6-8 hours × 24 hours = the total insulin amount of the whole day, then 80 percent of the total amount serves as the initial total dose, one half of each is used for basic and pre-prandial insulin dose (the specific dose should be adjusted according to the individual patient's diet) [32]. Medium-acting and long-acting insulin should be injected subcutaneously about 2 hours before stopping intravenous insulin infusion, and short-acting or pre-mixed insulin should be injected subcutaneously 30 minutes before stopping intravenous insulin infusion. And it is better to switch from intravenous use of insulin to subcutaneous use of insulin at mealtime, such as at breakfast or at lunch.

5. Perioperative glucose monitoring

5.1 Method of glucose monitoring

Fingertip blood glucose monitoring (capillary blood glucose) is recommended in generally healthy patients, while arterial/venous blood gas monitoring may be considered, if necessary, in critically ill, use vasopressor, or hypotensive patients [14].

5.2 Monitoring frequency

5.2.1 Frequency of blood glucose monitoring with intravenous insulin

Check blood glucose levels every hour and the frequency of monitoring should be increased for patients with blood glucose <6.0 mmol/L or a sharp drop in blood glucose. If blood glucose ≤ 3.9 mmol/L, it is recommended to monitor blood glucose every 10-15 min until blood glucose > 4.0 mmol/L. [22]

5.2.2 Frequency of blood glucose monitoring with subcutaneous insulin

For patients with a normal diet, monitoring with 7-point glycemic profiles (before breakfast, 2 h after breakfast, before lunch, 2 h after lunch, before dinner, 2 h after dinner, and before sleeping). Check blood glucose levels every 4-6 hours for fasting patients. [33]

6. Prevention of hypoglycemia

For non-diabetic patients, the diagnostic criterion for hypoglycemia is blood glucose <2.8 mmol/L, while the blood glucose level ≤3.9 mmol/L is in the category of hypoglycemia for diabetic patients [34]. Moderate hypoglycemia (2.3-3.9 mmol/L), especially severe hypoglycemia (<2.2 mmol/L), could greatly increase the mortality of patients in the perioperative period.

Clinical manifestations of hypoglycemia: it could be manifested as palpitations, tremors, nervousness, palpitation, irritability, anxiety, and other symptoms of sympathetic excitation, and changes in consciousness, dizziness, unresponsiveness, cognitive impairment, coma, and other central nervous system symptoms. Different patients have different feelings when hypoglycemia occurs. Therefore, when the patient feels any discomfort, it is recommended to monitor blood glucose immediately to avoid the occurrence of hypoglycemia.

For patients who cannot take insulin orally and give it intravenously, when the blood glucose of the patient is <6.0 mmol/L, the infusion rate should be reassessed and the drip rate adjusted. When the blood glucose is ≤3.9 mmol/L, the intravenous infusion of insulin should be stopped, and 75-100 ml of 20% glucose should be given intravenously for 10-15 minutes, and then the blood glucose should be monitored until the blood glucose is ≥4.0 mmol/L. Intravenous insulin should be restarted after blood glucose > 4.0 mmol/L and 100 ml/h of 10% glucose should be given (The discontinuation of intravenous insulin infusion is generally not more than 20 minutes. Because the half-life of intravenous insulin is very short, about 7-8 minutes, restarting the use of insulin as soon as possible can reduce the risk of ketosis).[26,27,35]

For conscious patients who could intake, when blood glucose is ≤3.9 mmol/L, immediately take 15-20 g of sugary foods (such as 2-5 glucose tablets) orally, and check blood glucose every 15 minutes until blood glucose rises to 4 mmol/L. After oral sugar food for three times, 150-200ml of 10% glucose can be given if the blood glucose is still ≤3.9 mmol/L. When the blood glucose is >4.0 mmol/L, but more than 1h before the next meal time, starch or protein-containing food can be given.

For patients with impaired consciousness, intravenous bolus 20-40 ml 50% glucose or intramuscular 0.5-1.0mg glucagon, and check blood glucose every 15 minutes until blood rising to 4.0 mmol/L. When the blood glucose is >4.0 mmol/L and the patient is conscious, 10% glucose 100 ml/h or oral starch or protein food can be given. In patients with hypoglycemia, blood glucose should be monitored for at least 24 to 48 hours. [34]

7. Nutritional therapy in the perioperative period

Nutritional support is an important part of perioperative management [36]. Current evidence suggests that reasonable nutritional support in the perioperative period can reduce the decomposition state of patients, facilitates early departure of patients from inpatient beds and recover as soon as possible. In addition, the incidence of postoperative complications and the risk of infection are significantly reduced [37].

Diabetes mellitus is a risk factor for malnutrition and poor clinical outcomes. We recommend using the Nutritional Risk Screening Form 2002 (NRS 2002) for preoperative assessment. Nutritional support plan should be formulated if the risk of malnutrition is found by the NRS 2002. The target energy requirement of patients in the perioperative period is about 25-30 kcal/kg·d. A permissive low intake strategy that in a short period to reduce the total energy to 20 -25 kcal/kg·d should be accepted for patients whom with diabetes mellitus or major surgical operations during parenteral nutrition [38]. We recommend that the total energy intake should follow the principle of a balanced diet, of which 45-60% comes from carbohydrates, 25-35% comes from fat, and 15-20% comes from protein.

Enteral nutrition has a lesser effect on blood glucose metabolism than parenteral nutrition [39]. Enteral nutrition can be the preferred method of nutritional support for patients with dysglycemia during perioperative period. Early enteral nutrition is beneficial to reduce insulin resistance and control hyperglycemia. Studies have found that taking a certain amount of carbohydrates orally before surgery has lower insulin resistance than patients who fasted overnight [40]. For perioperative patients, enteral nutrition can be implemented 24 to 48 hours after surgery as long as the internal environment is stable. Diabetic patients can choose enteral nutrition preparations suitable for diabetes.

Parenteral nutrition can be implemented for patients who cannot receive enteral nutrition. The appropriate ratio of glucose to energy is 50-60%, and the infusion rate should be controlled below 4 mg/(kg·min). For example, glucose should be routinely supplemented after surgery for patients who have undergone large and medium-sized complex surgeries or critically-ill. These patients can be infused with glucose solution 5-10 g/h (postoperative daily glucose is not less than 150 g) to supplement energy, reduce body fat and protein breakdown for energy supply to prevent ketoacidosis and hypoglycemia [25]. The glucose infusion should be neutralized by short-acting insulin (the ratio of glucose to insulin is about 3 ~ 4:1). The intravenous infusion of glucose can be discontinued when the patient resumes the diet and can obtain sufficient carbohydrates from food.

➢ Summary

Well glycemic control in the perioperative period is significance to improving the prognosis of patients. The management of blood glucose in perioperative patients can be strengthened through the physician-pharmaceutical co-management model in clinical practice. Individualized blood glucose control goals and treatment plans should be formulated according to the type of surgery and the specific conditions of the patient. Strict blood glucose monitoring should be carried out to avoid hypoglycemia and large fluctuations in blood glucose as much as possible during blood glucose management. Insulin is the first choice for perioperative blood glucose control. Multiple subcutaneous injections of rapid-acting insulin combined with long-acting insulin are the first choice before surgery, and regular insulin-glucose continuous intravenous infusion is selected during surgery (postoperative insulin infusion time should be more than 24 h) for non-critically-ill patients when they undergoing major surgery. Continuous short-acting insulin-glucose intravenous infusion during the perioperative period is the most effective and preferred method for critically-ill patients.

➢ Penners

WU Junyan Sun Yat-sen Memorial Hospital

SHEN jie The Third Affiliated Hospital of Southern Medical University

➢ Medical Advisors

LI Yan Sun Yat-sen Memorial Hospital

FENG Lie The First Affiliated Hospital of Jinan University

ZHANG Hua Zhujiang Hospital of Southern Medical University

RAN Jianming Guangzhou Red Cross Hospital

WANG Yan Guangzhou First People' s Hospital

LUAN Xiaojun Foshan First People's Hospital

ZHANG Gehua The Third Affiliated Hospita of Sun Yat-sen University

HE Mian The First Affiliated Hospital of Sun Yat-sen University

➢ Pharmaceutical Advisors

CHEN Xiao The First Affiliated Hospital of Sun Yat-sen University

YANG Min Guangdong Provincial People’s Hospital

➢ Members

CHEN Wenying The Third Affiliated Hospital of Southern Medical University

CHEN Jie The First Affiliated Hospital of Sun Yat-sen University

TANG Hongmei The First Affiliated Hospital of Guangzhou University of Chinese Medicine

LIU Chunxia Sun Yat-sen Memorial Hospital

HUANG Hongbing Sun Yat-sen University Cancer Center

LI Penghao Shenzhen Second People’s Hospital

WEI Li The First Affiliated Hospital of Guangzhou Medical University

WANG Ruolun The Second Affiliated Hospital of Guangzhou Medical University

ZHENG Zhihua Guangdong Pharmaceutical Association

WANG Yong Guangdong Pharmaceutical Association

➢ Secretaries

ZHAO Wenxia Sun Yat-sen Memorial Hospital
HU Shidi The Third Affiliated Hospital of Southern Medical University

REFERENCES

[1] Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery[J]. Diabetes Care, 2010,33(8):1783～1788.

[2] Kwon S, Thompson R, Dellinger P, et al. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program[J]. Ann Surg, 2013, 257(1):8～14.

[3] Vilar-Compte D, Alvarez de Iturbe I, Martín-Onraet A, et al. Hyperglycemia as a risk factor for surgical site infections in patients undergoing mastectomy[J]. Am J Infect Control, 2008, 36(3):192～198.

[4] Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia[J]. Lancet, 2009, 373(9677):1798～1807.

[5] Schricker T, Lattermann R. Perioperative catabolism[J]. Can J Anaesth, 2015, 62(2):182～193.

[6] Virkkunen J, Heikkinen M, Lepäntalo M, et al. Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia[J]. J Vasc Surg, 2004,40(4): 761～767.

[7] Farland MZ, Byrd DC, McFarland MS, et al.Pharmacist-physician collaboration for diabetes care: the diabetes initiative program [J].Ann Pharmacother, 2013, 47(6):781～789.

[8] Nguyen CT, Seto A, Rushakoff R, et al. Pharmacists' Impact on Glycemic Control Among Surgical Patients at a Large Academic Institution [J]. Clin Diabetes, 2016, 34(2):105～108.

[9] American Diabetes Association. Standards of medical care in diabetes 2013 [J]. Diabetes Care, 2013, 26 (suppl 1): 11～66.

[10] SHEN Chun-lian, LU Shao-feng, LI Jun, et al. Influence of Clinical Pharmacist Intervention on Blood Glucose Control and Medication Compliance in the Elderly Diabetic Inpatient [J].Pharmacy Today, 2013, 23(5)：285～287.

[11] Huang Jia, Mei Sheng-hui, Zhao Zhi-gang. Discussion on Patterns of Domestic and Foreign Pharmaceutical Care for Diabetic Patients [J]. Chin Pharm J, 2014,49（11）：951～954.

[12] Pasquel FJ, Lansang MC, Dhatariya K, Umpierrez GE. Management of diabetes and hyperglycaemia in the hospital[J]. Lancet Diabetes Endocrinol. 2021, 9(3):174-188..

[13] American Diabetes Association. Diabetes Care in the Hospital[J]. Diabetes Care, 2016, 39(Suppl 1):S99～S104.

[14] Jinjing W, Kang C, Xufei L, et al. Chinese clinical practice guidelines for perioperative blood glucose management[J]. Diabetes Metab Res Rev. 2021, 37(7):e3439.

[15] Sebranek JJ, Lugli AK, Coursin DB. Glycaemic control in the perioperative period[J]. Br J Anaesth. 2013, 111 (Sl):i18～i34.

[16]Endocrinology and metabolism Branch of the Chinese Medical Doctor Association. Expert consensus on blood glucose management for chinese inpatients[J]. Chin J Endocrinol Metab. 2017,33(1):1-10.

[17] WANG Tong, XIAO Xin-hua. Glycemic control in diabetic patients during perioperative period[J]. Chin J Endocrinol Metab, 2010,26(6): 527～528.

[18] Finfer S, Heritier S, NICE Study Management Committee and SUGAR Study Executive Committee. The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: statistical analysis plan[J].Crit Care

Resusc. 2009, 11(1):46～57.

[19] Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients[J]. N Eng J Med, 2009, 360(13):1283～1297.

[20] Griesdale DEG, de Souza RJ, van Dam RB, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data[J]. Can Med Associa J, 2009, 18.:821～827.

[21] Moghissi ES, Korytkowski MT, DiNardo M, et al. AACE and ADA consensus steatement on

inpatient glycemic control[J]. Endocrine Pract, 2009,15:1～17.

[22] Australian diabetes society, peri-operative diabetes management, 2012.

[23] Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline[J]. J Clin Endocrinol Metab, 2012, 97(1):16～38.

[24] Miriam A, Korula G. A simple glucose insulin regimen for perioperative blood glucose control: the Vellore regimen[J]. Anesth Analg, 2004, 99(2):598～602.

[25] Sudhakaran S, Surani SR. Guidelines for prioperative mnagement of the dabetic patient[J]. Surg Res Pract. 2015;2015:284063. doi: 10.1155/2015/284063.

[26] Membership of the Working Party, Barker P, Creasey PE, et al.

Peri-operative management of the surgical patient with diabetes 2015: Association of Anaesthetists of Great Britain and Ireland[J]. Anaesthesia, 2015, 70(12):1427～1440.

[27] American Diabetes association, Standards of Medical Care in Diabetes-2017[J]. Diabetes Care, 2017, 40

(Suppl. 1):1～142.

[28] Jacobi J, Bircher N, Krinsley J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients[J]. Crit Care Med, 2012,40:3251～3276.

[29] Editorial Board of Chinese Journal of General Practitioners of Chinese Medical Association，Expert consensus on insulin use in primary care of type 2 diabetes mellitus [J]. Chin J Gen Pract，2021, 20(7): 726-736.

[30]Chinese Society of endocrinology, Chinese diabetes society, Chinese endocrinologist association. China Insulin pump clinical guideline(2021) [J] . Chin J Endocrinol Metab, 2021, 37(8): 679-701.

[31] George S, Dale J, Stanisstreet D. A guideline for the use of variable rate intravenous insulin infusion in medical inpatients[J]. Diabet Med, 2015, 32(6): 706～713.

[32] O'Malley CW, Emanuele M, Halasyamani L, et al. Bridge over troubled waters: safe and effective transitions of the inpatient with hyperglycemia[J]. J Hosp Med, 2008，3(5 Suppl):55～65.

[33] Chinese Diabetes Society. Clinical application guideline for blood glucose monitoring in China (2021 edition) [J]. Chin J Diabetes Mellitus, 2021,13(10): 936～948.

[34]Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in China（2020 edition）[J].Chin J Endocrinol Metab, 2021,37(4):311～398.

[35] Joint British Diabetes Societies for inpatient care. The use of variable rate intravenous insulin inf usion (VRIII) in medical inpatients.http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_VRIII.pdf

[36] Chinese Society for Parenteral and Enteral Nutrition. Guidelines for perioperative nutritional support for adults [J]. Chin J Surg，2016,54（9）：641～657.

[37] Zhang JX, Kang K, Shu XL. Effect of nutritional support on clinical outcomes in perioperative malnourished patients: a meta-analysis [J]. Asia Pac J Clin Nutr. 2015, 24(3): 367～378.

[38] Chinese Diabetes Society. Chinese diabetes medical nutrition treatment guideline (2013). Chin J Diab Mell. 2015(2):73-88.

[39] Petrov MS, Zagainov VE. Influence of enteral versus parenteral nutrition on blood glucose control in acute pancreatitis: a systematic review[J]. Clin Nutr, 2007, 26(5): 514～523.

[40] Ljungqvist O. Modulating postoperative insulin resistance by preoperativecarbohydrate loading[J]. Best Pract Res Clin Anaesthesiol. 2009, 23(4): 401～409.

Appendix 1 Effects of perioperative medication on blood glucose

Drugs that can affect blood glucose in the perioperative period include anesthetics, glucocorticoids etc(Appendix 2). Anesthetics affect blood glucose control adversely, but different anesthetics have different effects on blood glucose. Among them, diethyl and ethyl chloride had a greater effect on blood glucose, while etomidate and propofol had less effect on blood glucose.

Drugs can also enhance or weaken the hypoglycemic effect through interaction with hypoglycemic drugs. For example, anticoagulants, non-steroidal anti-inflammatory drugs, sulfonamides, and methotrexate can compete with insulin for binding to plasma proteins, which can increase the level of free insulin in the blood, enhance the hypoglycemic effect. Beta-adrenergic receptor blockers (such as propranolol) can prevent adrenaline from raising blood glucose and interfere with the body's ability to regulate blood glucose. Concomitant use with insulin increases the risk of hypoglycemia.

Appendix 1. Drugs that affect blood glucose

Types of drugs	Mechanism	Effects on blood glucose
Glucocorticoid	Stimulation of hepatic gluconeogenesis and inhibition of peripheral tissues take in and utilize glucose, it also has "permissive" and "synergistic" effect on raising blood glucose of Glucagon, Epinephrine, Growth hormone	Hyperglycemia
Anesthetics (ether/chloroethane)	Inhibition of the sympathetic nervous system and suppression of insulin secretion	Hyperglycemia
Growth hormone	Inhibition of the uptake of glucose by fat and muscle, and the glucose used by cells, increased the secretion of glucagon by islet cells	Hyperglycemia
Tacrolimus Cyclosporine	Tacrolimus、cyclosporine have direct toxicity on islet β cells, and increase islet cell apoptosis	Hyperglycemia (Tacrolimus>Cyclosporine)
Thiazide diuretic	Hypokalemia and hypomagnesium decrease secretion of insulin	Hyperglycemia
Quinolone (gatifloxacin)	Inhibition of the ATP-sensitive potassium channels in islet β-cells，increases the release of islet β-cells，and induces β-cell vacuolar degeneration and decrease insulin secretion	Hypoglycemia or Hyperglycemia
Antipsychotics (Clozapine, Olanzapine)	Antagonize serotonin receptors and reduce islet β-cell reactivity	Hyperglycemia(Risperidone and Haloperidol are not prone to diabetes)
Octreotide	Inhibition of growth hormone、glucagon and insulin. Delay gastric emptying and slow down gastrointestinal peristalsis	Hypoglycemia
Asparaginase	Deficiency of asparagine decrease insulin receptor synthesis	Hyperglycemia
Thyroid gland hormone	Promotion of human catabolism, which lower insulin levels	Hyperglycemia
Progesterone(oral contraceptive)	Inhibition of glucose uptaken by fat and muscle,reduce the utilization of glucose by cells, and increase the secretion of glucagon by islet alpha cells	Hyperglycemia
Non-selective beta blockers	Interference of glycemic response, hinder decomposition of liver glycogen, cover up the alert symptoms of hypoglycemia, such as palpitations, sweating and other reactions	Hypoglycemia

Appendix 2 Classification of Insulin

According to the source and chemical structure, insulin is divided into animal insulin, human insulin and insulin analogs. According to the speed of onset of action, insulin can be divided into fast-acting insulin analogue, short-acting insulin analogue, intermediate-acting insulin analogue, long-acting insulin analogue and premixed insulins See Appendix 2 for details. The availability of insulin analogs is similar to human insulin. But insulin analogs are superior to human insulin in mimicking physiological insulin secretion and reducing the risk of hypoglycemia.

Appendix 2. Comparison of Action Characteristics of Commonly Used Insulin Preparations in China

Type		Type of Insulin	Appearance	Action time			Administration route	Subcutaneous injection time
				Onset	Peak	Duration		
Prandial insulin	rapid-acting	Insulin Lispro	clear	10-15min	1-1.5 h	4-5 h	subcutaneous injection,insulin pump,intravenous	injected immediately before meals, administered immediately after meals if necessary
		Insulin Aspart		10-15min	1-2 h	4-6 h		
		Insulin Glulisine		10-15min	1-2 h	4-6 h		
	short-acting	Recombinant Human Insulin	clear	30-60min	2-4 h	5-8 h	subcutaneous injection,insulin pump,intravenous	before the meal30min
		Human Biosynthetic Insulin						
basal insulin	intermediate-acting	Protamine Zinc Recombinant Human Insulin	cloudy	2.5-3 h	5-7 h	13-16h	subcutaneous	before sleepsubcutaneous
	long-acting	Insulin Glargine	clear	2-3 h	None	Up to30h	subcutaneous	before sleepsubcutaneous
		Insulin Detemir	clear	3-4 h	3-14 h	Up to24h		
	Ultra long-actin	Insulin Degludec	clear	-	None	Up to42h	subcutaneous	Flexible injection
premixed		Premixed Human Insulin 70/30、or 30R	cloudy	30 min	2-12h	14-24h	subcutaneous	before meal30 min
		Premixed Human Insulin 50R		30 min	2-8h	10-24h		
		Premixed Insulin Aspart 30		10-20min	1-4h	14-24h		injected immediately before meals, administered immediately after meals if necessary
		Premixed Insulin Lispro 25		15 min	30-70 min	16-24h		
		Premixed Insulin Lispro 50		15 min	30-70 min	16-24h		
		Premixed Insulin Aspart 50		10-20min	1-4h	16-24h		

Appendix 3

Assessment Form

Patients' basic information

Medical record number________ Name________ Sex______ Department________ Bed No.______
Diagnosis______________________ Height/Weight/Waistline________________ BMI______________

Management condition of blood glucose

Fasting blood glucose_______Blood glucose 2h after breakfast________Blood glucose before lunch_________
Blood glucose 2h after lunch______Blood glucose before dinner______Blood glucose 2h after dinner_________
Blood glucose at bedtime__________ HbA_{1c}___________
Whether it is diabetes □Yes □No Type of diabetes □Type1 □Type2
Course of diabetes_____________ History of hypoglycemia________________

Assessment of complication

Blood pressure_______ LDL-C______ TG__________ Cr__________ AST___________ ALT___________
WBC__________ NET_____________
Whether it is combined with cardiovascular diseases □Yes □No
Surgery size □major surgery □Minor surgery □Plastic and other delicate surgery
Whether the surgery requires fasting □Yes □No Fasting time____________
Anesthesia □General anesthesia □Local anesthesia or spinal epidural anesthesia

Control goal of blood glucose

□General (fasting or preprandial blood glucose: 6.1-7.8 mmol/L;
postprandial orrandom blood glucose when unable to eat: 7.8-10.0 mmol/L)
□Strict (fasting or preprandial blood glucose: 4.4-6.1 mmol/L;
postprandial or random blood glucose when unable to eat: 6.1-7.8 mmol/L)
□Loose (fasting or preprandial blood glucose: 7.8-10.0 mmol/L;
Postprandial or random blood glucose when unable to eat : 7.8-13.9 mmol/L)

Appendix 4

blood glucose control methods

<table>
<tr>
<td rowspan="7">non-critically-ill patients</td>
<td rowspan="5">major surgery</td>
<td rowspan="3">Preoperative</td>
<td rowspan="2">subcutaneous injection（Prandial insulin +basal insulin (preferred) or premixed insulin</td>
<td>Prandial insulin （Preferred rapid-acting)</td>
<td>□Biosynthetic human insulin
□Recombinant Human Insulin（Subcutaneous injection 30 minutes before meals）
□insulin aspart
□Insulin lispro
□Insulin glulisine
（Inject immediately before meals)</td>
<td>+ basal insulin (Preferred long-acting)</td>
<td>□Low protamine zinc human insulin
□Insulin detemir
□Insulin glargine
□Insulin degludec
（subcutaneous injection at bedtime)</td>
<td>Dose___</td>
</tr>
<tr>
<td>premixed insulin</td>
<td>□premixed insulin aspart 30
□premixed insulin lispro 25
□premixed insulin aspart 50
□premixed insulin lispro 50
□premixed human insulin 50
□premixed human insulin 30</td>
<td colspan="3">Dose___</td>
</tr>
<tr>
<td>Insulin Pump</td>
<td>short/rapid-acting insulin （Preferred rapid-acting)</td>
<td>□Biosynthetic human insulin
□Recombinant Human Insulin
□insulin aspart
□Insulin lispro
□Insulin glulisine</td>
<td>Base rate____</td>
<td colspan="2">Dose before morning/noon/dinner____</td>
</tr>
<tr>
<td>Intraoperative</td>
<td colspan="6">Intravenous insulin infusion（Preferred short-acting）□Recombinant Human Insulin □Biosynthetic human insulin
□insulin aspart
□Insulin lispro
□Insulin glulisine
Preparation of Insulin Micropump：insulin 50 U+NS 49.5 ml（concentration 1U/ml） pump speed：___ Common preparation of insulin for intravenous administration：insulin 25U+NS250ml（concentration 0.1U/ml） Speed of intravenous infusion：_______</td>
</tr>
<tr>
<td>postoperative</td>
<td colspan="6">Insulin intravenous infusion for at least 24 hours. After returning to diet, change to subcutaneous injection Program: ____</td>
</tr>
<tr>
<td rowspan="2">minor surgery</td>
<td>Preoperative</td>
<td colspan="2">□ original program
□subcutaneous insulin injection</td>
<td colspan="4">Program:____</td>
</tr>
<tr>
<td>Intraoper</td>
<td colspan="2">If blood glucose is high, subcutaneous short/rapid-acting insulin (rapid-acting preferred)</td>
<td colspan="4">□insulin aspart □Insulin lispro □Insulin glulisine
□Recombinant Human Insulin □Biosynthetic human insulin Dose____</td>
</tr>
</table>

<table>
<tr><td rowspan="3"></td><td rowspan="3"></td><td>ative</td><td></td><td colspan="3"></td></tr>
<tr><td rowspan="2">postoperative</td><td colspan="2">Before recovery diet: high blood glucose, subcutaneous short/rapid-acting insulin</td><td>Program：__</td><td>Dose___</td></tr>
<tr><td colspan="4">After resuming the diet, switch to the original treatment program Program____</td></tr>
<tr><td rowspan="2">critically-ill patients</td><td colspan="2">Preoperative and intraoperative</td><td>□ Intravenous insulin infusion</td><td colspan="3">□ Recombinant Human Insulin □Biosynthetic human insulin
□insulin aspart □Insulin lispro □Insulin glulisine
Preparation of the micropump: human insulin 50U+NS49.5ml pump speed：_______Insulin intravenous infusion rate：__</td></tr>
<tr><td colspan="2">postoperative</td><td colspan="4">The intravenous infusion of insulin can be switched to subcutaneous insulin when the condition of patients is stable and the diet resumes Program__</td></tr>
</table>

Appendix 5

Blood Glucose Monitoring and Tracking Table

Date	6:00 Before breakfast	9:00 After breakfast	11:00 Before lunch	14:00 After lunch	17:00 Before dinner	20:00 After dinner	22:00 Before sleep	medication regimen