15 Using Continuous Glucose Monitoring for Patients with Fulminant Type 1 Diabetes

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Fulminant type 1 diabetes was first reported by Imagawa et al. [1] in 2000 and is characterized by a sudden onset of severe metabolic disorders, markedly elevated blood glucose with normal or slightly elevated glycated hemoglobin A_{1c} (HbA_{1c}), and almost complete, irreversible loss of islet function. Fulminant type 1 diabetes can be classified as one subtype of idiopathic type 1 diabetes (type 1B), with an acute onset of ketosis or ketoacidosis. The associated serious complications such as rhabdomyolysis, acute renal failure, and cerebral edema have been reported [2–4], and the outcomes could be fatal if without timely diagnose and treatment. Therefore, fulminant type 1 diabetes, as an acute and critical disease of the endocrine and metabolic system, requires special attention by all clinicians. In addition, due to almost complete, irreversible damage of islet function, patients exhibit large blood glucose variability and significantly increased risk of hypoglycemia and continue to need long-term therapy of insulin replacement. Therefore, it is necessary to comprehensively understand the characteristics of blood glucose variability through various monitoring techniques including self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) technology in particular, in order to optimize the hypoglycemic regimen.

15.1 Overview of Fulminant Type 1 Diabetes Mellitus

15.1.1 The Concept of Fulminant Type 1 Diabetes

The 1997 American Diabetes Association (ADA) and the 1999 World Health Organization (WHO) have proposed the classification of diabetes mellitus [5–7], which divides diabetes into four types, namely, type 1 diabetes, type 2 diabetes, special types of diabetes, and gestational diabetes. Among them, type 1 diabetes is divided into two subtypes, namely, autoimmune-mediated diabetes (type 1A) and type 1B. Furthermore, three distinct stages of type 1 diabetes can be identified according to the latest ADA diabetes criteria (2017; Table 15.1) [8].

In 2000, Imagawa et al. [1] found a group of 11 patients with newly diagnosed type 1 diabetes that was characterized by a remarkably abrupt onset, the absence of insulitis and diabetes-related antibodies, and the high level of serum pancreatic enzyme concentrations. This was referred to a special type of type 1 diabetes and named “fulminant type 1 diabetes”.

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Table 15.1 Staging of type 1 diabetes [8] (Reprinted with permission from *Diabetes Care*)

	Stage 1	Stage 2	Stage 3
Stage	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 5.6–6.9 mmol/L (100–125 mg/dL) • 2hPG 7.8–11.0 mmol/L (140–199 mg/dl) • HbA_{1c} 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in HbA_{1c}	• Clinical symptoms • Diabetes by standard criteria

IGT impaired glucose tolerance, *IFG* impaired fasting glucose, *FPG* fasting plasma glucose, *2hPG* 2-hour postload glucose

15.1.2 Diagnostic Criteria for Fulminant Type 1 Diabetes

There is no uniform diagnosis criterion of fulminant type 1 diabetes. The 2012 Japan Diabetes Society (JDS) criteria (Table 15.2) are commonly used for the diagnosis of fulminant type 1 diabetes, which include the screening criteria and diagnostic criteria [9].

For the diagnosis of fulminant type 1 diabetes, the following aspects need to be supplemented:

1. For patients with impaired glucose regulation, their HbA_{1c} level is relatively high. Thus, the cutoff point [HbA_{1c} < 8.7% (72 mmol/mol) (NGSP)] is not applicable to such patients.
2. For patients with the manifestations of diabetic ketosis or ketoacidosis, fulminant type 1 diabetes should be routinely screened. Further tests for islet autoantibody, HbA_{1c}, islet function, and liver function are required in patients with suspected fulminant type 1 diabetes.
3. Fulminant type 1 diabetes can be diagnosed if three of the JDS diagnostic criteria are met; the diagnosis is highly suspected if two of the diagnostic criteria are met with a disease course exceeding 1 week.
4. The onset of fulminant type 1 diabetes is often preceded by influenza-like symptoms or gastrointestinal symptoms and, thus, is often misdiagnosed as acute respiratory infection or acute gastroenteritis. Therefore, improvements are needed in the early detection, early diagnosis, and early treatment of fulminant type 1 diabetes.

15.1.3 Epidemiology of Fulminant Type 1 Diabetes

According to the previous case reports, fulminant type 1 diabetes most commonly occurs in Asian countries, with the highest incidence in Japan, followed by China and South Korea. It is rarely reported in Europe and the USA. Preliminary epidemiological studies show that the ketosis-onset fulminant type 1 diabetes accounted for 19.4% (43/222) [10] and 7.1% (7/99) [11] of cases of type 1 diabetes in Japan and South Korea. The prevalence rate in China was 9.1% among type 1 diabetes patients, accounting for 14.0% of type 1 diabetes with ketosis or ketoacidosis-onset over 18 years of age.

The existing evidence shows that fulminant type 1 diabetes has the following epidemiological characteristics:

1. Sporadic distribution.
2. Racial and ethnic variations in incidence rates. The incidence is higher in Asians than in Caucasians, with no reports so far in African American.
3. Average age at onset of 39.1 years (most cases over 20 years old). Women showed a younger age at onset than men.
4. No significant difference in the morbidity between men and women, although morbidity increases with age in males.
5. Greater morbidity associated with pregnancy.

Table 15.2 Criteria for definite diagnosis of fulminant type 1 diabetes mellitus (2012) [9] (Reprinted from *Journal of Diabetes Investigation*)

Criteria for screening: 1. Ketosis or ketoacidosis within 1 week after the onset of hyperglycemic symptoms 2. Plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) at first visit
Criteria for definite diagnosis: 1. Occurrence of diabetic ketosis or ketoacidosis soon (approximately 7 days) after the onset of hyperglycemic symptoms (elevation of urinary and/or serum ketone bodies at first visit) 2. Plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) and glycated hemoglobin A_{1c} level <8.7% (NGSP value) [72 mmol/mol (IFCC value)][a] at first visit 3. Urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/mL (<0.10 nmol/L) and <0.5 ng/mL (<0.17 nmol/L) after intravenous glucagon (or after meal) load at onset
Other findings in fulminant type 1 diabetes mellitus: 1. Islet-related autoantibodies, such as antibodies to glutamic acid decarboxylase antibody (GAD-Ab), islet-associated antigen 2 (IA-A2) and insulin, are undetectable in general 2. Duration of the disease before the start of insulin treatment can be 1–2 weeks 3. Elevation of serum pancreatic enzyme levels (amylase, lipase, or elastase-1) is observed in 98% of the patients 4. Flu-like symptoms (fever, upper respiratory symptoms, etc.) or gastrointestinal symptoms (upper abdominal pain, nausea and/or vomiting, etc.) precede the disease onset in 70% of patients 5. The disease can occur during pregnancy or just after delivery 6. Association with HLA *DRB1*0405-DQB1*0401* is reported

HLA human leukocyte antigen, *NGSP* National Glycohemoglobin Standardization Program, *IFCC* International Federation of Clinical Chemistry

[a]This value is not applicable for patients with previously diagnosed glucose intolerance

15.1.4 Etiology of Fulminant Type 1 Diabetes

The etiology and pathogenesis of fulminant type 1 diabetes are not yet clear and are currently thought to be associated with genetic, environmental (viral infection), and autoimmune factors (Fig. 15.1).

15.1.4.1 Genetic Susceptibility

The results of previous studies have shown that a genetic polymorphism of human leukocyte antigen II (HLA-II) is associated with the occurrence of fulminant type 1 diabetes (Table 15.3). The results indicate that HLA *DR4-DQ4* is associated with the onset of Japanese fulminant type 1 diabetes mellitus, especially the *DRB1*0405-DQB1*0401*, *DQA1*0303-DQB1*0401* and *DQA1*0302-DQB1*0303* haplotypes. Tsutsumi et al. [12] found that 32.6% of fulminant type 1 diabetes patients carried the *DRB1*0405-DQB1*0401* genotype, which was significantly higher than 14.2% of individuals in the normal control group. Therefore, the 2012 JDS diagnostic criteria for diagnosis of fulminant type 1 diabetes mellitus include the characteristic of "association with HLA *DRB1*0405-DQB1*0401*" [9]. Moreover, studies have shown that HLA *DRB1*0405-DQB1*0401* is a susceptibility gene in Japanese patients with negative GAD-Ab, whereas the HLA *DRB1*0901-DQB1*0303* genotype is more common in GAD-Ab positive and fulminant type 1 diabetes associated with pregnancy [12, 13]. The results of a study in South Korea also showed the involvement of HLA *DRB1*0405-DQB1*0401* in fulminant type 1 diabetes [14]. HLA *DQA1*0102-DQB1*0601* may be a susceptibility gene for the Chinese population [15].

In addition, there is evidence for genetic heterogeneity in fulminant type 1 diabetes. A pair of twins in South Korea had the same HLA *DR-DQ* haplotype but different phenotypes, namely, fulminant type 1 diabetes and autoimmune-mediated diabetes, type 1A [16].

15.1.4.2 Viral Infection

Most fulminant type 1 diabetes patients have a history of infection 2 weeks before onset, suggestive of an association between viral infection and the onset of fulminant type 1 diabetes. A Japanese national survey showed that 71.7% of fulminant type 1 diabetes patients had influenza-like symptoms before the onset and 72.5% had abdominal symptoms [17]. Also, some

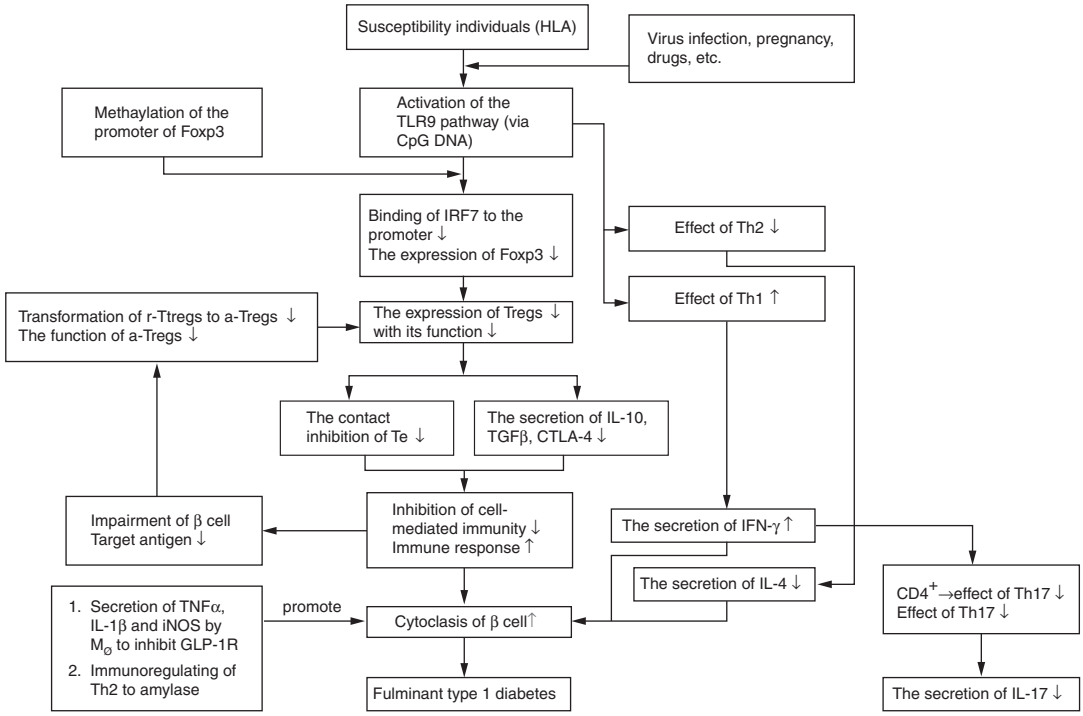


Fig. 15.1 The etiology and pathogenesis of fulminant type 1 diabetes. *HLA* human leukocyte antigen, *Foxp3* forkhead box protein 3, *IRF7* interferon regulatory factor 7, *CTLA-4* cytotoxic T-lymphocyte antigen 4, *Th1* helper T cell 1, *Th2* helper T cell 2, *Th17* helper T cell 17, M_D macrophage, *IL-1β* interleukin-1β, *IL-4* interleukin-4, *IL-10* interleukin-10, *IL-17* interleukin-17, *TNFα* tumor necrosis factor α, *TGFβ* transforming growth factor β, *iNOS* inducible nitric oxide synthase, *CpG DNA* non-methylated DNA, *TLR9* Toll-like receptor 9, *Te* effector T cell, *GLP-1R* glucagon like peptide-1 receptor, T_{regs} regulatory T cell, *a-*T_{regs} activated regulatory T cell, *r-*T_{regs} rest regulatory T cell

Table 15.3 Fulminant type 1 diabetes mellitus-related HLA genotype

Japan
HLA *DRB1*0405-DQB1*0401* [mostly in GAD-Ab (−)]
HLA *DQA1*0303-DQB1*0401*
HLA *DQA1*0302-DQB1*0303*
HLA *DRB1*0901-DQB1*0303* [mostly in GAD-Ab (+) and PF]
China
HLA *DQA1*0102-DQB1*0601*
South Korea
HLA *DRB1*0405-DQB1*0401*

HLA human leukocyte antigen, *PF* fulminant type 1 diabetes associated with pregnancy, *GAD-Ab* glutamic acid decarboxylase antibody

patients had significantly high titers of IgA antibodies to enterovirus [18]. The common viruses identified are herpes simplex virus (HSV), human herpesvirus 6 (HHV6), cytomegalovirus (CMV), coxsackie virus, etc. (Table 15.4).

Imagawa et al. [19] found elevations in a variety of antibodies after viral infection, suggesting that the virus-induced immune response, rather than viruses themselves, triggered the fulminant type 1 diabetes. Tanaka et al. [20] found the presence of enterovirus in islet cells and exocrine tissues, and immune response to enterovirus infection might be involved in the onset of fulminant type 1 diabetes.

15.1.4.3 Autoimmunity

At the initial discovery of fulminant type 1 diabetes, Imagawa et al. [1] found that islet autoantibody was negative in 11 fulminant type 1 diabetes patients and, thus, eliminated an association of fulminant type 1 diabetes with autoimmune disease, which distinguished it from type 1A diabetes. However,

Table 15.4 Fulminant type 1 diabetes mellitus-related virus

	Cases in China	Cases in other countries
Herpes simplex virus 1 (HSV1)	Zhou ZG, et al. Chinese Journal of Endocrinology and Metabolism, 2010	Nagaoka T, et al. Tonyobyo (J Japan Diab Soc), 2001
Human herpesvirus 6 (HHV6)	–	Imagawa A, et al. Tonyobyo (J Japan Diab Soc), 2008
Cytomegalovirus (CMV)	Liu F, et al. Chinese Journal of Endocrinology and Metabolism, 2009	Imagawa A, et al. Tonyobyo (J Japan Diab Soc), 2008
Coxsackie virus (A4.5.6, B3.4)	Zhou ZG et al. Chinese Journal of Endocrinology and Metabolism, 2010	Nishida W, et al. Tonyobyo (J Japan Diab Soc), 2005
Chlamydia	Liu F, et al. Chinese Journal of Endocrinology and Metabolism, 2009	–
ECHO virus	–	Vreugdenhill GR, et al. Clin Infect Dis, 2008
Influenza virus	Liu F, et al. Chinese Journal of Endocrinology and Metabolism, 2009	Sano H, et al. Diabetes Res Clin Pract, 2008
Rotavirus	–	Imagawa A, et al. Tonyobyo (J Japan Diab Soc), 2008
Parvovirus B19	–	Nishiumi T, et al. J Diabetes Investig, 2014
Epstein-Barr virus	Wang T, et al. Chin Med J (Engl), 2008	Sekine N, et al. JAMA, 2001
Mumps virus	–	Goto A, et al. Endocr J, 2008
Norovirus	–	Koyano HM, et al. Intern Med, 2013
Encephalomyocarditis virus (EMV)	–	Sano H, et al. Biochem Biophys Res Commun, 2011
Parainfluenza virus	–	Ohara N, et al. Int Heart J, 2015
Hepatitis A virus	–	Hwang YC, et al. Diabet Med, 2010

the follow-up study found some fulminant type 1 diabetes patients were positive for GAD-Ab or also had Graves' disease or Hashimoto's thyroiditis. A small number of patients presented with lymphocyte infiltration in pancreatic tissues [10, 21]. These data suggest that immune factors are involved in the occurrence of this disease.

A subsequent study has confirmed cellular or humoral immune abnormalities in a portion of fulminant type 1 diabetes patients. Aida et al. [22] found T cell and macrophage infiltration in and around the islets in three cases of fulminant type 1 diabetes, suggesting that both innate and acquired immunity are involved in the occurrence of this disease. It has also been reported that macrophage-mediated insulitis may be a more important cause of β-cell damage than T cells ($CD8^+$ T cells were originally thought to cause fulminant type 1 diabetes) [23, 24].

Moreover, the recent study showed that the Toll-like receptor-9/interferon regulatory factor-7 (TLR9/IRF7) pathway is involved in the occurrence of fulminant type 1 diabetes, mainly through cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and transcription factor forkhead box P3 (Foxp3). Zhou et al. [25] found that Foxp3 promoter hypermethylation in human peripheral blood mononuclear cells prevented IRF-7 binding to the Foxp3 promoter, downregulated the expression of TLR9 and Foxp3, and thus impaired the function of regulatory T cells (T_{reg}) and decreased CTLA-4. T_{reg} immunodeficiency in peripheral blood and islets resulted in failure of the body to produce effective immune tolerance, which triggered a sustained autoimmune destruction of β-cells and finally led to fulminant type 1 diabetes.

15.1.4.4 Pregnancy

The fulminant type 1 diabetes can be divided into pregnancy-related fulminant type 1 diabetes and nonpregnancy-related fulminant type 1 diabetes

according to its relationship with pregnancy. The study performed by Imagawa et al. [1] showed that almost all cases of abrupt onset of type 1 diabetes during pregnancy are fulminant type 1 diabetes, mostly occurring during late pregnancy or 2 weeks after delivery. Shimizu et al. [13] compared the clinical characteristics of the two types of the disease and found that fulminant type 1 diabetes associated with pregnancy might be related to the hormone levels and metabolic disorders of pregnant women: sex hormones during pregnancy can promote the Th2-type immune response and antagonize the Th1-type immune reaction. In addition, there is a case report of fulminant type 1 diabetes occurring 10 days after artificial abortion, revealing that abortion may also increase the risk of fulminant type 1 diabetes.

15.1.4.5 Others

Some medications (carbamazepine, mexiletine, ibuprofen, tegafur-uracil, pembrolizumab, etc.) may be involved in the occurrence of this disease by drug-induced hypersensitivity syndrome [26–28]. Onuma et al. [29] reported that compared with general population, patients with drug-induced hypersensitivity syndrome had a higher probability of developing fulminant type 1 diabetes, with a susceptibility gene HLA-B62, suggesting that in addition to genetic susceptibility, the use of specific drugs is associated with the occurrence of this disease.

15.1.5 Clinical Characteristics of Fulminant Type 1 Diabetes

Most fulminant type 1 diabetes patients are adults with no difference in the incidence between men and women. Pregnant women are at higher risk of this disease. Compared with type 1A diabetes, fulminant type 1 diabetes has the following clinical characteristics:

1. Prodromal symptoms. Patients often develop prodromal symptoms 2 weeks before the onset of fulminant type 1 diabetes, for instance, influenza-like symptoms (fever, upper respiratory tract infection, etc.) or gastrointestinal symptoms (diarrhea, nausea, vomiting, etc.), with fever (60%) being most common.
2. Hyperglycemia and ketoacidosis. The onset is very sudden, with typically <1 week from the presentation of typical hyperglycemic symptoms (polyuria, polyphagia, polydipsia, and weight loss) to the occurrence of ketosis or ketoacidosis. Sekine et al. [30] reported a case of a patient who had blood glucose within normal range 1 day before the onset, followed by a sudden increase in blood glucose and a sudden drop in C-peptide level the next day. Some researchers have even observed hypoglycemic events before the onset, probably due to a rapid release of synthesized insulin into the blood resulting from the rapid destruction of islets. As the course of the disease is very short, the HbA_{1c} at onset is close to normal or only mildly increased.
3. Severe metabolic disorders. Approximately 90% of fulminant type 1 diabetes begins with ketosis or ketoacidosis and half with disturbance of consciousness. At the onset, hyperglycemia, ketoacidosis, and electrolyte imbalance are more serious than type 1A diabetes.
4. Almost complete, irreversible loss of islet function. The existing evidence shows permanent destruction of islet α- and β-cells in patients with fulminant type 1 diabetes.
5. Serious complications such as rhabdomyolysis, liver dysfunction, and kidney dysfunction. Some patients exhibit multiple organ dysfunction such as loss of liver, kidney, heart, and striated muscle function, as manifested by an elevation in hepatic enzymes, pancreatic enzymes (amylase, lipase, elastase, etc.), and myokinases, or severe conditions like rhabdomyolysis, acute renal failure, cerebral edema, and even cardiac arrest [2–4] (Table 15.5).
6. Others. Most cases of pregnancy-related type 1 diabetes are fulminant type 1 diabetes and mostly occur during the late pregnancy or 2 weeks after delivery [1, 17]. The clinical symptoms of fulminant type 1 diabetes associated with pregnancy appear to be much

Table 15.5 Complications, comorbidities and related disorders of fulminant type 1 diabetes mellitus

Complications/ comorbidities	Cases in China	Cases in other countries
Rhabdomyolysis	Zhou J, et al. Chinese journal of internal medicine, 2007	–
Sjogren's syndrome	Zhang J, et al. Chin J Diabetes, 2013	–
Multiple organ failure (MOF)	Liang DC, et al. Chinese Critical Care Medicine, 2012	Ochi F, et al. Nihon Naika Gakkai Zasshi, 2008
Fetal death in utero (FDIU)	Zhang Z, et al. Chinese Journal of Perinatal Medicine, 2012	Bresson L, et al. J Gynecol Obstet Biol Reprod (Paris), 2010
Acute pancreatitis	Cao FL, et al. International Journal of Endocrinology and Metabolism, 2010	Tanaka S, et al. Endocrine J, 2013
Acute liver failure	Xiao J, et al. Journal of Internal Intensive Medicine, 2013	–
Myocarditis	Wei Q, et al. Jiangsu Med J, 2012	Makino K, et al. BMC Res Notes, 2013
Acute renal failure	–	Mizutani T, et al. Leg Med (Tokyo), 2011
Glycogen liver disease	–	Murata F, et al. Endocr J, 2012
Drug rash with eosinophilia and systemic symptoms (DRESS)	–	Dubois-Laforgue D, et al. Diabetes Care, 2013
Drug hypersensitivity syndrome (DHS)	–	Minegaki Y, et al. Int J Dermatol, 2013
Hashimoto's thyroiditis	–	Minegaki Y, et al. Int J Dermatol, 2013
Insulin autoimmune syndrome (IAS)	–	Kim HS, et al. Diabet Med, 2012
Thrombocytopenia	–	Yasuda H, et al. Diabet Med, 2012
Coronary microcirculation disorder	–	Yamada H, et al. J Diabetes Investig, 2014
Acanthosis nigricans	Lu ZY, et al. Chin J Diabetes, 2009	–
Encephaledema	Dong HM, et al. J Forensic Leg Med, 2014	–

more serious, with lower HbA_{1c} and arterial pH value. Fulminant type 1 diabetes associated with pregnancy can result in severe maternal and fetal complications, for instance, an extremely high incidence of abortion and stillbirth.

15.2 Treatment and Prognosis of Fulminant Type 1 Diabetes Mellitus

15.2.1 Treatment of Fulminant Type 1 Diabetes

At present, the evidence on the treatment of fulminant type 1 diabetes is mainly derived from case reports. According to its characteristics, the treatment is divided into acute-phase treatment and long-term insulin therapy.

15.2.1.1 Acute-Phase Treatment

Fulminant type 1 diabetes is characterized by an abrupt onset of the disease mostly with ketosis and ketoacidosis, accompanied by severe

metabolic disorders and remarkably elevated blood glucose concentration. Once fulminant type 1 diabetes is suspected, the patient should be treated immediately for diabetic ketoacidosis including rehydration; small doses of intravenous insulin infusion; correction of electrolyte and acid-base imbalance, along with symptomatic and supportive treatment; and prevention and management of complications.

In addition, the following points need to be noted:

1. Given the acute onset with severe metabolic disorders, fulminant type 1 diabetes should be diagnosed and treated in a timely manner with (1) rapid establishment of two intravenous accesses, one for continuous intravenous insulin infusion and the other for rehydration and anti-infection treatment, and (2) due to severe dehydration and poor subcutaneous absorption of insulin, it is recommended to use intravenous insulin infusion rather than insulin pump therapy.
2. In serious cases, rhabdomyolysis and resultant acute renal failure may occur. (1) Pay attention to the presence or absence of muscle weakness, swelling, pain, and brown urine; (2) the serum creatine kinase level is the most specific indicator of rhabdomyolysis, which should be routinely tested and used for constant monitoring of dynamic changes during the early diagnosis and treatment of fulminant type 1 diabetes.
3. Fulminant type 1 diabetes associated with pregnancy can result in severe maternal complications and stillbirth. Key measures to save the fetus include shortening of hyperglycemia-lasting duration, timely correction of ketoacidosis, and performing a cesarean section in a timely manner.

15.2.1.2 Long-Term Insulin Therapy

As there is almost complete, irreversible destruction of islet α- and β-cells in fulminant type 1 diabetes, the patient usually has extremely poor islet function, large blood glucose variability, and increased incidence of hypoglycemia. Therefore, patients usually require four times of intensive treatment with subcutaneous rapid-acting or short-acting insulin combined with intermediate-acting or long-acting insulin. In addition, an insulin pump, which simulates the physiological insulin secretion, can be used to improve blood glucose control in patients [3]. It improves inter- and intra-day glucose variability [3, 31]. The use of an insulin pump as long-term insulin replacement therapy is suggested, with a significantly higher insulin dosage than that used for type 1A diabetes [32].

15.2.2 Prognosis of Fulminant Type 1 Diabetes

Due to the sudden onset and severe metabolic disorders of fulminant type 1 diabetes, the mortality rate is high in the absence of early diagnosis and timely treatment. After correction of ketosis or ketoacidosis, abnormal hepatic enzyme, pancreatic enzyme, and myokinase levels will return to normal within 2–3 weeks; however, fulminant type 1 diabetes causes permanent destruction of islet α- and β-cells, which requires long-term insulin replacement therapy. Compared with type 1A diabetes, fulminant type 1 diabetes results in worse islet function, more severe β-cell destruction, higher insulin requirement, and increased risk of hypoglycemia and diabetic microvascular diseases. However, Koyano et al. [33] reported the partial recovery of pancreatic α-cells after treatment from fulminant type 1 diabetes in a case of 34-year-old male, but his serum C-peptide level was still under the detection limit. Also, it was reported that early intensive treatment achieved partial recovery of β-cell function in a 44-year-old female patient who developed acute pancreatitis and concomitant fulminant type 1 diabetes [34]. Recently, a case of idiopathic type 1 diabetes with subsequent recovery of β-cell function has also been reported [35].

15.3 Use of CGM for Patients with Fulminant Type 1 Diabetes

Due to the almost complete destruction of islet β-cells, the blood glucose level is more easily influenced by exogenous insulin, and the patients exhibit large blood glucose variability and increased risks of hypoglycemia and diabetic

microvascular diseases. Thus, glucose monitoring is particularly important.

At present, SMBG and CGM are commonly used glucose monitoring methods for diabetes patients. HbA_{1c}, glycated albumin (GA), and other indicators can also reflect the recent glycemic control. SMBG represents the glucose concentration at a specific time-point, and it cannot reflect continuous, dynamic changes in blood glucose. CGM can detect occult hypoglycemia and hyperglycemia, which may be not easily detected by traditional methods. Thus, CGM is an effective supplement to traditional glucose monitoring methods. Moreover, CGM facilitates the understanding of trends in blood glucose variability and determination of the influences of meal uptake, exercise, and medication on blood glucose, so as to guide better improvements in lifestyle and adjustment of the treatment regimen. According to the Chinese clinical guideline for CGM (2012), CGM is desirable for type 1 diabetes patients [36]. Given that fulminant type 1 diabetes is a subtype of type 1 diabetes, CGM is also applicable to fulminant type 1 diabetes patients. CGM supports the management of type 1 diabetes by effectively detecting hyperglycemic and hypoglycemic events, providing data for blood glucose variability, and guiding the adjustment of treatment plan.

15.3.1 CGM Is an Effective Tool for Detecting Blood Glucose Variability

15.3.1.1 Detection of Hyperglycemic and Hypoglycemic Events

The results of the study performed by Melki et al. [37] showed that two-thirds of daily utilization of CGM was applied to monitor asymptomatic nocturnal hypoglycemia. Accumulating evidence has shown that CGM can detect asymptomatic nocturnal hypoglycemic events. Cheyne et al. [38] conducted a CGM study in ten type 1 diabetes patients with poor glycemic control and found that eight patients experienced asymptomatic hypoglycemia with blood glucose <3 mmol/L. For children with type 1 diabetes, CGM measurements suggested that about 70% of subjects had nocturnal hypoglycemia and 20% experienced nocturnal hypoglycemia for three consecutive nights [39]. CGM not only detects nocturnal hypoglycemia but also contributes to the detection of asymptomatic hypoglycemia during daytime [38, 39].

CGM also helps to detect postprandial hyperglycemia [40]. SMBG only represents the glucose concentration at a specific time-point, not the blood glucose levels throughout the day. Thus, it cannot detect all hyperglycemic events in a timely manner, especially postprandial hyperglycemia. Boland et al. [39] emphasized that CGM is an effective tool for detecting postprandial hyperglycemia in patients who only monitor fasting and bedtime blood glucose. Schaepelynck-Bélicar et al. [41] applied CGM in 12 patients with poor glycemic control and found that there were 24 postprandial hyperglycemic episodes in ten patients; five patients experienced prolonged nocturnal hyperglycemia; and four had the dawn phenomenon. Also, CGM facilitates the distinction between asymptomatic hypoglycemia and the dawn phenomenon [42].

15.3.1.2 Comprehensive Understanding of Glucose Variability

CGM not only detects hyperglycemic and hypoglycemic events but also contributes to the understanding of the characteristics of blood glucose variability [40–43]. Bhide et al. [44] believe that the biggest advantage of CGM is that it is capable of revealing the dynamic trends of blood glucose concentration so that practitioners can guide the adjustment of the treatment plan accordingly. Moreover, CGM also provides information about the causes of glycemic variability in diabetes patients.

15.3.2 Use of CGM to Guide Adjustments to Therapy

In clinical practice, CGM can be used to monitor the detailed changes in blood glucose variability throughout the day. It can improve the management of blood glucose levels and reduce hypoglycemic events by guiding the fine regulation of blood glucose. Long-term use of CGM helps improving the HbA_{1c} [45–51]. However, improper use of CGM

may also have a potentially negative impact: CGM provides interstitial fluid glucose readings, which lag behind capillary glucose levels. Moreover, overtreatment of hyperglycemia or hypoglycemia may increase blood glucose variability.

Fulminant type 1 diabetes developed rapidly and accompanied with more severe dysfunction of islets when compared with type 1A diabetes mellitus resulted in dramatic glycemic variability. However, HbA_{1c} levels are more commonly normal at the early stage of the disease. Thus, the application of CGM mainly focuses on improving and maintaining the stability of blood glucose levels at the initial stage. CGM can also help improving the HbA_{1c} when HbA_{1c} is markedly elevated.

In our previous study, we analyzed the CGM results of three patients with fulminant type 1 diabetes who were treated in our hospital from January 2007 to March 2008, and the therapeutic regimens were adjusted accordingly (Table 15.6) [3].

Case 1 (Fig. 15.2): A patient treated with subcutaneous insulin injection four times daily with insulin dose of 0.67 U/(kg·d). The mean blood glucose (MBG) was 8.9 mmol/L, and standard deviation of blood glucose (SDBG) was 3.6 mmol/L, indicating the presence of high glycemic variability. The patient also had hypoglycemia, and the percentage of time (PT) spent with glucose ≤3.9 mmol/L was 4% with no time spent with blood glucose ≤2.8 mmol/L (Fig. 15.2a). Six months later, the glucose variation was still quite large (SDBG was 3.0 mmol/L), and MBG decreased to 6.5 mmol/L. Thus, the patient had a potentially increased risk of hypoglycemia. The PT spent with glucose ≤3.9 mmol/L and ≤2.8 mmol/L were 21% and 6%, respectively (Fig. 15.2b).

Case 2 (Fig. 15.3): A patient was treated with an insulin pump with insulin dose of 0.57 U/(kg·d). CGM revealed good glycemic control. The MBG was 6.3 mmol/L, SDBG was 2.2 mmol/L, and the PT spent with glucose ≤3.9 mmol/L was 10%

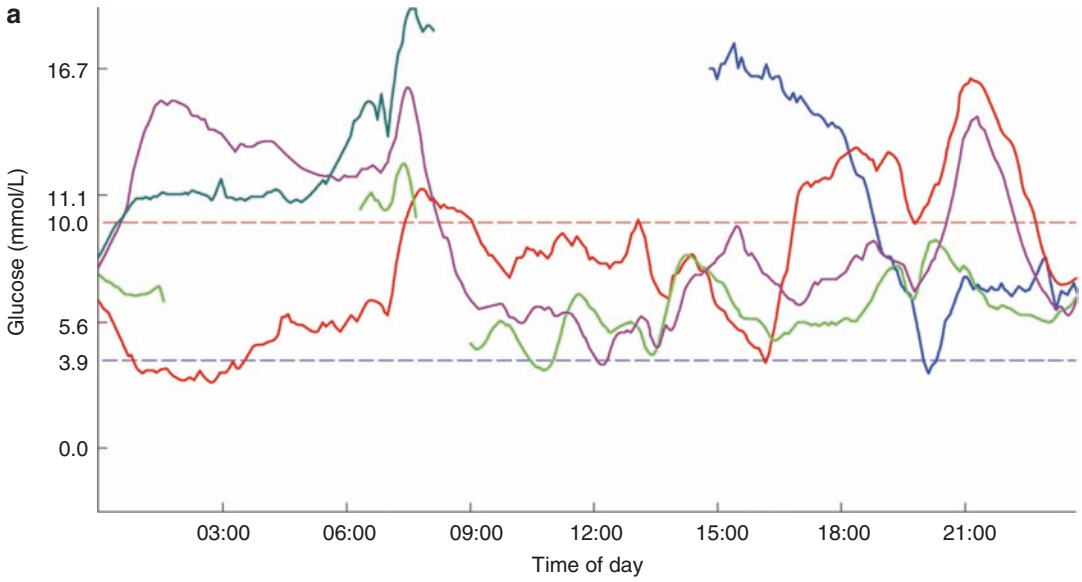
Table 15.6 Clinical characteristics of three cases of fulminant type 1 diabetes [3] (Reprinted with permission from *Chinese Journal of Diabetes Mellitus*)

Cases	Gender	Age (year)	BMI (kg/m^2)	Duration (day)	Glucose (mmol/L)	Urine ketone	Arterial blood pH	BE (mmol/L)
1	Male	31	23.3	4	38.9	+++	7.25	−17.0
2	Male	43	21.5	2	>38.9	+++	7.14	−25.2
3	Male	29	22.3	2	60.5	++++	7.02	−24.0

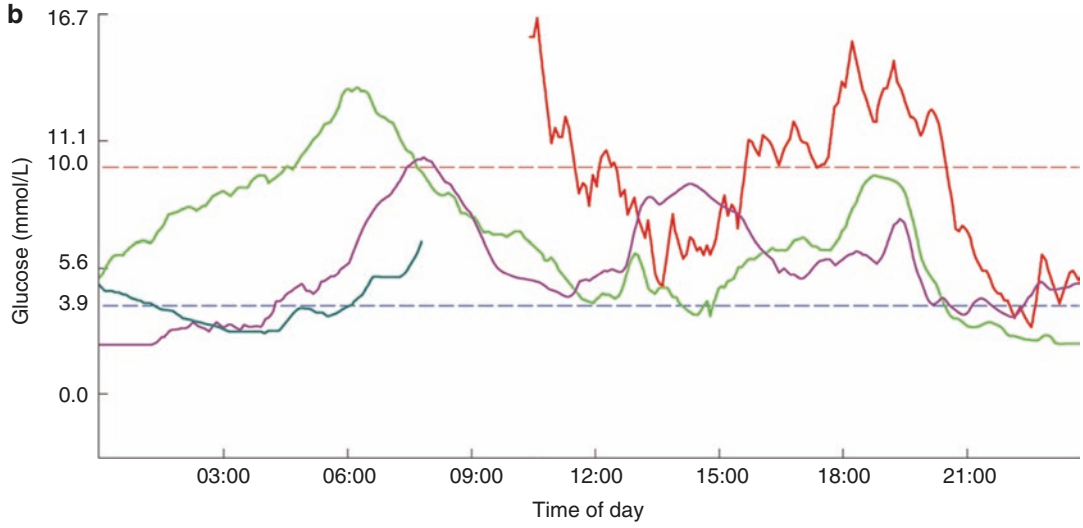
Cases	ALT (U/L)	AST (U/L)	Cr (μmol/L)	Na^+ (mmol/L)	K^+ (mmol/L)	CK (U/L)	LDH (U/L)	CK-MB (ng/ml)
1	293	366	230	117	7.3	11,754	1461	114.43
2	64	27	300	134	9.2	1,283	561	6.59
3	449	801	255	131	8.6	12,239	2147	42.71
Reference value	0–65	8–37	53–115	135–155	3.5–5.5	21–190	313–618	0–5

Cases	cTn (ng/ml)	Mb (ng/ml)	AMY (U/L)	UAMY (U/L)	Lipase (U/L)	HbA_{1c} (%[mmol/mol])	GA (%)	GAD-Ab (U/ml)
1	8.29	961.90	263	1015	830	6.2 (44)	22	0
2	0.118	–	387	>1300	812	6.3 (45)	24	3.6
3	1.27	>1000	2319	859	859	6.2 (44)	15	0
Reference value	0–1.5	0–110	30–110	32–641	0–190	4.3–6.5 (23–48)	11–17	0–7.5

		OGTT			Arginine stimulating test			
Cases	IA_2-Ab (U/ml)	CP_0 (ng/ml)	CP_{30} (ng/ml)	CP_{120} (ng/ml)	CP_0 (ng/ml)	CP_2 (ng/ml)	CP_4 (ng/ml)	CP_6 (ng/ml)
1	0	0.01	0.02	0.05	0.08	0.22	0.14	0.21
2	0	0.01	0.01	0.01	0.01	0.01	0.01	0.01
3	0	0.01	0.02	0.11	0.01	0.01	0.01	0.01
Reference value	0–7.5	0.5–1.5	–	–	0.5–1.5	–	–	–



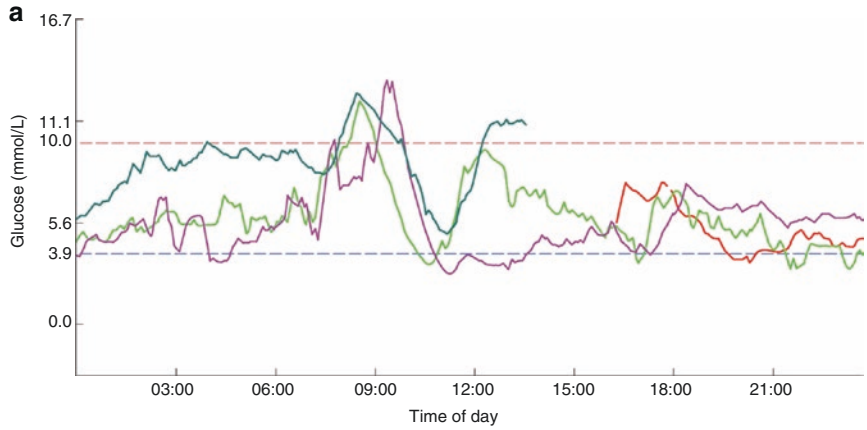
GLUCOSE EXPOSURE	GLUCOSE VARIABILITY	Dangerously Low	Low	GLUCOSE RANGES In Target Range	High	High
MBG mmol/L	SDBG mmol/L	≤ 2.8 mmol/L	≤ 3.9 mmol/L	3.9< GLUCOSE <10.0 mmol/L	≥ 10.0 mmol/L	≥ 11.1 mmol/L
8.9	**3.6**	**0%**	**4%**	**60%**	**36%**	**28%**



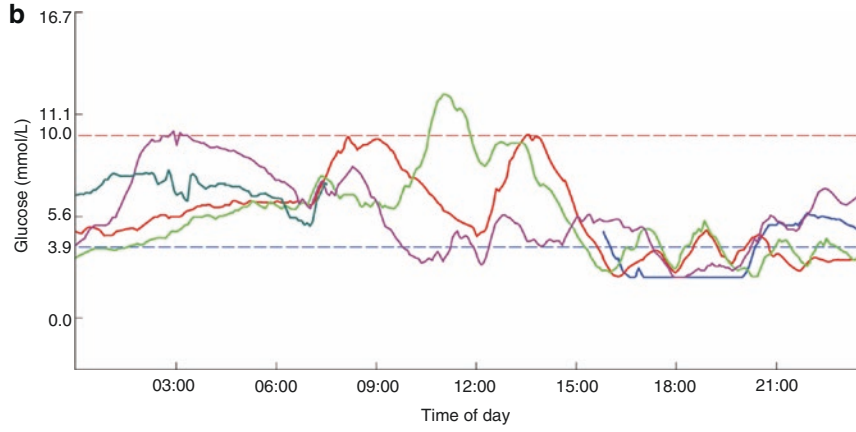
GLUCOSE EXPOSURE	GLUCOSE VARIABILITY	Dangerously Low	Low	GLUCOSE RANGES In Target Range	High	High
MBG mmol/L	SDBG mmol/L	≤ 2.8 mmol/L	≤ 3.9 mmol/L	3.9< GLUCOSE <10.0 mmol/L	≥ 10.0 mmol/L	≥ 11.1 mmol/L
6.5	**3.0**	**6%**	**21%**	**65%**	**14%**	**9%**

Fig. 15.2 Case 1: The CGM profiles of one case of fulminant type 1 diabetes treated with four-time daily subcutaneous insulin injections before and 6 months later

with no time spent with blood glucose ≤2.8 mmol/L (Fig. 15.3a). After follow-up for 6 months, the MBG was reduced to 5.5 mmol/L, and the SDBG was unchanged (2.2 mmol/L). Thus, the PT spent with glucose ≤3.9 mmol/L and ≤2.8 mmol/L were 27% and 9%, respectively, indicating an increased duration of hypoglycemic events, which were mainly concentrated in the period after dinner and before bedtime (Fig. 15.3b). These data demonstrated that hypoglycemia was associated with MBG, and a lower blood glucose level caused an increased risk of hypoglycemia, if the blood glucose fluctuation was basically unchanged. In conclusion, the blood glucose level of the patient was kept too low. Thus, we adjusted the therapy by reducing



GLUCOSE EXPOSURE	GLUCOSE VARIABILITY	Dangerously Low	Low	GLUCOSE RANGES In Target Range	High	High
MBG mmol/L	SDBG mmol/L	≤ 2.8 mmol/L	≤ 3.9 mmol/L	3.9< GLUCOSE <10.0 mmol/L	≥ 10.0 mmol/L	≥ 11.1 mmol/L
6.3	**2.2**	**0%**	**10%**	**83%**	**7%**	**3%**

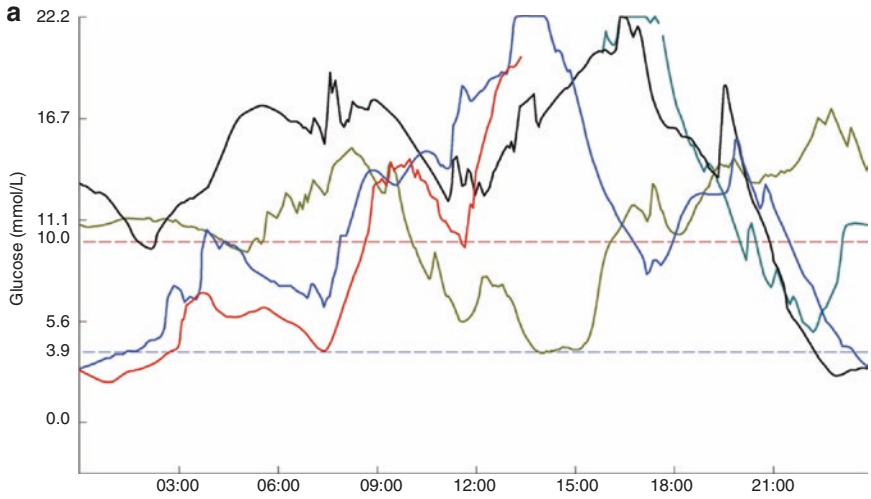


GLUCOSE EXPOSURE	GLUCOSE VARIABILITY	Dangerously Low	Low	GLUCOSE RANGES In Target Range	High	High
MBG mmol/L	SDBG mmol/L	≤ 2.8 mmol/L	≤ 3.9 mmol/L	3.9< GLUCOSE <10.0 mmol/L	≥ 10.0 mmol/L	≥ 11.1 mmol/L
5.5	**2.2**	**9%**	**27%**	**71%**	**2%**	**1%**

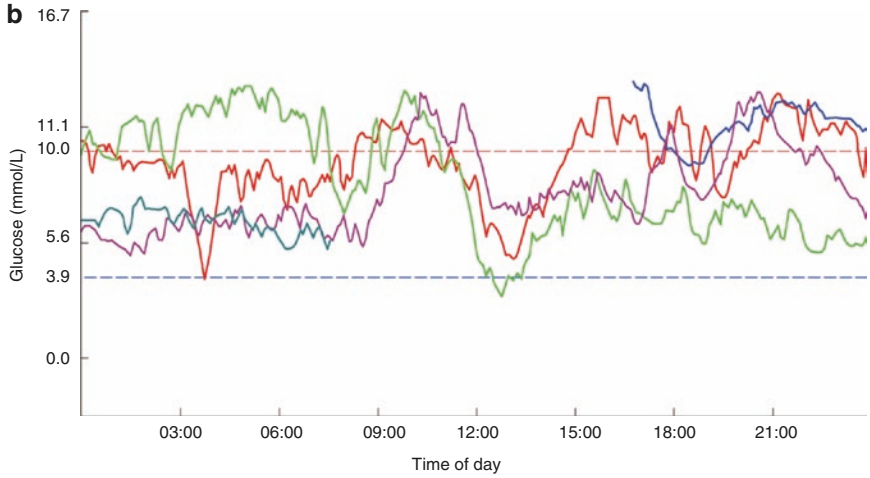
Fig. 15.3 Case 2: The CGM profiles of one case of fulminant type 1 diabetes treated with an insulin pump before and 6 months later

the basal rate of the insulin pump from before dinner to bedtime, in order to increase the target glucose level.

Case 3 (Fig. 15.4): A patient was initially treated with four times daily subcutaneous insulin injections with insulin dose of 0.95 U/(kg·d),



GLUCOSE EXPOSURE	GLUCOSE VARIABILITY	Dangerously Low	Low	GLUCOSE RANGES In Target Range	High	High
MBG mmol/L	SDBG mmol/L	≤ 2.8 mmol/L	≤ 3.9 mmol/L	3.9< GLUCOSE <10.0 mmol/L	≥ 10.0 mmol/L	≥ 11.1 mmol/L
11.5	**5.0**	**2%**	**7%**	**29%**	**64%**	**54%**



GLUCOSE EXPOSURE	GLUCOSE VARIABILITY	Dangerously Low	Low	GLUCOSE RANGES In Target Range	High	High
MBG mmol/L	SDBG mmol/L	≤ 2.8 mmol/L	≤ 3.9 mmol/L	3.9< GLUCOSE<10.0 mmol/L	≥ 10.0 mmol/L	≥ 11.1 mmol/L
8.7	**2.3**	**0%**	**1%**	**66%**	**33%**	**20%**

Fig. 15.4 Case 3: The CGM profiles of a fulminant type 1 diabetes patient changing from subcutaneous insulin injection to insulin pump therapy

but the patient had poor control of blood glucose, with MBG of 11.5 mmol/L, SDBG of 5.0 mmol/L, and largest amplitude of glycemic excursion (LAGE) of 6.1 mmol/L (reference range < 1.4 mmol/L), and the occurrence of asymptomatic nocturnal hypoglycemia (Fig. 15.4a). After transferring to insulin pump treatment with an insulin dose of 0.9 U/(kg·d), there were significant improvements in the blood glucose levels and the degree of variability. The MBG was 8.7 mmol/L, SDBG was 2.3 mmol/L, and LAGE was decreased to 2.9 mmol/L (Fig. 15.4b). The results showed that the CGM facilitated the understanding of the patient's blood glucose variability, and the insulin pump might help to control blood glucose variability in fulminant type 1 diabetes patients, thereby reducing the incidence of hypoglycemia and achieving satisfactory glycemic control.

Statement on Consent for Participation

All the clinical trials carried out by the authors in this book have been reported to the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital already and were in accordance with the Good Clinical Practice and Standards of China Association for Ethical Studies (approval number: 2007-45).

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