Annals of Clinical Case Reports

Case Report
Published: 05 Sep, 2022

Adult-Onset, Obesity and Serious Insulin Resistance are New Characteristics for T1DM

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Abstract

Adult-onset obese T1DM with serious insulin resistance is difficult to distinguish from Latent Autoimmune Diabetes in Adults (LADA) and T2DM. Hence, it will be ignored and misdiagnosed in the clinical activities, especially for the remote districts without well-equipped medicine. The doctors can be misled by the clinical experience. In this case, a 31-years old patient with adult-onset T1DM complicated with obesity and serious insulin resistance suffering from ketoacidosis was treated as T2DM by insulin injection based on the adult-onset, high BMI and serious insulin resistance. However, the blood glucose was beyond normal level obviously even we gave her a large amount of insulin from the continuous injection pump to short-acting combining with long-acting insulin (0.95 U/kg/d). The pre-meal glucose level fluctuated at 9 mM and the post-prandial glucose concentration waved at 15 mM. This phenomenon confused us and made us doubt the diagnosis. We examined the insulin and c-peptide at fasting and 1-h postprandial points. The insulin concentrations were 185.90 μIU/mL and 133.9 μIU/mL while the c-peptide was 0.48 ng/ml and 0.65 ng/ml, respectively. After, the patient completed the related antibodies examinations which showed that glutamic acid decarboxylase was over 2000.0 IU/mL. We diagnosed the patient as adult-onset T1DM with serious insulin resistance rather than LADA or T2DM. This was the first time to report adult-onset obese T1DM with serious insulin resistance. This case indicates that it is necessary to detect the autoimmune antibodies and OGTT to identify diabetes.

Keywords: T1DM; T2DM; Adult-onset; Insulin resistance; Obesity

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Received Date: *16 Aug 2022*
Accepted Date: *01 Sep 2022*
Published Date: *05 Sep 2022*

Citation:
Fen Y, Wenbin W, Hui D, Fuer L. Adult-Onset, Obesity and Serious Insulin Resistance are New Characteristics for T1DM. Ann Clin Case Rep. 2022; 7: 2295.

ISSN: 2474-1655.

Introduction

Diabetes is one of the most popular diseases around the world and increases risk of mortality for its complications [1]. It brings the heavy economic burden to the society [2]. It is well known that Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) are the major types of diabetes. In the past, the much higher incidence of T2DM and its serious complications, such as metabolism diseases, nerve-system disease, cardiovascular and kidney disease and so on, earn more attention [3-6]. T2DM is a metabolic disease featured with insulin resistance and relative insulin deficiency, while without autoimmune antibodies [7]. It usually happens to middle and elder-ages in the past several decades and is always progressed by pre-diabetes after several years or decades [8]. However, it has been certified that the increasing incidence of T2DM occurs among young people called youth-onset T2DM with higher mortality than elder people [9,10]. Whatever in the period of pre-diabetes or diabetes stage, optimizing lifestyle by enhancing activities and improving diets intake is well recommended and the patient can reverse abnormal glucose and prevent its progressing [11,12]. When it fails to hypoglycemic after three months, it is time to take oral drugs. Ultimately, the exogenous insulin is utilized to achieve the glucose target after oral hypoglycemia drugs failing or emergent situation, such as glucose toxicity [11,12].

T1DM is featured with absolutely deficient insulin for the autoimmune attack and always happens to children and adolescents [13]. However, adult-onset T1DM should be paid more attention. In detail, adult-onset T1DM is divided into classic adult-onset T1DM and Latent Autoimmune Diabetes of Adults (LADA) which can be distinguished by injecting insulin immediately or not [14]. To be specific, LADA shows the characteristics of both T1DM and T2DM, which is called 1.5 types of diabetes in the past. Its diagnosis criteria are following: the onset age is more than 30 years; one of the autoantibodies Including Antibodies to Insulin (IAA), Protein Tyrosine Phosphatase (IA-2),

Glutamic Acid Decarboxylase (GADA) or Islet Cell Autoantibodies (ICA) are positive at least; and insulin independence maintains 6 months after diagnosis [15]. Unlikely to T2DM, most T1DM patients should inject insulin or its analogs essentially and immediately once been diagnosed [16].

Based on the accumulated evidence, the differences between T1DM and T2DM include insulin-dependence or independence, symptoms, BMI and autoantibodies, complications such as microvascular disease and metabolic syndrome [17]. However, LADA make the differences vague and a further study has demonstrated that 5% to 10% LADA patients are misdiagnosed as T2DMl [18]. This reflects that it is not always easy to clarify T1DM and T2DM in some cases. In addition, the increasing of T2DM among children and teenagers and serious insulin resistance happening to T1DM patients make it harder to identified T1DM from T2DM in complicated situations [19,20]. Consequently, the clinical doctors should conduct thoughtful laboratory examinations and inquiry medical history, especial for young adult-onset diabetes.

We described a case of confused diagnosis as LADA or adult-onset T1DM with serious insulin resistance or T2DM. This case may illustrate that the young adult-onset diabetes needs more convincing evidence to be diagnosed.

Case Presentation

A 31 years old lady was delivered to emergency department for main complaint of thirsty for a half month as well as omitting and fatigue one day on 2:00 am of January 18th, 2021. The history of present illness was as following: The lady felt thirsty a half month ago without any reasons, she wanted to drink and urinate more than before at the same time. She ignored those symptoms and did not receive any treatment. Then, she had the omitting and fatigues a day before and was complicated with the dyspnea and restlessness and then was delivered to emergency department. The physical detection found that her BMI was 28.4 kg/m^2 and she had a full moon face with coma and rapid breath (41 times/min). Some moist rale and rough respiration had been heard in the lung. The pupils were same size in round and the diameter was about 2.5 mm. The light reflex was normal. The past history included hypothyroidism with serum Antithyroglobulin Antibody (TGAb) ranging from 22.4 IU/mL to 64 IU/mL and Antithyroid Peroxidase Antibody (TPOAb) ranging from 123 IU/mL to 440.8 IU/mL and she took euthyrox according to the doctors' guideline by monitoring thyroid hormone. She delivered her second baby by cesarean section at April 2020. During the whole pregnant period, the blood glucose levels including FBG and 2hPG and urine glucose were normal. However, the random blood glucose was 28.4 mM by glucose monitor at emergency department. The doctor diagnosed as diabetic ketoacidosis and assigned her to the ICU. After, the detailed detections were carried out. The blood routine showed that the WBC and neutrophil were 13.51 × 10^9/L and 11.34 × 10^9/L, respectively. The monocyte was 0.76 × 10^9/L. The percentage of lymphocyte decreased to 10.1 %. The RBC was 5.51 × 10^{12}/L and hemoglobin was 156.0 g/L. The platelet was 369.0 × 10^9/L. The HbA1c was 13.2%. Based on arterial blood gas analysis, PH value was 6.958; partial Pressure of Carbon Dioxide (PCO2) and concentration of HCO3- were 8.1 mmHg and 1.8 mmol/L, separately. The routine biochemistry analysis showed that serum iron K decreased to 3.16 mM while serum Na increased to 154.2 mM. At the same time, the concentration of HCO3- declined to 5.2 mM. Light liver damage had been found and blood ammonia rose up to 81 umol/L. The urine routine showed that red and white cells were strong positive. Additionally, both glucose and urine ketone bodies increased remarkably. The results of CT scanning of head and abdomen were normal. There was some gas in the mediastinum by CT scanning for the falling down during the transporting. The treatment in ICU focused on decreasing blood glucose by insulin injection pump and eliminating ketoacidosis by CRRT for 39 h and transfusing large liquid. When the situation was stable, she was transferred to our department for following therapy on January 20th, 2021. During this period, the patient never felt uncomfortable, except for high blood glucose. The patient was still treated by the insulin syringe pump (3 U/h to 5 U/h) and the finger glucose was detected every 2 h until to morning on January 23th. After that, the glucose was monitored by before and after meals and 9 pm because of transferring to use the short-time insulin and long-time insulin. According to the glucose status, we continually adjusted insulin dose. The blood glucose levels were showed in Figure 1. It demonstrated that the glucose levels were far from normal even treating with a large amount of insulin. Finally, we adjusted the pre-meal insulin from 8 U to 12 U, 14 U and 14 U. The insulin at 9 pm maintained 28 U. The glucose was still out of control. This phenomenon forced us to conduct deep detection of fasting and 2 h post-meal insulin and c-peptide levels. The fasting and post-meal insulin concentrations were 185.90 uIU/mL and 133.90 uIU/mL, while the fasting and post-meal c-peptide levels were 0.48 ng/mL and 0.65 ng/mL. Although it was essential to examine the antibodies, it was inconvenient in the branch hospital to conduct and the patient

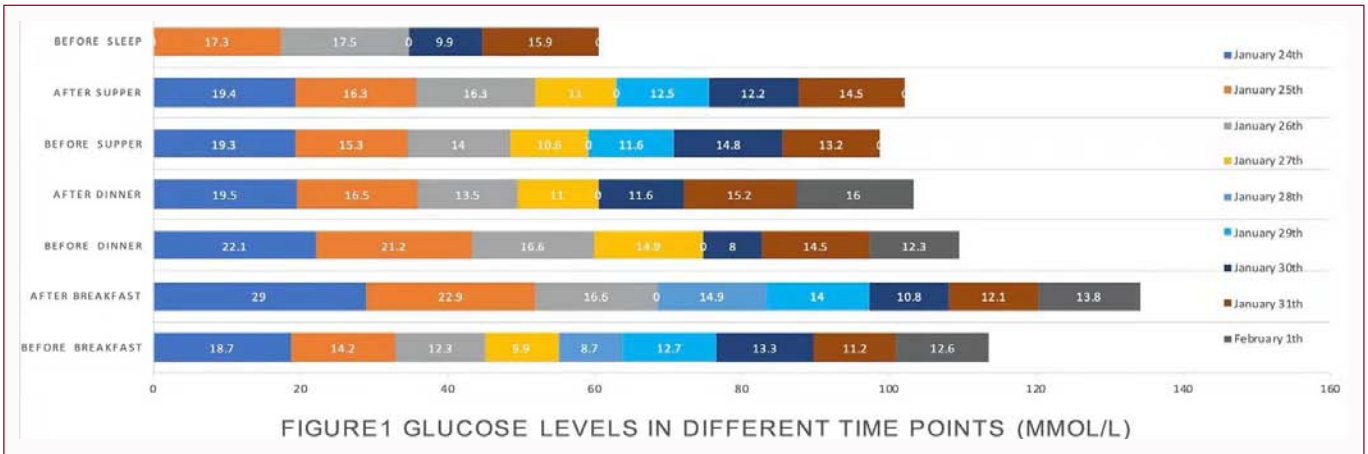

Figure 1: Glucose levels in different time points (MMOL/L).

refused to detect immediately. Finally, she decided to leave hospital even with high blood glucose on January 28th. We advised her to detect the antibodies in our headquarters and change her lifestyle to lose weight. In addition, she must adjust the dose of insulin based on finger glucose levels. After 10 days later, she went to the headquarters for her seriously high glucose level. The antibodies were identified and the concentrations of GADA and ICA were beyond 2000.0 IU/mL and 34.4 COI while IAA was normal. As a result, she obtained an improved hypo-glucose schedule: Short-time and long-time insulin combining oral drugs. The detail was that she injected 8 U short-time insulin pre-meal and 28 U long-time insulin at 9 pm. At the same time, she took Kashuangping composing of pioglitazone and metformin for 1 pill twice as well as the Invokana for 1 pill once per day. The fasting and postprandial blood glucose was approximately decreased to 5 mM and 8 mM, respectively. Based on the fluctuating glucose level, the patient persisted taking oral hypo-glucose drugs and cut down short-time insulin to 5 U and long-time insulin to 24 U. During this period, the glucose level fluctuated at 5 mM and she loses weight 5 kg successfully. Besides, the patient felt well, except for constipation. After two months, the patient decided to cease the pre-meal insulin and merely take oral drugs since the blood glucose was controlled well and stably by 4 U for every pre-meal. However, the glucose went up obviously after stopping the short-time insulin for a half of month. The patient continued injecting 10U insulin before meals and the blood glucose did not decreased ideally.

Discussion

Age is just a big trap for differing T1DM and T2DM. It is well-known that most of T1DM are diagnosed at childhood and teenager and more than 85% of them are below 20 years [21]. Besides, the increasing rate of pediatric T1DM is about 3% to 5% every year [22]. It proves that incidence of T1DM among children and adolescents are serious and make pediatric experts nervous. Nevertheless, one clinical study demonstrates that adult-onset T1DM is also popular and the authors appeal that it is time to test islet antibodies for diabetes patients as a routine item [23]. In further, LADA, a majority of adult-onset T1DM, which is characteristic with positive pancreatic antibodies, slower beta-cell lesion and some metabolic syndromes. The similarities between LADA and T2DM mislead investigators. A data shows that 2% to 12% of diagnosed T2DM belong to LADA [24]. Concurrently, numerous evidences demonstrate that T2DM is more and more prevalent at childhood and adolescent [25]. A large data analysis proves that the morbidity of young T2DM goes up 4.4 folds from 2002 to 2016 in Korea [26]. Compared with adult-onset T2DM, T2DM in children and adolescents is more aggressive with rapid beta-cell deterioration, serious complicated diseases. Also, it is hard to distinguish from T1DM [27]. Another study shows that there is an overlap between T1DM and T2DM and suggests that the diagnosed T2DM should be detected related antibodies and a new subtype of diabetes may be identified [28]. In conclusion, it is not easy to apart T1DM from T2DM by age which is a weak principle for diagnosis.

Obesity and insulin resistance are prevalent complications for the T1DM. In the past, T1DM patients is lean and sensitive to insulin. In this case, we considered the patient as the T2DM at first depending on adult-onset age, high BMI and serious insulin resistance. However, the blood glucose did not decrease well; even we had up-regulated insulin injection to 0.95 U/kg/d. The outcomes astonished us for the extraordinary insulin and little c-peptide. The extensive exogenous insulin injection contributed to the outstanding serum insulin concentration. The poor c-peptide reflected actual terrible secretion function of pancreatic beta cell. Those meant that the patient suffered serious pancreas impairment and remarkable insulin resistance. It was weird for the new diagnosed "T2DM" since nearly entire loss of beta cell and woeful insulin resistance. In fact, obesity and insulin resistance are not any more the features for T2DM based on the existed evidence. A comprehensive analysis shows that the ratio of overweight and obesity increase 20.1% and 9.5% in children and adolescent T1DM, respectively. Besides, the metabolic syndrome grows up from 3.2% to 29.9% [29]. Multiple researches illustrate that the incidence of overweight or obese T1DM ranges from 12.8% to 20.2% in different countries and districts and there is a growing up trend in recent decades [30-32]. A large scale of clinical study proves that adult-onset T1DM is 5.49% in 17,349 newly diabetes and LADA contribute 65%. Additionally, the ratio of overweight or obese T1DM is 5.84% and LADA patients account for 79.2% [23]. In summary, obesity and insulin resistance are popular complications in both T1DM and T2DM.

Autoimmune diseases may be a great clue for T1DM diagnosis. T1DM has a close relationship with other Autoimmune Diseases (AID), such as thyroid disease, rheumatoid arthritis, collagen vascular diseases, and autoimmune enteropathy (Crohn's and Ulcerative Colitis) [33,34]. There is an evidence illustrates that the additional autoimmune disease has been verified in 33% of new T1DM. It is relatively high rate and reminders us to detect other antibodies essentially [35]. What's more, the risk for additional AID for late-onset T1DM over 30 years is much higher than that of children and adolescent onset and it also reveals that the female prefers to have AID compared with the male [36]. Moreover, Autoimmune Thyroid Disease (ATD) has higher incidence in patient with T1DM and LADA is an independent risk for it. A clinical study shows that 23% children and/or adolescent T1DM patients have been diagnosed as ATD [37]. Another clinical investigation also proves that the patient with T1DM is susceptible to ATD which may attribute to susceptible genes [38]. In this case, the young lady had been diagnosed as hypothyroidism with TPOAb positive. It is an important clue for T1DM diagnosis. In clinical practice, the physician should ask the history carefully and find hints.

Diagnosis of Diabetes Mellitus (DM) would be more difficult than before for the changes of characteristics (age and complications) and it is time to combine insulin and oral hypo-glucose drugs to reverse uncontrollable glucose, regardless of whatever types of DM. Accumulating data show that the patient with T1DM have the features of T2DM which is called double diabetes, such as insulin resistance, metabolic disease [39,40]. It also means that those people have higher risk for suffering from serious complications including kidney disease, cardiovascular lesions. Meanwhile, the change of onset age makes it hard to distinguish them by age. Regarding to the treatment, it is important to combine insulin and oral drugs to decrease glucose level. In this report, we just gave her insulin injection at first for protecting the pancreatic beta-cell function based on the recent studies [41,42]. However, the high level of glucose was never be reversed due to extremely severe insulin resistance. After giving her insulin and oral drugs at the same time, the glucose can be controlled and maintained in target. In summary, considerate therapy schedule should be made based on the right diagnosis and insulin combing with oral drugs is the optimal choice for T1DM with insulin resistance.

Conclusion

Adult-onset, obesity and serious insulin resistance are new

characteristics for T1DM. It is essential for every newly diagnosed patient to carry out OGTT and detect glucose, c-peptide and insulin levels in different time points, especially for young people. At the same time, autoimmune antibodies should be taken into consideration. Those measures will help doctors to diagnose correctly and make right treatment plan to assure patient to obtain effective medicine as soon as possible.

Author Contributions

Yuan Fen collected original data and wrote the manuscript. Wu Wenbin sorted data and corrected references. Don Hui and Lu Fuer revised the manuscript. All authors devoted to the article and agreed with the submission.

Funding

This article was supported by the National Natural Science Foundation of China (No. 82004358).

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