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Efficacy of New Short-Term Intensive Insulin Therapy in a Newly Diagnosed Diabetes Patient Infected with COVID-19: Case Report

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Abstract

The current COVID-19 pandemic brings about a worldwide health crisis, especially in subjects with metabolic abnormalities. We devised New Short-Term Intensive Insulin Therapy (N-SIIT) to avoid hypoglycemia and mitigate glucotoxicity and Insulin Resistance (IR). Here, we show a newly diagnosed diabetic subject with COVID-19 who was efficiently treated using N-SIIT. A 43-year-old male was hospitalized due to high fever, wet cough and loss of taste and smell. SARS-Cov-2 was positive in PCR test. Chest CT image showed pneumonia. Immediately, we started N-SIIT, but pneumonia drastically aggravated on day 3. However, by continuing N-SIIT, clinical data were improved, and various symptoms disappeared on day 8. The required insulin dose was decreased and finally replaced by oral diabetes agents. He was discharged on day 13 under stable conditions. Pulmonary infiltration in the chest CT completely disappeared. We did not use any antiviral medicine or steroids, but COVIT-19 was cured by N-SIIT. Indeed, N-SIIT mitigated hyperglycemic adverse effects, leading to reduction of inflammatory cytokines and decrease of angiotensin-converting enzyme 2 expressions which is known to act as a receptor for SARS-CoV-2. We also assume that the mitigation of glucotoxicity and IR might have revived his own healthy metabolism and immune response. It is necessary to perform further clinical trials with a large number of subjects to establish practical therapeutic strategies.

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Introduction

The current COVID-19 pandemic caused by SARS-CoV-2 infection represents a worldwide health crisis causing severe illness and death [1,2]. Although COVID-19 has a broad spectrum of severity ranging from asymptomatic conditions to Acute Respiratory Distress Syndrome (ARDS), a great risk of severe COVID-19 has been reported in patients with old age, obesity, diabetes and hypertension [3-6]. Many reports have shown that patients with such risk factors and COVID-19 suffer from synergistic aggravation of both diseases [7-10]. In particular, the mortality of COVID-19 was higher in newly diagnosed diabetes subjects than in non diabetic or preexisting diabetes subjects [11-14]. It is possible that the virus enters pancreatic beta-cells via the Angiotensin-Converting Enzyme 2 (ACE-2) receptor, injures beta-cells and induces Insulin Resistance (IR), leading to the onset of diabetes mellitus or the aggravation of pre-existing diabetes [15-18]. Early glycemic control may be an important therapeutic strategy to reduce poor outcomes in hyperglycemic COVID-19 patients. Insulin is a safe choice under poor glycemic situations and is considered the first-line treatment in hyperglycemic and critically weakened patients [19,20]. Although insulin therapy sometimes brings about hypoglycemia, insulin can substantially mitigate beta-cell glucotoxicity and IR in a relatively short period of time, which likely leads to the improvement of abnormal metabolism and lowered immune activity in each patient. Here, we show a newly diagnosed diabetic subject with COVID-19 who we efficiently treated using New Short-Term Intensive Insulin Therapy (N-SIIT) [21], which is a basal-bolus insulin injection therapy based on the concept of "treat to target" to avoid hypoglycemia and eliminate glucotoxicity and IR.

Methods

We used New Short-Term Intensive Insulin Therapy (N-SIIT) based on the concept of "treat to

Table 1: Blood glucose levels and amount of injected insulin during short-term intensive insulin therapy of 12 days.

Hospital days	1		2		3		4		5		6		7		8		9		10		11		12	
Before breakfast			258		219		209		212		198		158		147		148		135		111		118	
2 h after breakfast			282		352		216		266		250		154		173		114		190		156		188	
Before lunch			199		275		252		308		292		207		187		96		138		125		155	
2 h after lunch			339		247		315		310		166		157		176		157		151		161		118	
Before dinner	359		207		216		213		162		122		136		131		161		109		117		120	
2 h after dinner	410		276		288		264		284		232		217		168		194		192		170		176	
Before bed time	307		251		281		287		234		235		212		179		129		108		145		147	
Plan, Additional	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad	Pl	Ad
Lyumjev breakfast			10	2	16	3	20	2	24	3	29	3	30	0	30	0	30	0	15	2	8	0	3	0
Lyumjev lunch			10	3	16	2	20	3	25	3	30	0	30	0	30	0	30	0	15	0	8	0	3	0
Lyumjev dinner	10	2	14	2	16	2	20	4	26	3	30	2	30	0	30	0	30	0	15	0	8	0	3	0
Glargine-U300	20		24		28		32		38		42		46		46		46		20		10		10	
Total	32		61		75		101		122		136		136		136		136		67		34		19	

Lyumjev: New ultra-rapid-acting insulin (insulin lispro-aabc) (units); Pla: Planned insulin dosage; Add: Additional insulin injection. One basal insulin and three bolus insulin were used but the determination of amount of each insulin was different from conventional procedure. Pre-meal insulin was defined as "treat" insulin, and blood glucose level which was determined by "treat" insulin was converged within "target" glucose range (90 mg/dl to 140 mg/dl)" by daily insulin titration. Initial daily dose was determined by the patient's body weight (95 kg) (0.5 units/kg/day, 47.5 units/day). We started insulin therapy with 10 units of lyumjev before each meal and 20 units of glargine U300 before dinner and adjusted as follows. For example, since blood glucose level 2 h after dinner was 410 mg/dl which was higher than 200 mg/dl, 2 units of lyumjev was optionally injected at that time. Also, blood glucose level before bed time was 307 mg/dl which was higher than 140 mg/dl, we added 2 units of lyumjev and planned 14 (10+2+2) units for day 2.

target" [21]. This is different from conventional basal-bolus injection [19]. In brief, 40% of the initial total daily dose of insulin (0.4 units/kg to 0.6 units/kg) was delivered with glargine U300 before dinner as basal insulin, and 20% was applied with Lyumjev before each meal as a bolus injection. On the following day, insulin dose was titrated according to the latest blood glucose level based on the concept of "treat to target" (Table 1).

The relationship between insulin and glucose levels is as follows: Lyumjev before breakfast reduces elevated blood glucose levels after breakfast and determines blood glucose levels before lunch. Similarly, Lyumjev before lunch and dinner determines blood glucose levels before dinner and bed time, respectively. Basal insulin glargine U300 before dinner determines fasting blood glucose level on the next morning. Through the above relation, titration of four insulin injections reduces blood glucose levels down to the "target" glucose range (90 mg/dl to 140 mg/dl). When the pre-meal blood glucose level was less than 90 mg/dl, the insulin dose was reduced by 2 units the next day to avoid hypoglycemia. To perform it more efficiently, we optionally injected 2 to 3 units of Lyumjev as additional pre-meal insulin at that time, only when the blood glucose level 2 h after a meal was over 200 mg/dl. Capillary blood glucose measurement and insulin injection were performed using capillary blood measurement devices and pen-type insulin injectors. Doctor or nurse gave instruction about insulin amount to each patient.

Statistical analyses were performed using a nonparametric method (n=7). Wilcoxon signed rank tests were applied for comparison of the data. In the comparison of three groups, p values were adjusted by Bonferroni-Holms calculation formula.

Case Presentation

Here, we present the case of a 43-year-old Japanese male patient admitted to our hospital due to three days of a high body temperature of 39.0°C and wet cough with blood-tinged sputum, shortness of breath, headache, sore throat, and loss of taste and smell. He had no

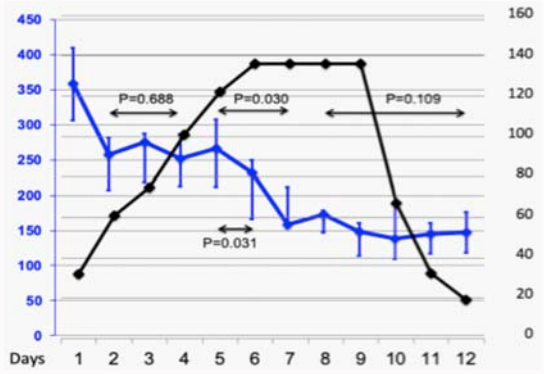

Figure 1: Total daily insulin (black line and right longitudinal axis, units/day) and blood glucose level (blue line and left longitudinal axis, mg/dl) (median, error bar: Interquartile Range (IQR)). Arrows indicate P values between blood glucose levels on different days (Wilcoxon's signed rank test). The insulin dose was stepwise increased, but blood glucose levels were not decreased for several days (from day 2 to day 4). After day 5, however, blood glucose levels were significantly decreased after adjustment with Bonferroni-Holm's calculating formula. In addition, after day 9, the insulin dose was considerably reduced, but blood glucose levels were not increased. These findings clearly indicate that the patient was substantially relieved from hyperglycemia, glucotoxicity and IR.

symptoms or history of diabetes before this episode, but his mother and maternal aunt had diabetes mellitus. He was a non-smoker and social drinker. On admission, his height, body weight and BMI were 175 cm, 95 kg and 31.0 kg/m^2 respectively. Although the patient had several symptoms as described above, his consciousness was clear, and he actively communicated with other people. There were no abnormalities or abnormal sounds in the heart, and respiration was smooth with a small crackle on auscultation. He had occasional nausea but had enough appetite to eat meals regularly. Initial vital signs were as follows: body temperature, 39.0°C; blood pressure, 148/98 mmHg; heart rate, 82 beats/min; respiratory rate, 20/min; oxygen saturation on room air, 95%. C-Reactive Protein (CRP) was

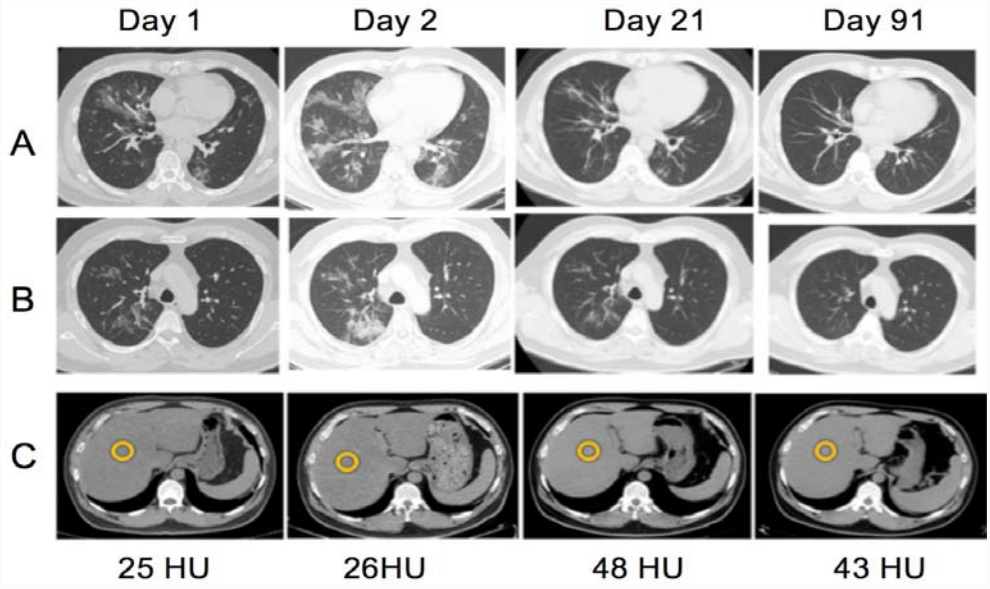

Figure 2: (A,B) Chest CT. Pneumonia was aggravated on day 3 but it was improved on day 21 and completely dissolved on day 91. (C) Abdominal CT. Fatty liver on day 1 and 3 was improved on day 21 and 91. HU: Hounsfield Unit; Yellow rings are spots in which CT values were measured (normal >40 HU).

Table 2: Time course of various clinical parameters in this subject.

	normal range	day 1	day 3	day 9	day 21	day 91
γ-GTP	13-64 U/L	157		143	69	78
AST	1.3-30 U/L	57	61	42	31	30
ALT	1.0-42 U/L	79	69	76	53	47
LDH	124-222 U/L		342	255	165	
Feritin	25.0-280.0 ng/ml	938	955		651	
C-peptide	0.61-2.06 ng/ml	5.59		1.21	6.2	
CRP	0.00-0.14 mg/dl	9.33	7.76	1.11	0.24	0.68
HbA1c	4.9-6.0 %	11.8			10.1	7.2
Glucose	70-126 mg/dl	337	126	88	148	146
Absolute lympho	1,500-4,000/μl	930	770	1,822	1,586	1,500
Fibrinogen	200-400 mg/dl		482			
D-dimer	< 1.0 μg/ml	0.3	0.2			

γ-GTP: γ-Glutamyl Transpeptidase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein; Absolute lympho: Absolute Lymphocyte.
Increased levels of AST, ALT, CRP, C-peptide, HbA1c, and blood glucose and lowered absolute lymphocyte number on day 1 or 3 were improved on day 21 and 91.

increased up to 9.33 mg/dL, and chest CT images showed pneumonia with ground glass infiltration. SARS-CoV-2 was positive in PCR test. High CRP, ferritin, LDH and liver enzymes and low absolute lymphocyte counts were compatible with SARS-CoV-2 infection and subsequent cytokine storm. HbA1c and blood glucose levels were as high as 11.8% and 337 mg/dL, respectively. C-peptide was high (5.59 ng/mL), and anti-GAD antibody was negative. Such high HbA1c, blood glucose and C-peptide indicated that this subject had hyperglycemic crisis with IR. To obtain good glycemic control, we started N-SIIT immediately after admission.

As shown in Table 1 and Figure 1, the injected insulin dose was increased step by step, but blood glucose levels were not decreased for several days (from day 2 to day 4). After day 5, however, blood glucose levels started to decrease significantly with the same dose of insulin (136 units/day). In addition, after day 9, the insulin dose was considerably reduced, but blood glucose levels were not increased. These findings clearly indicate the mitigation of glucotoxicity and IR, as reported previously [21]. Lab data were improved, and several symptoms subsided by day 8 without bringing about hypoglycemia (Table 1, 2).

Various symptoms, such as loss of smell and taste and cough, subsided, and finally, fever and bloody sputum disappeared on day 8. C-peptide on day 9 was lowered presumably by a feedback mechanism due to adequate insulin injection for beta-cell rest (Table 2). Then, insulin was replaced by empagliflozin 10 mg/day on day 8, voglibose 0.6 mg/day and mitiglinide 30 mg/day on day 9 and linagliptin 5 mg/day on day 11. He was finally discharged to home 12 days after hospitalization under stable conditions, and then diabetes control and evaluation of COVID-19 were performed at the outpatient clinic of Shigei Medical Research Hospital.

In addition, as shown in Figure 2, although abdominal Computed Tomography (CT) images showed fatty liver on days 1 and 3, it was markedly improved on day 21, which was probably due to a reduction

in glucotoxicity in the liver. Furthermore, and interestingly, although chest CT images showed pneumonia with ground glass infiltration on day 1, which was progressively aggravated on day 3, such alteration was drastically improved on day 21 accompanied by a marked reduction in CRP, and finally, pneumonia infiltration disappeared completely on day 91. Taken together, intensive insulin therapy with N-SIIT at an early stage of diabetes in this subject not only protected pancreatic β-cells against glucotoxicity and ameliorated fatty liver but also saved this subject from COVID-19; otherwise, this subject might have become involved in life-threatening problems due to COVID-19.

Discussion

We accepted this patient as an emergency case impending the severe stage of COVID-19 or diabetic ketoacidosis because of typical symptoms, laboratory results and aggravating pneumonia (CT on day 1 and day 3). On admission, the patient was classified in phase 2A [22]. In this phase, it is possible that worsening of the cytokine storm leads to irreversible phase 2B and phase 3. It is well known that intensive insulin therapy is very important in critically weakened patients with diabetes and COVID-19 [5,9,22,23]. On the other hand, to reduce cytokine storms, steroid therapy is often performed in COVID-19 patients. However, it is also known that systemic corticosteroid therapy induces hyperglycemia, primarily by increasing postprandial blood glucose levels, IR and pancreatic beta-cell dysfunction and that steroid therapy weakens immunity to infection [24]. Therefore, we have to be very careful when we start steroid therapy in patients with poorly controlled diabetes and COVID-19. In this subject, to interrupt the vicious cycle of diabetes and COVID-19 [10], we performed N-SIIT21 to [21] relieve glucotoxicity and IR rather than steroid therapy to subside the cytokine storm. Hyperglycemia promotes the production of inflammatory cytokines [25,26] and increases the expression of ACE-2 [27,28]. Increased ACE-2 acts as the receptor for SARS-CoV-2 and the dominant path of virus entry into various cells. We believe that N-SIIT reduces hyperglycemia stepwise into the glucose target range, attenuating cytokine storms and viral entry into cells.

SARS-CoV-2 infection is likely associated with a rapid increase in the required insulin dose, namely due to increased levels of inflammatory cytokines [9]. In this patient, the insulin dose was increased up to 136 units per day. Then, blood glucose levels were decreased to less than 180 ng/dl and glucotoxicity was eliminated. As shown in Figure 1, blood glucose levels were decreased with the same dosage of insulin for 4 days (days 6 to 9), indicating the mitigation of IR as reported previously [21]. Then, insulin therapy was replaced by oral agents, but blood glucose levels were not increased, indicating that this patient was substantially relieved from glucotoxicity and IR [21]. During the period of N-SIIT, various symptoms subsided, and laboratory data improved (Table 2). We did not treat him with antiviral medicine or steroid hormone, but COVID-19 was cured after N-SIIT. Since most native patients infected with SARS-CoV-2 without risk factors are asymptomatic or self-limited and spontaneously cured within 2 weeks, probably with their own healthy innate and acquired immune response, we assume that the mitigation of glucotoxicity and IR with N-SIIT led to revival of his own healthy metabolism and immune response in this subject. Normalized lymphocyte counts might have contributed to recovery of immune response. This hypothesis is supported by convalescent plasma transfusion, in which the infusion of plasma obtained from cured COVID-19 patients with higher titers of anti-SERS-CoV-2 antibody was effective for the treatment of other COVID-19 patients [29], indicating that neutralizing antibody works well. Therefore, we think there is a possibility that a neutralizing antibody to SARS-CoV-2 was produced in this patient after N-SIIT and saved him from COVID-19.

IR is often observed in subjects with obesity, hypertension and cardiovascular disease (metabolic syndrome) preceding the onset of type 2 diabetes. Thinking from high BMI, elevated C-peptide and fatty liver, this patient had serious IR. However, after blood glucose levels entered the target range with N-SIIT, the required insulin dose was decreased, indicating that the patient recovered insulin sensitivity reported previously [21]. These data clearly indicate that we should start intensive insulin therapy as soon as possible in subjects with newly diagnosed and poorly controlled diabetes and with COVID-19. Intensive insulin therapy ameliorates glycemic control, which mitigates hyperglycemic adverse effects, produces inflammatory cytokine [25,26] and increases ACE-2 [27,28]. Indeed, in this subject, chest CT showed ground glass infiltration on day 1, which was aggravated on day 3 but was improved by N-SIIT and finally completely disappeared. In addition, fatty liver was observed in the CT image, but it was also improved by N-SIIT, as reported previously (ref 21 Supplementary Dataset Case 2 and 3). Sodium-Glucose Co Transporter 2 (SGLT2) inhibitors also have anti-inflammatory effects and have drawn much attention recently. However, we think that SGLT2 inhibitors should not be used as the first-line medicine in subjects with COVID-19 because dehydration and ketoacidosis are likely brought about in such subjects [5,6,9,22,23]. In this patient, an SGLT2 inhibitor was used after good glycemic control was obtained by N-SIIT, and it was useful without any side effects.

In patients with both diabetes and COVID-19, diabetes risk factors and COVID-19 risk factors aggravate the patients' conditions independently or cooperatively. As intrinsic risk factors for diabetes, hyperglycemia, glucotoxicity and IR might dysregulate metabolism and injure many organs, especially the vascular system. Patients with diabetes are vulnerable to infectious diseases due to weak innate and acquired immunity. In particular, it is likely that diabetic ketoacidosis drastically disturbs metabolism. Hyperglycemia is a risk factor even in non diabetic disease, as described above. On the other hand, as inherent risk factors for COVID-19, infection reduces the number of natural killer cells. SARS-CoV-2 deteriorates glycemic control by increasing IR and impairing insulin secretion and can induce ketosis/ketoacidosis [30], although its main pathological site is vascular damage of the lung. Diabetes and COVID-19 have a common and related pathogenesis, leading to the establishment of a synergistic mechanism to aggravate pathophysiological conditions by creating a vicious circle [9,10], although it remains unclear which is the first perpetrator in such a vicious circle. In this case, N-SIIT not only improved glycemic control but also healed COVID-19 pneumonia without any antiviral medicine or steroid therapy for SARS-CoV-2. It is conceivable that N-SIIT recovered normal metabolism by relieving this subject from such a vicious cycle and restoring the immune response to SARS-CoV-2, leading to recovery from COVID-19 pneumonia. We think that these findings further strengthen the evidence reported in many articles that diabetes is a risky comorbidity in COVID-19 patients. Taken together, while the current COVID-19 pandemic brings about a worldwide health crisis, this case report clearly indicates that we should start insulin therapy as soon as possible in subjects with newly diagnosed and poorly controlled diabetes infected with COVID-19. We are sure that this case report will lead to the establishment of a new therapeutic strategy

for COVID-19, although it is necessary to perform further clinical trials with a large number of subjects to demonstrate our working hypothesis.

Conclusion

Newly diagnosed diabetes and poorly controlled diabetes are risk factors of COVID-19 infection. Previously we devised a New Short-Term Intensive Insulin Therapy (N-SIIT) on the concept of "Treat to Target" to avoid hypoglycemia and to converge adequate insulin dosage for the patient's individual pathophysiology. We successfully treated a case of newly diagnosed diabetes impending to severe stage using N-SIIT. Without steroid therapy N-SIIT exerted favorable effects in the patient with COVID-19 infection. Although hyperglycemia induced cytokine storm, N-SIIT efficiently treated hyperglycemia and led to subside cytokine storm. Therefore, we think that it is very important to treat risk factors of COVID-19 such as hyperglycemia.

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Ethics Statement

This research was approved by the research ethics board of Okamura Issindow Hospital (No 18000151-2021(5)) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the individual's for the publication of any potentially identifiable images or data included in this article.

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