

# Fatty liver formation in fulminant type 1 diabetes

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## Summary

A 32-year-old woman presented with 3 days of epigastric pain and was admitted to our hospital (day 3 of disease). We diagnosed acute pancreatitis based on epigastric abdominal pain, hyperamylasemia, and an inflammatory reaction of withdrawn blood, pancreatic enlargement, and so on. Her condition improved with treatment; however, on day 8, she had decreased level of consciousness. Laboratory results led to a diagnosis of fulminant type 1 diabetes mellitus (FT1DM) with concomitant diabetic ketoacidosis. Insulin therapy improved her blood glucose levels as well as her symptoms. Fatty liver with liver dysfunction was observed on day 14, which improved by day 24. Blood levels of free fatty acids (FFAs) increased rapidly from 440  $\mu\text{Eq/L}$  (normal range: 140–850  $\mu\text{Eq/L}$ ) on day 4 to 2097  $\mu\text{Eq/L}$  on days 7–8 (onset of FT1DM) and subsequently decreased to 246  $\mu\text{Eq/L}$  at the onset of fatty liver. The rapid decrease in insulin at the onset of FT1DM likely freed fatty acids derived from triglycerides in peripheral adipocytes into the bloodstream. Insulin therapy rapidly transferred FFAs from the periphery to the liver. In addition, insulin promotes the *de novo* synthesis of triglycerides in the liver, using newly acquired FFAs as substrates. At the same time, inhibitory effects of insulin on VLDL secretion outside of the liver promote the accumulation of triglycerides in the liver, leading to fatty liver. We describe the process by which liver dysfunction and severe fatty liver occurs after the onset of FT1DM, from the perspective of disturbed fatty acid metabolism.

## Learning points:

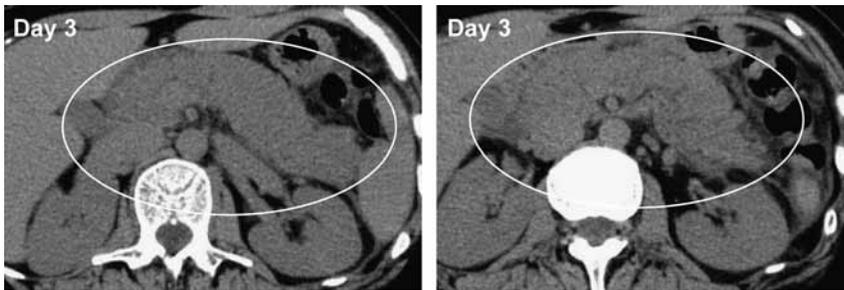
- FT1DM is rare but should be considered in patients with pancreatitis and a decreased level of consciousness.
- Fatty liver should be considered in patients with FT1DM when liver dysfunction is observed.
- Insulin is involved in mechanisms that promote fatty liver formation.
- Pathophysiological changes in fatty acid metabolism may provide clues on lipid metabolism in the early phases of FT1DM.

## Background

Although rare, elevations in liver enzymes can occur after the onset of fulminant type 1 diabetes mellitus (FT1DM) with fatty liver (1, 2, 3, 4). We describe the process by which liver dysfunction and severe fatty liver occurs after the onset of FT1DM, from the perspective of disturbed fatty acid metabolism. We report on a patient to clarify disease conditions, including lipid metabolism, which may present in the context of FT1DM.

## Case presentation

Patient: 32-year-old female. Chief complaint: Epigastric pain. Medical history: No history of obesity. Bronchial asthma diagnosed at 31 years of age. Family history: Older sister with type 2 diabetes. Social history: No history of smoking or drinking. Past medical history: She delivered a healthy full-term infant vaginally in October 2014. No abnormalities of lipid metabolism, liver function, or blood glucose levels occurred during pregnancy, and no



**Figure 1**  
Unenhanced abdominal computed tomography images on day 3. The diffuse and enlarged pancreas was indicative of acute pancreatitis.

abnormalities were detected via abdominal ultrasound when she was pregnant. History of present illness: She experienced discomfort in the upper abdomen in April 2015 (day 1 of disease). On the next day (day 2), she visited a healthcare provider complaining of epigastric pain. Blood glucose levels were normal at 90mg/dL; however, hyperamylasemia was confirmed and she was admitted to our hospital (day 3).

### Investigation

Condition on admission to the hospital (day 3): Height was 166.2cm. Weight was 56.4kg, Body mass index (BMI) was 20.5kg/m<sup>2</sup>. Blood pressure was 121/84mmHg, and pulse was normal at 73beats/min. Respiratory rate was 12breaths/min. Body temperature was 37.5°C. No evidence of conjunctival pallor, scleral icterus, goiter, or abnormal heart or pulmonary sounds was observed. She had epigastric tenderness and a slightly hard, flat abdomen. No abdominal rebound tenderness was observed. No aggravation or weakening of reflexes in the extremities was observed.

The abdominal computed tomography (CT) findings at the time of hospitalization are as follows: diffuse pancreatic enlargement (Fig. 1), with no fatty liver or hepatomegaly; Blood drawn under fasting and continuous infusion of nutrition solution (356kcal/day) confirmed an increased inflammatory response and elevated exocrine pancreatic enzymes (Table 1). Blood glucose was 148mg, blood serum insulin was 8.59μIU/mL, and blood serum C-peptide was 2.51 ng/mL, suggesting that endogenous insulin secretion was intact on day 3 (Table 1).

### Treatment

Clinical progression: Fever and epigastric pain were confirmed at the time of hospitalization, and blood tests suggested an increased inflammatory reaction and elevated exocrine pancreatic enzymes (Table 1). Abdominal CT

confirmed a diffuse, enlarged pancreas. The patient was diagnosed with acute pancreatitis. She began a treatment program consisting of fasting and gabexate mesilate (100mg thrice daily). On day 6, her condition improved and abdominal magnetic resonance imaging (MRI) did not detect signals that would indicate pancreatitis with diffusion-weighted images.

### Outcome and follow-up

On day 7, she started experiencing thirst and nausea, and on day 8, she developed the onset of cold extremities, hyperpnea, and a decreased level of awareness (Glasgow Coma Scale 7, E1V2M4). Arterial blood gas analysis confirmed metabolic acidosis. Blood tests revealed elevated levels of ketone bodies and glucose (Table 1). Serum C-peptide levels were below the limits of detection before and after glucagon loading, and impaired endogenous insulin secretion was confirmed (Table 1). Hemoglobin A1c (HbA1c) was normal and she tested negative for both anti-glutamic acid decarboxylase (GAD) and anti-insulinoma-associated protein 2 (IA-2) antibodies. These findings led to a diagnosis of FT1DM with concomitant diabetic ketoacidosis. Insulin aspart administration (0.91 U/kg/day) dramatically improved her blood glucose levels as well as her symptoms. Meals were restarted on day 13. At the same time, her treatment regimen was switched to subcutaneous basal-bolus injections of insulin lispro and insulin degludec (Fig. 2), which stabilized her blood glucose levels.

Fatty liver, which was not visualized on the initial abdominal CT scan (day 3), was observed on day 14. There was improvement on day 24 (Fig. 3). Liver transaminase levels started increasing on day 13, peaked on day 23, and decreased by day 37. Serum levels of free fatty acids (FFAs) increased rapidly from 440μEq/L (normal range: 140–850μEq/L) on day 4 to 2097μEq/L on days 7–8 (onset of FT1DM), and subsequently decreased to 246μEq/L at the onset of fatty liver (Fig. 2).

**Table 1** Laboratory results on day 4 and days 7–8.

| Parameters                                      | Laboratory data            |   |
|---|----------------------------|---|
|   | Day 4                      | Days 7–8  |
| <b>Hematology</b>                               |                            |   |
| WBC   | 4900/μL                    | 10 500/μL   |
| RBC   | 452 × 10 <sup>4</sup> /μL  | 453 × 10 <sup>4</sup> /μL   |
| Hb  | 13.5 g/dL                  | 13.4 g/dL   |
| Hct   | 38.2%                      | 38.7%   |
| Plt   | 19.6 × 10 <sup>4</sup> /μL | 30.6 × 10 <sup>4</sup> /μL  |
| <b>Biochemistry/serology</b>                    |                            |   |
| TP  | 6.1 g/dL                   |   |
| Alb   | 3.3 g/dL                   |   |
| T-Bil   | 0.8 mg/dL                  |   |
| AST   | 20 IU/L                    | 21 IU/L   |
| ALT   | 32 IU/L                    | 28 IU/L   |
| ALP   | 172 IU/L                   |   |
| LDH   | 148 IU/L                   |   |
| Amylase   | 917 IU/L                   | 124 IU/L  |
| Lipase  | 1118 U/L                   | 39 U/L  |
| Elastase 1                                      | 1600 ng/dL                 | 2600 ng/dL  |
| BUN   | 5.9 mg/dL                  |   |
| Cr  | 0.5 mg/dL                  |   |
| Na  | 135 mEq/L                  |   |
| K   | 3.5 mEq/L                  |   |
| Cl  | 100 mEq/L                  |   |
| FFA   | 440 μEq/L                  | 2097 μEq/L  |
| TG  | 71 mg/dL                   | 77 mg/dL  |
| T-chol  | 148 mg/dL                  | 180 mg/dL   |
| HDL-chol  |                            | 34 mg/dL  |
| LDL-chol  |                            | 130 mg/dL   |
| CK  | 20 IU/L                    |   |
| CRP   | 4.89 mg/dL                 | 1.65 mg/dL  |
| <b>HLA typing</b>                               |                            |   |
|   |                            | DRB1*04:05:01<br>DRB1*09:01:02/21<br>DQB1*03:03:02<br>DQB1*04:01:01 |
| <b>Ketone body</b>                              |                            |   |
| Total ketone                                    |                            | 14 701 mmol/L   |
| Acetoacetic acid                                |                            | 12 809 mmol/L   |
| β-Hydroxybutyric acid                           |                            | 11 892 mmol/L   |
| <b>Arterial blood gas analysis*</b>             |                            |   |
| pH  |                            | 6.99  |
| PaO <sub>2</sub>                                |                            | 150 mmHg  |
| PaCO <sub>2</sub>                               |                            | 9.4 mmHg  |
| HCO <sub>3</sub> <sup>-</sup>                   |                            | 2.3   |
| Anion gap                                       |                            | 25.7 mEq/L  |
| <b>Diabetes-related examinations</b>            |                            |   |
| PG <sup>†</sup>                                 | 148 mg/dL                  | 767 mg/dL   |
| 1.5 AG  | 11.7 μg/mL                 | 2.2 μg/mL   |
| Serum CPR                                       | 2.51 ng/mL                 | <0.03 ng/mL   |
| HbA1c   |                            | 5.4%  |
| IRI   | 8.59 μU/mL                 |   |
| Anti-GAD antibody                               |                            | 0.9 U/mL  |
| Anti-IA-2 antibody                              |                            | <0.4 U/mL   |
| <b>Glucagon-loading test (serum CPR values)</b> |                            |   |
| Pre-loading (baseline)                          |                            | <0.03 ng/mL   |
| Post-loading (6 min)                            |                            | <0.03 ng/mL   |
| <b>Endocrinology</b>                            |                            |   |
| TSH   | 2.97 μU/mL                 |   |
| FT <sub>4</sub>                                 | 0.95 ng/dL                 |   |
| FT <sub>3</sub>                                 | 1.94 pg/mL                 |   |

\*At room temperature; †under continuous drip infusion.

## Discussion

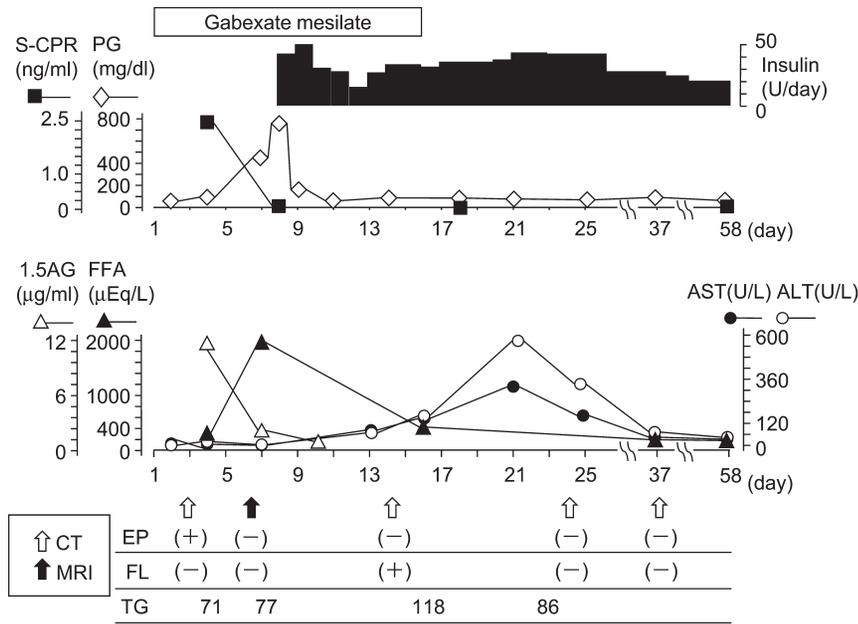
HLA genotyping in this patient revealed the presence of DRB1\*04:05 and DRB1\*04:01, which confer susceptibility to FT1DM (Table 1) (5, 6). Although we did not test for viral antibodies in the blood, the fact that the patient experienced fever, epigastric pain, an inflammatory reaction, an increase in exocrine pancreatic enzymes, and diffuse pancreatitis suggests that viral infection, given her genetic background, might have induced the onset of FT1DM.

Takaïke *et al.* showed transiently elevated transaminase levels in 60.4% of patients after the onset of FT1DM (3). In many of these patients, liver dysfunction peak between days 10 and 20 of disease, with laboratory values returning to near-normal levels by day 30. Our patient showed a similar course (Fig. 2).

Previous reports have shown unenhanced CT images to be useful for predicting the degree of fatty infiltrations in the liver parenchyma (7, 8, 9, 10, 11, 12, 13). Steatosis results in decreased attenuation of the liver, which can be measured in Hounsfield units (HUs). Park *et al.* used CT for the assessment of hepatic steatosis; they concluded that unenhanced CT performs well in the qualitative diagnosis of macrovesicular steatosis of 30% or more, with 82% sensitivity and 100% specificity (14). In their study, a liver-to-spleen attenuation ratio cut-off of 0.8 had similar sensitivity for diagnosing fatty liver. In our patient, the liver-to-spleen attenuation ratio decreased from 1.17 on day 3 to 0.5 on day 14 and was used to diagnose fatty liver on day 14 (Fig. 3).

In the liver, free fatty acid influx and accumulation of lipids impair the oxidative capacity of hepatocytes, with beta-oxidation confined to the mitochondria (15, 16, 17, 18, 19, 20) and peroxisomes (15, 16, 20, 21, 22) and omega-oxidation occurring in the endoplasmic reticulum (15, 16, 23, 24). As a result, increased production of reactive oxygen species in hepatocytes causes oxidative stress and cell death, thereby inducing liver dysfunction.

In addition to fatty liver, liver dysfunction after onset of FT1DM may be caused by glycogenic hepatopathy (GH), which is hepatomegaly caused by glycogen accumulation (25, 26, 27, 28). Gradient-dual-echo MRI sequence could be a useful tool for diagnosis of GH (25), and we did not undergo the MRI examination on day 14 in this case. However, most cases of GH involve hepatomegaly and are generally associated with increased CT attenuation values of liver (28), and we did not observe hepatomegaly or increased liver CT values in our patient; therefore, the liver dysfunction was thought to be caused by fatty liver

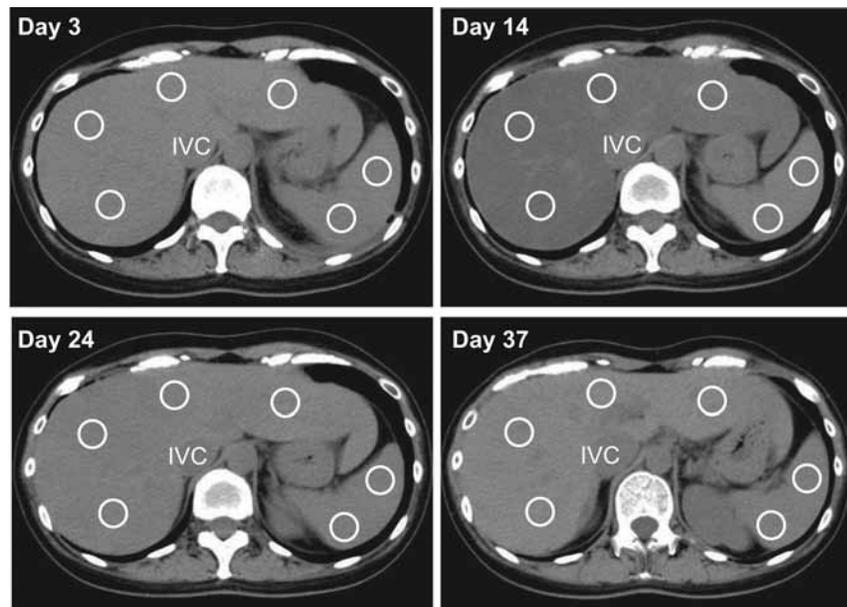


**Figure 2** Clinical course. Laboratory and imaging tests throughout the patient's clinical course showed dramatic changes in lipid and glucose metabolism. 1,5 AG, 1,5-anhydroglucitol; EP, enlarged pancreas; FFA, free fatty acid; FL, fatty liver; PG, plasma glucose; S-CPR, serum C-peptide; TG, triglycerides.

in this case. Although a liver biopsy would histologically provide a definitive diagnosis, we did not perform the procedure due to its invasiveness.

A previous study suggests that 22.6% of FT1DM cases are associated with fatty liver (3). In our patient, fatty liver was not observed at the time of admission and occurred

only on day 14. However, by day 24, the symptoms of fatty liver were less severe (Fig. 3). Takaïke *et al.* reported the presence of fatty liver in three patients with autoimmune type 1 diabetes and ketoacidosis. They noted that fatty liver became more severe at approximately 3 months after the start of insulin therapy, but became less severe



| Day             | 3    | 14   | 24   | 37   |
|-----------------|------|------|------|------|
| mean hepatic HU | 52.8 | 23.9 | 48.5 | 55.8 |
| mean splenic HU | 46.2 | 47.8 | 46.9 | 46.8 |
| CT L/S          | 1.17 | 0.50 | 1.04 | 1.19 |

**Figure 3** Unenhanced computed tomography images and attenuation within the liver and spleen. Circular areas with a diameter of 15 mm show regions of interest (ROIs) for measuring attenuation. Table 1 shows the mean HU data for calculating attenuation for the ROIs. CT L/S, mean hepatic HU/mean splenic HU; HU, Hounsfield unit; IVC, inferior vena cava.

by 6 months (3). However, two cases showed that fatty liver after the onset of FT1DM resolves in approximately 2 weeks, similar to the progression we observed (1, 2). When Nagao *et al.* (1) compared autoimmune type 1 diabetes with FT1DM, they concluded that large rapid decreases in insulin secretion of FT1DM could cause the different durations in the progression of fatty liver formation described above.

Insulin is involved in the following four mechanisms of triglyceride accumulation in the liver: (i) influx of FFAs into the liver from food or adipose tissue (29, 30, 31, 32, 33); (ii) *de novo* synthesis of triglycerides in the liver (29, 34, 35, 36); (iii) FFA oxidation in the liver (29, 36, 37, 38, 39); and (iv) the balance of synthesis, secretion, and breakdown of very low-density lipoproteins (VLDL) (29, 40, 41).

In our patient, serum levels of triglycerides and cholesterol were within the normal range throughout the disease course, but serum FFA levels changed dramatically (Fig. 2). First, the rapid decrease in insulin at the onset of FT1DM likely freed fatty acids derived from triglycerides in peripheral adipocytes into the bloodstream, leading to a rapid increase in serum FFA levels (Fig. 2) (42, 43). The large amount of insulin administered as treatment rapidly activated mTOR Complex 1 (44, 45, 46, 47), which, through the activity of sterol regulatory element-binding protein (SREBP)-1, transferred the FFAs in the periphery to the liver (48, 49, 50, 51, 52). This led to the decrease in serum FFA levels observed in our patient (Fig. 2). In addition, insulin promotes *de novo* synthesis of triglycerides in the liver, using the newly available FFAs as substrates (42, 43). At the same time, insulin suppresses VLDL secretion outside of the liver, promoting the accumulation of triglycerides in the liver (33, 40, 41, 53, 54), leading to fatty liver.

The mechanism underlying the suppression of VLDL secretion depends on insulin's inhibitory activity on forkhead box protein O1 (FoxO1) or apo B mRNA, and this activity ultimately suppresses the synthesis of apo-CIII or apo-B100 (33, 40, 41, 53). In addition, insulin may also suppress the activation of microsomal triglycerine transporter protein, which is involved in the synthesis of VLDL particles, leading to the accumulation of triglycerides in the liver (54). Via either mechanism, insulin contributes to the formation of fatty liver.

The patient received intravenous administration of 100 mg synthetic protease inhibitor, gabexate mesilate (GM), over 60 min every 8 h from admission (day 3) through day 16. In rabbits, GM administration suppresses the elevation in plasma FFA levels induced by endotoxin

injection (55). In the present case, although the effect of GM on changes in serum FFA levels is not precisely known, we noted the following two points. First, neither GM dose nor frequency changed from admission (day 3) to day 8, when the onset of FT1DM associated with a drastic increase in serum FFA levels was noticed, and to day 16, when serum FFA levels decreased after insulin administration. Second, blood concentrations of GM decrease exponentially after intravenous administration (10 mg/kg). It is promptly cleared, with a short half-life of 55 s in humans (56, 57). In the present case, as serum FFA levels were measured 4–5 h after GM administration, it was unlikely that FFAs levels were affected by GM. Consequently, we hypothesize that serum insulin level was the major factor contributing to variations in serum FFA levels and fatty liver development and that GM administration did not have a major effect.

We observed a rare case of fatty liver development in the context of liver dysfunction in a patient with FT1DM. Although fatty liver after the onset of FT1DM had been previously reported (1, 2, 3, 4), this is the first report detailing the progression of disturbances in fatty acid levels over time, and we expect that it will be a useful example in future cases.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Patient consent

A written informed consent was obtained from the patient for publication of this case report.

#### Author contributions and acknowledgements

All co-authors listed contributed substantially to the preparation of this manuscript.

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