Author’s response to reviews

Title: Severe hypertriglyceridemia in a subject with disturbed life style and poor glycemic control without recurrence of acute pancreatitis: A case report

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Author’s response to reviews:

Dr. James Mockridge

Editor-in-Chief, BMC Endocrine Disorders

Dear Dr. Mockridge

Thank you very much for having reviewed our manuscript. We are very much pleased to read the favorable comments of both reviewers. We totally agree with all these comments and incorporated them to the revised version. Red indicates the parts that we changed according to the reviewers’ suggestion.

We hope that you would evaluate this revised version positively.

Sincerely yours,

Takatoshi Anno, MD, PhD
Editor Comments:

The reviewers and I consider that this an interesting manuscript, however the reviewers have expressed a number of important criticisms that the authors need to address before this work can be considered further.

We appreciate the insights and helpful comments and have revised the manuscript according to your kind suggestions.

For example, the possibility of an underlying familiar hyperlipidemia should be ruled out (or in) backed by laboratory lipid profiling tests to explain this extremely high level of plasma triglycerides.

Thank you very much for valuable suggestion. According to your kind suggestion, we cited the related paper as Ref. 7 and we added the following description in discussion section as a limitation in the revised version of the manuscript: (page 13 lines 1-7 from the bottom and page 14, lines 1-12).

“There is a limitation in this case reports. His genetic background and laboratory data for primary hyperlipidaemia such as familial hyperlipidaemia were not clear. In general, in order to perform its definite diagnosis, it is necessary to examine several points such as the Apolipoprotein activity, phenotype of Apolipoprotein and LPL activity. First, he had no family history of hyperlipidaemia. Second, there were no findings in physical examination such as xanthelasma palpebrarum, tuberous xanthoma and plane xanthoma and atherosclerosis in computed tomography, magnetic resonance imaging and echocardiography. In addition, although he had elevated VLDL and MIDBAND fractions in lipoprotein fractions under severe
hypertriglyceridemia, VLDL and MIDBAND fractions were decreased under stable
dyslipidemia. Moreover, his various Apolipoprotein levels were elevated but were not deleted
under stable dyslipidemia. His pre-heparin LPL levels were slightly decreased under stable
dyslipidemia, while it was reported that pre-heparin LPL levels were suppressed under metabolic
syndrome and T2DM1,7. However, since we did not examine the basal and post-heparin LPL
activities before insulin treatment, we failed to provide the improved LPL activities by insulin
treatment. Therefore, although we think that very severe hypertriglyceridemia in this subject was
induced by markedly disturbed life style and poorly controlled type 2 diabetes mellitus, we
cannot exclude the possibility that he had primary hyperlipidaemia such as familial
hyperlipidaemia.”

There are also doubts about how the treatment approach in this patient.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the
detail of medication in case presentation section in the revised version of the manuscript:

“Although during hospitalization period we treated him with intensive insulin therapy for T2DM,
after the improvement of acute pancreatitis, he was taking 400mg/day of bezafibrate and
1800mg/day of ethyl icosapentate for the treatment of dyslipidemia and 30mg/day of mitiglinide,
0.6mg/day of voglibose, 1500mg/day of metformin and insulin therapy (4units of glargine) for
T2DM at discharge. His triglyceride levels were 64-734mg/dL for 2 years after discharge of
acute pancreatitis, but he stopped the medication for dyslipidemia on his own judgement. We
started 10mg/day of ezetimibe for the treatment of dyslipidemia because his triglyceride level
was as high as 1921mg/dL, and after then his triglyceride level was decreased to 416mg/dL. His
HbA1c levels were 7.0-9.1% for 2 years after discharge of acute pancreatitis in outpatient clinic
in spite of stopping insulin. At that time, he was treated with mitiglinide, 0.6mg/day of
voglibose, 1500mg/day of metformin and 0.9mg/day of liraglutide, but he stopped the
medication for T2DM on his own judgement. We started the same medication and added
2.5mg/day of luseogliflozin for the treatment of T2DM because his HbA1c levels were as high as
12.9%. However, after 6 months, he stopped receiving the treatment for about 1.5years on his
own judgement. In outpatient clinic, his body weight were 111.6-120.0kg” (from page 6, line 7
from the bottom, to page 7, line 10).

“He did not agree to the hospitalization and frequent insulin injection. In addition, his
dyslipidemia and T2DM had been improved with previous oral medication.” (page 8, line 3-5).

“He frequently visited our office every 1-2 week, and we increased insulin therapy little by little
(from 8 to 14units of degludec) in outpatient clinic.” (page 9, line 5-7).
“At that time, his medication was 160mg/day of fenofibrate for the treatment of dyslipidemia and insulin therapy (18 units of glargine) for T2DM.” (page 9, lines 1-2 from the bottom).

Additionally, the discussion needs to be strengthened by elaborating on the possible causes of this severe hypertriglyceridemia in addition to poor diabetes control and disturbed life style. The details of the issues raised by the reviewers are described in the Comments to Author below.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the following description in discussion section in the revised version of the manuscript: (page 11 lines 1-2 from the bottom and page 12, lines 1-8).

“Surprisingly, his triglyceride levels were elevated to over 10,000mg/dL at least twice. At that time, his life style was markedly disturbed with high calorie diet including large amounts of both fat and carbohydrate and he had very severe obesity among Japanese subjects. As a result, his previous laboratory data sometime showed about 3,000mg/dL of hypertriglyceridemia. In addition, it seemed that his severe hypertriglyceridemia was induced by obesity together with insulin resistance. Moreover, his severe hypertriglyceridemia was aggravated by uncontrolled T2DM. At that time, he suffered from ketosis and his insulin effect were not enough at all. On the other hand, his severe hypertriglyceridemia was improved by diet therapy with low lipid and carbohydrate and medication with fibrate and insulin.”

Thank you very much again for your thoughtful comments that have led to strengthening our manuscript.

Response to Reviewer 1’s comments

In this manuscript, the authors reported a case of marked hypertriglyceridemia without developing to pancreatitis. It is a very interesting case, however, some points are rewritten for accepting.

We appreciate the insights and helpful comments and have revised the manuscript according to your kind suggestions.
1. When acute pancreatitis occurred, the lipid profile was quite different? It is necessary to describe the lipid profile at that time.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the following description in case presentation section in the revised version of the manuscript: (page 6, lines 3-9).

“dyslipidemia (total cholesterol, 644mg/dL; Low Density Lipoprotein (LDL)-cholesterol, 127mg/dL; High Density Lipoprotein (HDL)-cholesterol, 23mg/dL; triglyceride, 3,207mg/dL) and T2DM (plasma glucose, 244mg/dL; hemoglobin A1c (HbA1c), 10.3%). At that time, his height, body weight and BMI were 180.0cm, 121.5kg and 37.5kg/m2, respectively. Acute pancreatitis markers were as follows: lipase, 987U/L; trypsin, 6662ng/mL; pancreatic phospholipase A2, 1150ng/dL; pancreatic amylase, 290IU/L.”

2. There is no description about body weight change as well as diet contents precisely.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the following description in case presentation section in the revised version of the manuscript: (page 6, lines 6-7).

“In outpatient clinic, his body weight were 111.6-120.0kg” (page 7, line 10).

“After then, his body weight were reduced to under 110kg.” (page 10, line 8).

3. The authors concluded that the causes of severe hypertriglyceridemia are patient's undesirable lifestyle and poor controlled diabetes. However, this case is an extremely high level of hypertriglyceridemia even considering it. What can be considered as a cause is what can be considered in many obese and diabetic patients. There is insufficient discussion to explain the extremely high triglyceride levels in this case.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the following description in discussion section in the revised version of the manuscript: (page 11 lines 1-2 from the bottom and page 12, lines 1-8).
“Surprisingly, his triglyceride levels were elevated to over 10,000mg/dL at least twice. At that time, his life style was markedly disturbed with high calorie diet including large amounts of both fat and carbohydrate and he had very severe obesity among Japanese subjects. As a result, his previous laboratory data sometime showed about 3,000mg/dL of hypertriglyceridemia. In addition, it seemed that his severe hypertriglyceridemia was induced by obesity together with insulin resistance. Moreover, his severe hypertriglyceridemia was aggravated by uncontrolled T2DM. At that time, he suffered from ketosis and his insulin effect were not enough at all. On the other hand, his severe hypertriglyceridemia was improved by diet therapy with low lipid and carbohydrate and medication with fibrate and insulin.”

4. There is no possibility of familial hyperlipidemia in this case? In the manuscript, the authors state no family history of dyslipidemia, but it is necessary to actually confirm the lipid profile of the family. Also, it is possible that minor genetic abnormalities related to lipid metabolism.

Thank you very much for valuable suggestion. According to your kind suggestion, we cited the related papers as Refs. 7 and we added the following description in discussion section as a limitation in the revised version of the manuscript: (page 13 lines 1-7 from the bottom and page 14, lines 1-12).

“There is a limitation in this case reports. His genetic background and laboratory data for primary hyperlipidaemia such as familial hyperlipidaemia were not clear. In general, in order to perform its definite diagnosis it is necessary to examine several points such as the Apolipoprotein activity, phenotype of Apolipoprotein and LPL activity. First, he had no family history of hyperlipidaemia. Second, there were no findings in physical examination such as xanthelasma palpebrarum, tuberous xanthoma and plane xanthoma and atherosclerosis in computed tomography, magnetic resonance imaging and echocardiography. In addition, although he had elevated VLDL and MIDBAND fractions in lipoprotein fractions under severe hypertriglyceridemia, VLDL and MIDBAND fractions were decreased under stable dyslipidemia. Moreover, his various Apolipoprotein levels were elevated but were not deleted under stable dyslipidemia. His pre-heparin LPL levels were slightly decreased under stable dyslipidemia, while it was reported that pre-heparin LPL levels were suppressed under metabolic syndrome and T2DM1,7. However, since we did not examine the basal and post-heparin LPL activities before insulin treatment, we failed to provide the improved LPL activities by insulin treatment. Therefore, although we think that very severe hypertriglyceridemia in this subject was induced by markedly disturbed life style and poorly controlled type 2 diabetes mellitus, we cannot exclude the possibility that he had primary hyperlipidaemia such as familial hyperlipidaemia.”
Thank you very much again for your thoughtful comments that have led to strengthening our manuscript.

Response to Reviewer 2’s comments

This case report showed a 40-year-old man with a marked hypertriglyceridemia (serum TG 11,175 mg/dl and up to 16,900 mg/dl) because of VLDL-TG and MIDBAND fraction by electrophoretic separation of lipoproteins. He was also suffered from poor controlled obese type 2 diabetes. Authors emphasized that acute pancreatitis was not complicated in these very high levels of serum hypertriglyceridemia.

Although this case shows very rare condition, the reviewer has an impression that the present information of the case is insufficient why does this case show very severe hypertriglyceridemia in obese type 2 diabetes and his disturbed lifestyle, but stopping drinking as causes for no signs of expression of acute pancreatitis.

The following points are essentials to prevent expression severe hypertriglyceridemia in obese patients with type 2 diabetes as follows;

1. What kinds of lifestyle relating to these severe conditions should be included in this manuscript? Furthermore, what kinds of intervention of life style were given in this patient?

   Thank you very much for valuable suggestion. According to your kind suggestion, we added the detail of medication in case presentation section in the revised version of the manuscript:

   “; for example, he drunk over 1.5L of PET bottle of juice, ate a lot of snacks and fruits and fast-food in eating out.” (page 8, line 7-8).

   “and diet therapy of 2200 kcal/day (about 30 kcal/ideal body weight kg)” (page 8, line 9-10).
2. The treatment course of type 2 diabetes and hypertriglyceridemia was unclear, since authors started treatments with 160mg fenofibrate and insulin (8 units of degludec) in a patient with very poor controlled diabetes (HbA1c 12.9%, hyperketonemia). Reviewer really think this type treatment will be very difficult to control these severe hyperglycemia and hypertriglyceridemia.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the detail of medication in case presentation section in the revised version of the manuscript:

“Although during hospitalization period we treated him with intensive insulin therapy for T2DM, after the improvement of acute pancreatitis, he was taking 400mg/day of bezafibrate and 1800mg/day of ethyl icosapentate for the treatment of dyslipidemia and 30mg/day of mitiglinide, 0.6mg/day of voglibose, 1500mg/day of metformin and insulin therapy (4units of glargine) for T2DM at discharge. His triglyceride levels were 64-734mg/dL for 2 years after discharge of acute pancreatitis, but he stopped the medication for dyslipidemia on his own judgement. We started 10mg/day of ezetimibe for the treatment of dyslipidemia because his triglyceride level was as high as 1921mg/dL, and after then his triglyceride level was decreased to 416mg/dL. His HbA1c levels were 7.0-9.1% for 2 years after discharge of acute pancreatitis in outpatient clinic in spite of stopping insulin. At that time, he was treated with mitiglinide, 0.6mg/day of voglibose, 1500mg/day of metformin and 0.9mg/day of liraglutide, but he stopped the medication for T2DM on his own judgement. We started the same medication and added 2.5mg/day of luseogliflozin for the treatment of T2DM because his HbA1c levels were as high as 12.9%. However, after 6 months, he stopped receiving the treatment for about 1.5years on his own judgement. In outpatient clinic, his body weight were 111.6-120.0kg” (from page 6, line 7 from the bottom, to page 7, line 10).

“He did not agree to the hospitalization and frequent insulin injection. In addition, his dyslipidemia and T2DM had been improved with previous oral medication.” (page 8, line 3-5).

“He frequently visited our office every 1-2 week, and we increased insulin therapy little by little (from 8 to 14units of degludec) in outpatient clinic.” (page 9, line 5-7).

“At that time, his medication was 160mg/day of fenofibrate for the treatment of dyslipidemia and insulin therapy (18units of glargine) for T2DM.” (page 9, lines 1-2 from the bottom).

3. The reviewer think that authors did not mention genetic background and laboratory data and signs and symptoms to show hypertriglyceridemia including hyperlipoproteinemia type III and familiar combined hyperlipidemia.
Thank you very much for valuable suggestion. According to your kind suggestion, we cited the related papers as Refs. 7 and we added the following description in discussion section as a limitation in the revised version of the manuscript: (page 13 lines 1-7 from the bottom and page 14, lines 1-12).

“There is a limitation in this case reports. His genetic background and laboratory data for primary hyperlipidaemia such as familial hyperlipidaemia were not clear. In general, in order to perform its definite diagnosis it is necessary to examine several points such as the Apolipoprotein activity, phenotype of Apolipoprotein and LPL activity. First, he had no family history of hyperlipidaemia. Second, there were no findings in physical examination such as xanthelasma palpebrarum, tuberous xanthoma and plane xanthoma and atherosclerosis in computed tomography, magnetic resonance imaging and echocardiography. In addition, although he had elevated VLDL and MIDBAND fractions in lipoprotein fractions under severe hypertriglyceridemia, VLDL and MIDBAND fractions were decreased under stable dyslipidemia. Moreover, his various Apolipoprotein levels were elevated but were not deleted under stable dyslipidemia. His pre-heparin LPL levels were slightly decreased under stable dyslipidemia, while it was reported that pre-heparin LPL levels were suppressed under metabolic syndrome and T2DM1,7. However, since we did not examine the basal and post-heparin LPL activities before insulin treatment, we failed to provide the improved LPL activities by insulin treatment. Therefore, although we think that very severe hypertriglyceridemia in this subject was induced by markedly disturbed life style and poorly controlled type 2 diabetes mellitus, we cannot exclude the possibility that he had primary hyperlipidaemia such as familial hyperlipidaemia.”

4. Authors should include lipid parameters such as apo E, Apo C III, LPL, RLP-cholesterol etc. in Table 1.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the lipid parameters (after 1.5 month lipid data, Apolipoprotein, lipoprotein fractions and pre-heparin LPL) in Table 2 in the revised version.

5. Do basal and post-heparin LPL activities were improved by insulin treatment?

Thank you very much for valuable suggestion. However, since we did not examine the basal and post-heparin LPL activities before insulin treatment, we failed to provide the improved LPL
activities by insulin treatment. Therefore, we added the following description in discussion section in the revised version of the manuscript:

“His pre-heparin LPL levels were slightly decreased under stable dyslipidemia, while it was reported that pre-heparin LPL levels were suppressed under metabolic syndrome and T2DM1,7. However, since we did not examine the basal and post-heparin LPL activities before insulin treatment, we failed to provide the improved LPL activities by insulin treatment.” (page 14, lines 4-9).

6. The sentences in this manuscript should be carefully reconsidered.

Thank you very much for valuable suggestion. According to your kind suggestion, we carefully checked again and amended the description throughout the manuscript.

Thank you very much again for your thoughtful comments that have led to strengthening our manuscript.