**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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**Version:** 2 **Date:** 01 Aug 2019

**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:

In this revised version of their manuscript the authors have successfully addressed some of the issues raised by the reviewers, however there some key points that require further clarification and discussion as detailed in the Comments to Authors shown below.

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

In essence, a more detailed discussion about the possible cause of the unusually high level of triglycerides in this case report since the explanation currently given seems insufficient to explain it. If the possibility of an underlying dyslipidemia is ruled out by the authors they should explain how exactly dietary factors plus uncontrolled diabetes may contribute to generate the very high levels of tryglicerides observed in the patient.

Thank you very much for your valuable suggestion. According to your kind suggestion, we added the following description about diet before very severe hypertriglyceridemia in the revised version of the manuscript (Case presentation section, page 8, lines 8-11 and page 9, lines 1-3 from the bottom and page 10 line 1-5).

“He enjoyed SUMOU, which is a traditional Japanese sport, in his high school days, and thereby he ate over 10,000 kcal/day of diet every day when he was young. For that reason, he sometimes ate 3,000-5,000 kcal of diet at once even recently.”

“He ate high calorie diet including large amounts of rice, which is known as a main source of carbohydrate in Japan. It was estimated that he ate over 1,000 kcal of rice. In addition, he ate large amounts of oily food such as fried chicken and fried potato. He failed to precisely explain how many amounts of fat he ate, but it was estimated that he ate 3,000-5,000 kcal of diet in total
at once. Moreover, he drank over 2.0L of PET bottle of juice and ate a lot of snacks at the same time. He stopped injecting insulin and his glycemic control was very poor (plasma glucose, 310mg/dL; HbA1c, 13.1%).”

The case should be discussed in the context of other previously reported similar cases. Any additional data that may be helpful to address the criticisms raised should be included.

Thank you very much for valuable suggestion. According to your kind suggestion, we added this point and referred this paper in the revised version (Discussion section, page 12, lines 6-7, Ref. 4).

“Furthermore, to the best of our knowledge, this triglyceride level in this subject is the highest in medical literature4.”

And we removed the following description from Discussion section in the revised version of the manuscript:

“Furthermore, considered from the elevation of glycoalbumin levels, his poor glycemic control was closely associated with elevated triglyceride levels. Also, serum ketone body levels were elevated with aggravation of hypertriglyceridemia. This elevated glycoalbumin and ketone body levels together with severe hypertriglyceridemia suggest that severe hypertriglyceridemia was caused by markedly disturbed life style and poorly controlled T2DM.”

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

Response to Reviewer 1’s comments

The authors give reasonable answers to questions #1, #2 and #4.

However, the response to Question #3 is insufficient.
We appreciate the insights and helpful comments and have revised the manuscript according to your kind suggestions.

The authors argue that 1.5 liters of soft drinks and much snacks, as well as uncontrolled diabetes, are the cause of terrible hypertriglyceridemia, which is often found in obese untreated diabetic patients generally. If the genetic background for dyslipidemia is unlikely, it is necessary to provide an approximate estimate of calorie intake that can be convincing as the cause of marked hypertriglyceridemia.

Thank you very much for your valuable suggestion. According to your kind suggestion, we added the following description about diet before very severe hypertriglyceridemia in the revised version of the manuscript (Case presentation section, page 8, lines 8-11 and page 9, lines 1-3 from the bottom and page 10 line 1-5).

“He enjoyed SUMOU, which is a traditional Japanese sport, in his high school days, and thereby he ate over 10,000 kcal/day of diet every day when he was young. For that reason, he sometimes ate 3,000-5,000 kcal of diet at once even recently.”

“He ate high calorie diet including large amounts of rice, which is known as a main source of carbohydrate in Japan. It was estimated that he ate over 1,000 kcal of rice. In addition, he ate large amounts of oily food such as fried chicken and fried potato. He failed to precisely explain how many amounts of fat he ate, but it was estimated that he ate 3,000-5,000 kcal of diet in total at once. Moreover, he drunk over 2.0L of PET bottle of juice and ate a lot of snacks at the same time. He stopped injecting insulin and his glycemic control was very poor (plasma glucose, 310mg/dL; HbA1c, 13.1%).”

Also, if it is marked calories, does not SGLT2 inhibitor contribute as the cause of hyperphagia?

Thank you very much for valuable suggestion. As you mention, in general the usage of SGLT2 inhibitor could lead to hyperphagia. However, this subject had hyperphagia since when he was young. Therefore, we added this point in the revised version (Case presentation section, page 8, lines 8-11).

“He enjoyed SUMOU, which is a traditional Japanese sport, in his high school days, and thereby he ate over 10,000 kcal/day of diet every day when he was young. For that reason, he sometimes ate 3,000-5,000 kcal of diet at once even recently.”
There is no mention of anything other than diet regarding the origin of neutral fat. Not only dietary lipids and carbohydrates, but also free fatty acids from endogenous lipolysis may be enough to achieve such high triglycerides?

Thank you very much for valuable suggestion. According to your kind suggestion, we added this point and referred this paper in the revised version (Discussion section, page 12, lines 4-6 from the bottom, Ref. 6).

“We assume that not only dietary lipids and carbohydrates but also free fatty acids secreted from adipocytes could be involved in pancreatic beta-cell dysfunction. Such phenomena are well known as lipotoxicity6.”

Also, is the influence of free fatty acids on pancreatic beta cells involved in the pathological condition? Please add your comments on this point to your discussion.

Thank you very much for valuable suggestion. According to your kind suggestion, we added the description about this point and referred the paper in the revised version (Discussion section, page 13, lines 6-8).

“We assume that not only dietary lipids and carbohydrates but also free fatty acids secreted from adipocytes could be involved in very severe hypertriglyceridemia in this subject.”

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

Response to Reviewer 3’s comments

The authors report a case of a patient with very high levels of triglycerides with poor adherence to diet and medical treatment. It is an interesting case report due to the high triglycerides reported and the absence of pancreatitis. It lacks of genetic test and test about LPL activity before treatment, but this situation is properly commented in the discussion section.
We appreciate the insights and helpful comments and have revised the manuscript according to your kind suggestions.

1) The title is long and some confusing. It could be misunderstood that "insulin effect" refers to pancreatic insulin deficit instead of suspension of insulin treatment. Furthermore, it is encompassed in the term "poorly controlled".

Thank you very much for valuable suggestion. According to your kind suggestion, we shortened the title as follows:

“Severe hypertriglyceridemia in a subject with disturbed lifestyle and poor glycemic control without recurrence of acute pancreatitis: A case report”

2) The authors state that as a part of treatment the patient was prescribed with a 2200 kcal/day diet. However, they didn't describe how many calories he was eating when triglyceride level raised to 16,900 mg/dl.

Thank you very much for your valuable suggestion. According to your kind suggestion, we added the following description about diet before very severe hypertriglyceridemia in the revised version of the manuscript (Case presentation section, page 8, lines 8-11 and page 9, lines 1-3 from the bottom and page 10 line 1-5).

“He enjoyed SUMOU, which is a traditional Japanese sport, in his high school days, and thereby he ate over 10,000 kcal/day of diet every day when he was young. For that reason, he sometimes ate 3,000-5,000 kcal of diet at once even recently.”

“He ate high calorie diet including large amounts of rice, which is known as a main source of carbohydrate in Japan. It was estimated that he ate over 1,000 kcal of rice. In addition, he ate large amounts of oily food such as fried chicken and fried potato. He failed to precisely explain how many amounts of fat he ate, but it was estimated that he ate 3,000-5,000 kcal of diet in total at once. Moreover, he drank over 2.0L of PET bottle of juice and ate a lot of snacks at the same time. He stopped injecting insulin and his glycemic control was very poor (plasma glucose, 310mg/dL; HbA1c, 13.1%).”
3) As far as I know, this triglyceride levels are the most high reported in medical literature, even higher than reported by Anika Toor et al. Case Rep Endocrinol 2019, 2019: 6273196. This could be commented in the discussion section.

Thank you very much for valuable suggestion. According to your kind suggestion, we added this point and referred this paper in the revised version (Discussion section, page 12, lines 6-7, Ref. 4).

“Furthermore, to the best of our knowledge, this triglyceride level in this subject is the highest in medical literature."”

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