Creatine Phosphokinase Level Accompanied with Macro-Creatine Phosphokinase Type 1 Negatively Correlates with Plasma Glucose Control in a Patient with Type 2 Diabetes Mellitus

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**Keywords**
Hypercreatinekinasemia · Macromolecular CPK type 1 · Type 2 diabetes mellitus · HbA1c

**Abstract**

**Introduction:** The macromolecular complex formed by creatine phosphokinase (CPK) is most probably an immune complex. Most of the macro-CPK migrates between CPK-MM and CPK-MB, exhibiting an atypical band on isozyme electrophoresis. Either IgA or IgG has been identified with its CPK link (termed as macro-CPK type 1). However, the biological and pathological significance of these complexes found in patients with wide-ranging disease states remains unclear. Herein, we first report a case of type 2 diabetes mellitus associated with hypercreatinekinasemia caused by macro-CPK type 1, with CPK levels negatively correlated with blood glucose control. **Case Presentation:** A 53-year-old Japanese woman with no complaints of muscle weakness, myalgia, and numbness of the extremities was diagnosed with hypercreatinekinasemia. Over the past years, she received empagliflozin, mitiglinide, voglibose, vildagliptin, metformin, methyl thiazide, and ezetimibe. Serum biochemistry revealed elevated CPK levels. The highest CPK value was 1,063 U/L, and the three major isozymes CPK-BB, CPK-MB, and CPK-MM accounted for 0%, 2%, and 98%, respectively. Notably, CPK isozyme electrophoresis performed on a cellulose acetate membrane detected an additional band that migrated between the CPK-MB and CPK-MM bands, suggesting macro-CPK type 1, which occupied 82% of the total CPK. The densitometric profile of the electrophoresis pattern revealed that CPK-BB, CPK-MB, and CPK-MM constituted 0%, 2%, and 16%, respectively. Moreover, serum CPK levels combined with macro-CPK showed a significant negative correlation with the HbA1c values ($r = -0.498$, $p < 0.001$). **Conclusions:** Serum CPK levels accompanied with macro-CPK type 1 negatively correlate with plasma glucose control. Although the pathophysiological role of macro-CPK remains unclear, our case report may provide a new viewpoint regarding macro-CPK etiology.

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Introduction

The macromolecular complex formed by creatine phosphokinase (CPK) and an immunoglobulin was first defined as macromolecular CPK (macro-CPK) by Yuu and Ishizawa [1]. Most probably, macro-CPK is an immune complex [2]. This CPK type has been detected not only in patients with ischemic heart disease, neoplastic disease, and muscle disorders but also in healthy people. Most of it migrates between CPK-MM and CPK-MB, exhibiting an atypical band on isozyme electrophoresis. Either IgA or IgG has been identified with its CPK link (termed as macro-CPK type 1) [3], and macro-CPK type 2 is another form of macro-CPK (or mitochondrial-CPK) [3]. However, the biological and pathological significance of these complexes found in patients with wide-ranging diseases remains poorly understood. Herein, we first report a case of type 2 diabetes mellitus (T2DM) associated with hypercreatinekinasemia caused by macro-CPK type 1 whose CPK levels negatively correlated with blood glucose control.

Case Report

A 53-year-old Japanese woman had been regularly visiting our hospital for T2DM and hyperlipidemia control since her diagnosis at 48 years old. Over the past years, she had been receiving empagliflozin (10 mg/day), mitiglinide (30 mg/day), voglibose (0.9 mg/day), vildagliptin (100 mg/day), metformin (750 mg/day), methyl thiazide (2 mg/day), and rosuvastatin (5.0 mg/day). She visited our hospital 34 times from January 26th, 2016, through April 22nd, 2021 (9, 11, 8, 1, 3, and 2 times in 2016, 2017, 2018, 2019, 2020, and 2021, respectively). She had no diabetic retinopathy but developed diabetic peripheral neuropathy, which caused slight bilateral peripheral numbness in her legs. She had no history of myopathy and rhabdomyolysis. Her urine albumin/creatinine ratio by spot urine test was normal (8.23 mg/gCr [normal: <30 mg/gCr]). Muscle weakness and myalgia were not reported. However, a laboratory screening test for ruling out rhabdomyolysis as a side effect of Rosuvastatin revealed hypercreatinekinasemia (473 U/L, May 27th, 2016). Her family history was unremarkable, and she had no recent history of excessive alcohol consumption. Thereafter, rosuvastatin was switched to ezetimibe (10 mg/day).

Her blood pressure was 138/72 mm Hg, and her pulse rate was regular at 68 times per minute. She was conscious and demonstrated normal neuropsychology. Furthermore, her sensory and cerebellar functions, muscle strength, and deep tendon reflexes were all normal.

Venous blood samples were collected in tubes containing ethylenediaminetetraacetic acid and fluoride. Within 1 h of sample collection, the plasma was separated from the cells. Then, the plasma glucose concentration was determined through the hexokinase method using the Synchro CX4/CX5 Glucose Analyzer (Beckman Instruments, Fullerton, CA, USA). The intra- and inter-assay coefficients of variation were both 12% (<7 mmol/L). Using the blood samples collected in ethylenediaminetetraacetic acid-containing tubes, we assessed the HbA1c value (normal range: 4.5%–6.2%) through high-performance liquid chromatography (Bio-Rad DIA-MAT, Ivry-sur-Seine, France). Total high-density lipoprotein, low-density lipoprotein (LDL), and triglyceride (TG) concentrations were also determined using an enzymatic method.

Regarding laboratory findings, her red blood cell count (438 × 10⁴/mm³), hematocrit (42.6%), hemoglobin (14.0 g/dL), and white blood cell count (7,930/μL) were all normal. Other serum parameters, as summarized in Table 1, were also within normal range. Electrocardiogram and thyroid function (TSH, FT3, and FT4 values) also showed normal findings.

Table 1. Laboratory findings

| Clinical test items                                    | Measured value | Normal range (unit) |
|--------------------------------------------------------|----------------|---------------------|
| Red blood cell count                                   | 438            | 376–516 × 10⁴/mm³   |
| Hematocrit                                             | 42.6           | 34.3–45.2%          |
| Hemoglobin                                             | 14             | 11.2–15.2 g/dL      |
| White blood cell count                                  | 7,930          | 3,500–7,900/mL      |
| Aspartate aminotransferase                             | 24             | 10–40 U/L           |
| Alanine aminotransferase                               | 3              | 5–45 U/L            |
| Lactate dehydrogenase                                  | 161            | 120–245 U/L         |
| Blood urea nitrogen                                    | 15.5           | 8.0–20.0 mg/dL      |
| Creatinine                                             | 0.67           | 0.46–0.82 mg/dL     |
| Na                                                     | 139            | 135–145 mEq/L       |
| K                                                      | 4.7            | 3.5–5.0 mEq/L       |
| Cl                                                     | 102            | 98–108 mEq/L        |
| Ca                                                     | 9.4            | 8.6–10.2 mg/dL      |
| P                                                      | 3.2            | 3.0–4.7 mg/dL       |
| Mg                                                     | 2              | 1.8–2.6 mg/dL       |
| Plasma renin activity                                  | 0.9            | 0.3–2.9 ng/mL/h     |
| Plasma aldosterone                                     | 53.5           | 35.7–240 ng/dL      |
| Anti-glutamic acid decarboxylase antibody              | <5.0           | <5.0 U/mL           |
However, serum biochemistry revealed elevated CPK levels (455.06 ± 191.67 U/L [mean ± SD, normal: 38–196, U/L]), with 1,063 U/L as the highest value even after Rosuvastatin was switched to ezetimibe. In addition, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase stayed in the normal range. Therefore, we examined the densitometric profile of the electrophoresis pattern on a cellulose acetate membrane to check the possibility of macro-CPK. We confirmed the three major isoenzymes, namely, CPK-BB, CPK-MB, and CPK-MM, constituted 0% (normal: 0%–2%), 2% (normal: 0%–6%), and 16% (normal: 87%–98%), respectively (shown in Fig. 1a). Notably, an additional band that migrated between the CPK-MB and CPK-MM bands was detected, eventually recognized as macro-CPK type 1, which occupied 82% of the total CPK (shown in Fig. 1a). Figures 1b, 2a, and 3 illustrate the changes in plasma CPK levels combined with macro-CPK levels, those of plasma glucose levels, and those of HbA1c levels from 2016 to 2021, respectively.

Given that our patient had been treated with T2DM, we evaluated how plasma glucose control condition affected plasma CPK levels combined with macro-CPK levels. To do that, we evaluated the correlation between serum CPK levels combined with macro-CPK and plasma glucose condition using all of the measurement values. Considering that statin or ezetimibe users manifest macro-CPK or myopathy, respectively [4–6], and our patient had been taking ezetimibe (10 mg/day) since June 24th, 2016, we evaluated the correlation between serum CPK levels combined with macro-CPK, LDL, and TG.

Furthermore, to know whether normal CPK and macro-CPK behaved similarly, we evaluated how plasma glucose control and plasma glucose levels affected the level of normal plasma CPK, which was not accompanied with macro-CPK in another patient with T2DM. All statistical data were analyzed using the SPSS software (version 10.0, SPSS Inc., Chicago, IL, USA). The linear correlation between variables was estimated.

The serum CPK levels combined with macro-CPK also significantly and negatively correlated with the HbA1c values (shown in Fig. 3; \( r = -0.498, p < 0.001 \)). Conversely, the serum CPK levels combined with macro-CPK did not correlate with LDL \( (r = -0.025, p = 0.906) \).

![Fig. 1. Presence of macro-CPK type 1 and change in CPK with time.](image)

**Fig. 1.** Presence of macro-CPK type 1 and change in CPK with time. **a** Presence of macro-CPK type 1. A representative densitometric scan is shown. Based on densitometer estimation, CPK-BB, albumin, CPK-MB, and CPK-MM constituted 0%, 0%, 2%, and 16%, respectively. CPK isozyme electrophoresis performed on a cellulose acetate membrane detected an additional band that migrated between the CPK-MB and CPK-MM bands, indicating the macro-CPK type 1, which occupied 82% of the total CPK (−): Negative pole (+): Positive pole BB: CPK-BB ALB: Albumin MB: CPK-MB MM: CPK-MM CPK: creatine phosphokinase. **b** Changes in CPK with time. The Y-axis represents the serum CPK levels combined with macro-CPK (U/L), and the X-axis represents the year and number of hospital visits each year between 2016 and 2021. Over the past years, she had been administered with empagliflozin (10 mg/day), mitiglinide (30 mg/day), voglibose (0.9 mg/day), vildagliptin (100 mg/day), metformin (750 mg/day), methyl thiazide (2 mg/day), and ezetimibe (10 mg/day).
Discussion/Conclusion

In general, when we find hypercreatinekinasemia, we need to consider the possibility of muscle cramps, muscle spasms, fatigue, hypothyroidism, etc. In this case report, the patient with T2DM demonstrated an elevated serum CPK level accompanied with an atypical CPK band. Although the mechanism of the generation of a complex between CPK and immunoglobulin remains poorly understood, the present evidence suggests that a complex is formed through an antigen–antibody reaction or a non-specific binding of denatured CPK with other proteins [2]. Thus, the CPK–immunoglobulin complex is generated through an antigen–antibody reaction.

According to a PubMed literature search, this case report is the first to demonstrate that serum CPK levels accompanied with macro-CPK negatively and significantly correlate with the HbA1c and plasma glucose levels. HMG-CoA reductase inhibitors or ezetimibe users have been reported to exhibit macro-CPK or myopathy, respectively [4–6]. However, the serum CPK levels combined with macro-CPK did not correlate with the LDL and TG concentrations. Therefore, the lipid lowering effect of ezetimibe was not likely to contribute to macro-CPK occurrence in the present case.

For the control, we examined how the plasma glucose control and plasma glucose levels affected the plasma CPK levels without macro-CPK by calculating the correlation coefficient values between the serum CPK levels and HbA1c values and the plasma glucose levels. Interest-
ingly, the serum CPK levels without macro-CPK did not correlate with the HbA1c value and plasma glucose levels. If hypercreatinekinasemia is detected in a laboratory screening test used for ruling out rhabdomyolysis as a side effect of HMG-CoA reductase inhibitors or ezetimibe [4], we are required to perform a careful examination of clinical feature, to examine cardiac markers such as troponin I besides CPK, and to check whether diluted samples produce linear results or not. Thereafter, the possibility of macro-CPK suggested to be considered, especially when the CPK levels inversely correlate with HbA1c. Further investigations are required to confirm whether the plasma glucose concentration interferes directly with CPK–immunoglobulin binding or is affected by the glycation step.

In conclusion, it was suggested that the plasma glucose control condition interferes with CPK–immunoglobulin binding or is affected by the glycation step. Although the pathophysiological role of macro-CPK remains unclear, our case report may provide a new viewpoint about macro-CPK etiology.

**Statement of Ethics**

The research complies with the guidelines for human studies in accordance with the World Medical Association Declaration of Helsinki. This case report “Creatine Phosphokinase Level Accompanied with Macro-Creatine Phosphokinase Type 1 Negatively Correlates with Plasma Glucose Control in a Patient with Type 2 Diabetes Mellitus” was reviewed and approved by the review boards of Hidaka Hospital as 2021–A-25 (May 27th 2021). The patient signed a written consent for the publication of the case and accompanying images.

**Conflict of Interest Statement**

None of the authors have any potential conflicts of interest associated with this case report.

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**Author Contributions**

K.K., K.O. (Ohshima), and S.O. are taking care of this patient. K.O. (Okada), J.O., and S.O. prepared the manuscript.

**Data Availability Statement**

The data that support the findings of this study are not publicly available due to the confidentiality of the participants, for example, they contain information that could compromise the privacy of research participants, but are available from the corresponding author on reasonable request.

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