LETTER TO EDITOR

Carnitine Administration and ^{123}I-BMIPP Washout Rate in Hemodialysis Patients with Triglyceride Deposit Cardiomyovasculopathy

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Abstract

Triglyceride deposit cardiomyovasculopathy (TGCV) is an emerging rare heart disease with high mortality, characterized by defective intracellular lipolysis of triglycerides (TG). We developed diagnostic criteria for TGCV, in which low washout rate of BMIPP (BMIPP-WR) is a key factor. The working group of the Japan Society of Nuclear Cardiology recently published practice recommendations for measuring BMIPP-WR. We reported that hemodialysis (HD) patients with TGCV exhibited a markedly higher cardiovascular risk than those without TGCV. Secondary carnitine deficiency is common in patients undergoing HD, as carnitine is removed from the circulation. However, clinical evidence linking carnitine levels to BMIPP-WR is limited. Here we report the effect of L-carnitine administration on the BMIPP-WR in 9 chronic HD patients with TGCV in a retrospective cohort. The mean age at TGCV diagnosis was 59 years. Following standard doses of oral L-carnitine administration, plasma free carnitine levels significantly increased. However, BMIPP-WR was not changed. In normal condition, most BMIPP taken up were esterified/incorporated into TG pool, hydrolyzed by intracellular lipases, and then transported by carnitine shuttle to mitochondria. In TGCV, intracellular TG lipolysis is defective. During the intracellular metabolism of BMIPP, carnitine shuttling occurs downstream of TG lipolysis. Therefore, even when carnitine levels were increased, BMIPP-WR did not change in patients with TGCV who underwent chronic HD. A phase IIb/III clinical trial for TGCV, is underway (jRCT2051210177). Increased awareness of the disease concept of TGCV, along with its diagnostic principles and procedures using BMIPP scintigraphy, is warranted.

Keywords: BMIPP, Carnitine, Hemodialysis, Triglyceride deposit cardiomyovasculopathy, Washout rate
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Dear Editor,

Triglyceride deposit cardiomyovasculopathy (TGCV) is an emerging rare heart disease characterized by defective intracellular lipolysis of triglycerides (TG) (1, 2), leading to severe heart failure (3), diffuse coronary artery disease with TG deposition (4), and ventricular arrhythmia with high mortality (5). ^{123}I-β-methyl-p-iodophenylpentadecanoic acid (BMIPP) is a useful radiopharmaceutical to evaluate metabolism of long-chain fatty acid (LCFA) and TG in various kinds of heart diseases since its approval in the 1990s (6). The Japan TGCV Study Group developed diagnostic criteria for TGCV, in which low washout rate of BMIPP (BMIPP-WR) is a key

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Table 1 Demographic and clinical characteristics of patients with TGCV investigated

	Patients (N=9)
Age of diagnosis	58.6 ± 11.1*
Sex: Male/Female (n)	6/3
Body mass index (kg/m^2)	19.1 ± 5.5*
Hemodialysis duration (days)	5,244 ± 4,249*
Etiologies of end stage renal disease (n)	ADPKD (1), Nephrosclerosis (2), Diabetic nephropathy (3), FSGS (1), Unknown (2)
Co-morbidities	
Diabetes mellitus (n)	4
Dyslipidemia (n)	2
Hypertension (n)	6
Hemoglobin (g/dL)	11.4 ± 1.3*
Serum lipid levels (mg/dL)	
Triglyceride	111 ± 47*
Low-density lipoprotein-cholesterol	72 ± 25*
High-density lipoprotein-cholesterol	50 ± 11*
Low LVEF (<40%) (n)	2
Diffuse coronary atherosclerosis (n)	7
Outcomes	
Follow-up period from TGCV diagnosis (days)	1,713 ± 1,996*
All-cause of death (n)	4

* Mean ± standard deviation
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; LVEF, left ventricular ejection fraction; N, number; TGCV, triglyceride cardiomyovasculopathy

factor (7). The working group of the Japan Society of Nuclear Cardiology recently published practice recommendations for measuring BMIPP-WR (8).

Patients undergoing chronic hemodialysis (HD) experience severe cardiovascular mortality, despite recent advances in medical and invasive revascularization therapies, including cholesterol-lowering therapies (9). Therefore, understanding the mechanisms underlying residual risk in these patients is crucial. We recently reported that the prevalence of TGCV was not uncommon in patients undergoing HD and those with TGCV exhibited a markedly higher cardiovascular risk than those without TGCV in a single-centered retrospective study (10).

Carnitine is an essential protein for the LCFA entry into mitochondria. Genetic defects of molecules in the carnitine shuttle lead to severe cardiomyopathy with cellular steatosis in children (11). Secondary carnitine deficiency is common in patients undergoing HD, as carnitine is removed from the circulation. However, clinical evidence linking carnitine levels to BMIPP-WR is limited. Only one previous study (12) reported that carnitine administration increased BMIPP-WR in non-TGCV patients on HD whose BMIPP-WR exceeded the TGCV diagnostic cutoff value (10%). Therefore, we aimed to report the effect of L-carnitine administration on the BMIPP-WR in HD patients with TGCV in a retrospective cohort.

From August 2015 to June 2021, the Japan TGCV Study Group identified 9 patients who met the following inclusion criteria: 1) underwent BMIPP scintigraphy both before and after carnitine administration and 2) underwent carnitine levels measurements both before and after administration. TGCV diagnosis was established based on the latest diagnostic criteria (7). The original BMIPP scintigraphy data were obtained from primary physicians and verified by an independent researcher of the Japan TGCV Study Group. This observational study was approved by the ethics review committee.

Table 1 shows the demographic and clinical characteristics of the patients with TGCV. The mean age at diagnosis was 59 years, and all patients had a long history of HD. Their mean body mass index was 19.1 kg/m^2. The etiologies of chronic kidney disease were heterogeneous, including diabetic nephropathy, nephrosclerosis, focal glomerular sclerosis, and polycystic kidney disease. The patients showed mild anemia, normal serum TG levels, and low-density lipoprotein-cholesterol levels under 100 mg/dL. Ultrasonography revealed reduced left ventricular ejection fraction (LVEF) in two

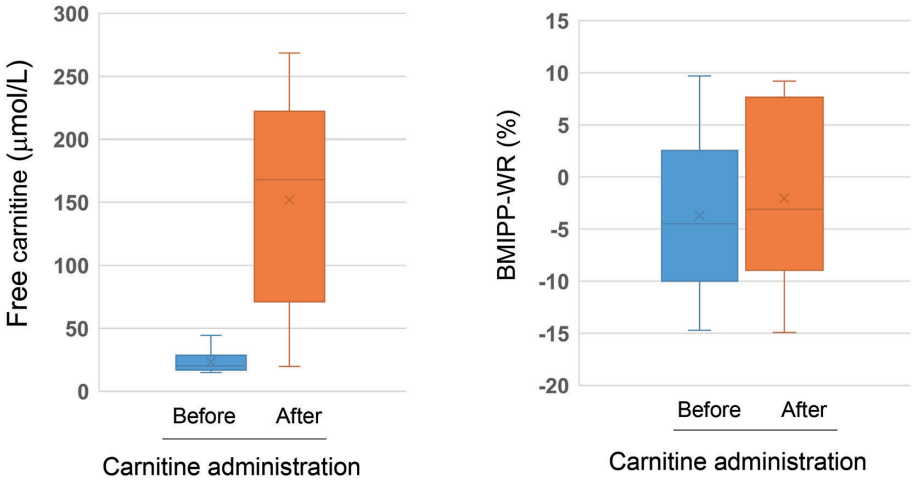

Figure 1 Changes in free carnitine levels (left) and BMIPP-WR (right) in patients with TGCV undergoing HD.

Free carnitine levels were markedly increased ($p<0.01$), whereas BMIPP-WR was not changed after L-carnitine administration.

Reference values of free carnitine: 36–74 μmol/L

BMIPP-WR of non-TGCV controls: 22.0 ± 6.4 % (13)

Abbreviations: BMIPP-WR, washout rate of ^{123}I-β-methyl-p-iodophenylpentadecanoic acid; HD, hemodialysis; TGCV, triglyceride deposit cardiomyovasculopathy

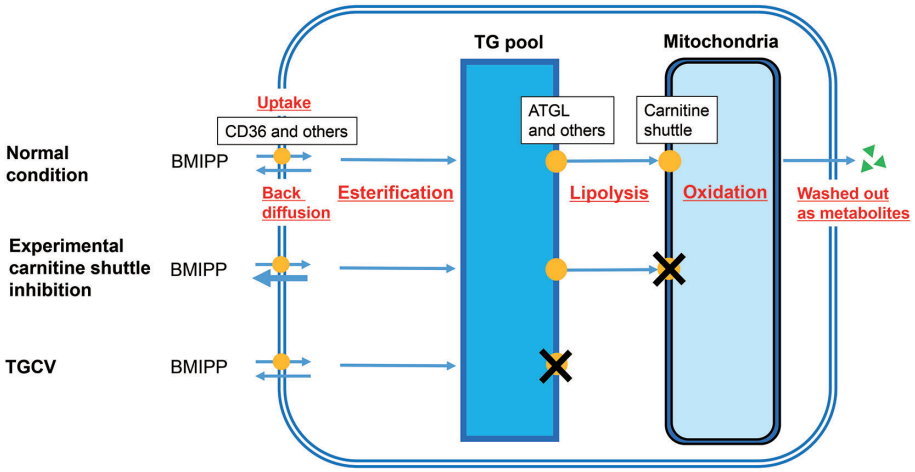

Figure 2 Cellular kinetics and metabolism of BMIPP in various conditions: normal (upper), experimental inhibition of carnitine shuttle (middle), and TGCV (lower).

Because most cellular BMIPP is esterified and incorporated into TG pool, this radiopharmaceutical is useful to evaluate cellular metabolism of TG as well as that of long-chain fatty acid. The defective lipolysis observed in TGCV is upstream of carnitine shuttle following mitochondrial oxidation, therefore carnitine administration did not alter BMIPP-WR in patients with TGCV (please see description in text).

Abbreviations: BMIPP-WR, washout rate of ^{123}I-β-methyl-p-iodophenylpentadecanoic acid; TGCV, triglyceride deposit cardiomyovasculopathy

patients. Seven demonstrated diffuse coronary atherosclerosis.

Following standard doses of oral L-carnitine administration (3.0 g/day), plasma free carnitine levels markedly increased (from 23.5 ± 9.0 to 151.8 ± 80.3 μmol/L, $p<0.01$). However, the changes in BMIPP-WR were not significant (from -3.6 ± 7.5 to -2.0 ± 8.1%, $p=0.78$) (Figure 1). Brain natriuretic peptide levels and LVEF did not differ significantly after carnitine administration (data not shown). During the observation period post-TGCV diagnosis (mean duration of 1,713 days), 4 patients died of cardiovascular events or suddenly.

The cellular kinetics and metabolism of BMIPP are illustrated in Figure 2, according to previous and recent literature. Approximately 75% of injected BMIPP enters the cells via LCFA transporters, including CD36 (14, 15). Approximately 90% of cellular BMIPP is esterified and incorporated into the TG pool, whereas the remainder is rapidly back-fluxed from cells following injection (15, 16).

TG with BMIPP are hydrolyzed by intracellular lipases, including adipose triglyceride lipase (ATGL) (3, 17). The released BMIPP enters through carnitine shuttle and is oxidized in the mitochondria. After alpha- and beta-oxidations, various metabolites are removed from cells (14, 15). Previous animal studies demonstrated that irreversible carnitine shuttle blockers altered BMIPP kinetics, increasing back diffusion and inhibiting catabolism (18, 19). In TGCV, intracellular TG lipolysis is defective due to genetic deficiencies of ATGL among other causes. During the intracellular metabolism of BMIPP, carnitine shuttling occurs downstream of lipolysis. Therefore, even when carnitine levels were increased, BMIPP-WR did not change in patients with TGCV who underwent chronic HD.

The limitations of the present study are as follows: 1) it would be of interest to know BMIPP-WR in genetic carnitine deficiency, even a pediatric orphan disease; 2) it remains to be investigated prevalence of TGCV among HD patients in larger multi-centered cohorts; 3) the relationship between defective TG lipolysis and cardiorenal systems needs further investigation, as we recently observed that genetic ATGL deficiency can cause a novel type of podocytopathy, in addition to TGCV (20).

A phase IIb/III clinical trial for TGCV, featuring a first-in-class orphan drug with tricaprin/trisdecanoin as the active ingredient, is currently underway (jRCT2051210177). Increased awareness of the disease concept of TGCV, along with its diagnostic principles and procedures using BMIPP scintigraphy, is warranted.

Acknowledgments

KH, the principal investigator of the Japan TGCV Study Group, analyzed the data and wrote the manuscript. KK collected the data and participated in scientific discussions. HM, YNagasawa, YNakano, MM, and TA participated in scientific discussions and reviewed the manuscript. KN confirmed the TGCV diagnosis using BMIPP-WR and reviewed the manuscript.

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Conflicts of interest

KH has held the position of Joint Research Chair in collaboration with Toa Eiyo Ltd. (Tokyo, Japan) since February 2021 and has served as a medical advisor for Toa Eiyo Ltd. since December 2021. KH has a patent pending. KN collaborated with Siemens Medical Solutions USA, Inc. (Princeton, NJ, USA), Spectrum Dynamics Medical (Caesarea, Israel), and PDRadiopharma, Inc. (Tokyo, Japan), and conducted research in a department supported by Siemens Healthcare Japan (Tokyo, Japan), PDRadiopharma, Inc. (Tokyo, Japan), and Nihon MediPhysics (Tokyo, Japan). The other authors declare no conflicts of interest.

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