Review

Significance of Levocarnitine Treatment in Dialysis Patients

Hiroyuki Takashima, Takashi Maruyama and Masanori Abe *

Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, 30-1 Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan; takashima.hiroyuki@nihon-u.ac.jp (H.T.); maruyama.takashi@nihon-u.ac.jp (T.M.)
* Correspondence: abe.masanori@nihon-u.ac.jp; Tel.: +81-3-3972-8111; Fax: +81-3-3972-8311

Abstract: Carnitine is a naturally occurring amino acid derivative that is involved in the transport of long-chain fatty acids to the mitochondrial matrix. There, these substrates undergo β-oxidation, producing energy. The major sources of carnitine are dietary intake, although carnitine is also endogenously synthesized in the liver and kidney. However, in patients on dialysis, serum carnitine levels progressively fall due to restricted dietary intake and deprivation of endogenous synthesis in the kidney. Furthermore, serum-free carnitine is removed by hemodialysis treatment because the molecular weight of carnitine is small (161 Da) and its protein binding rates are very low. Therefore, the dialysis procedure is a major cause of carnitine deficiency in patients undergoing hemodialysis. This deficiency may contribute to several clinical disorders in such patients. Symptoms of dialysis-related carnitine deficiency include erythropoiesis-stimulating agent-resistant anemia, myopathy, muscle weakness, and intradialytic muscle cramps and hypotension. However, levocarnitine administration might replenish the free carnitine and help to increase carnitine levels in muscle. This article reviews the previous research into levocarnitine therapy in patients on maintenance dialysis for the treatment of renal anemia, cardiac dysfunction, dyslipidemia, and muscle and dialytic symptoms, and it examines the efficacy of the therapeutic approach and related issues.

Keywords: carnitine; carnitine deficiency; end-stage kidney disease; peritoneal dialysis; hemodialysis

1. Introduction

Carnitine, with a molecular weight of 161 Da, is a water-soluble quaternary amine. It is derived from lysine and methionine, which are two essential amino acids. Its primary role is in facilitating the transport of long-chain fatty acids to the mitochondrial matrix. These substrates are delivered for β-oxidation and the subsequent production of energy. Carnitine is primarily biosynthesized in the kidney and liver and is found in virtually all tissues but predominantly in cardiac and skeletal muscle.

Patients on hemodialysis often have carnitine deficiency [1]. Carnitine deficiency is associated with several clinical disorders, such as erythropoiesis-stimulating agent (ESA)-resistant anemia, muscle weakness, myopathy, and intradialytic muscle cramps and hypotension. Additional clinical disorders of carnitine deficiency include dyslipidemia, cardiac arrhythmia, cachexia, insulin resistance, and glucose intolerance [2–4]. The characteristic features of dialysis-associated carnitine deficiency are reduced levels of free carnitine and elevated levels of acylcarnitine. Free carnitine levels are mainly decreased by its removal during hemodialysis, whereas the accumulation of acylcarnitine and an aberrantly elevated plasma acylcarnitine to free carnitine ratio are due to deficient renal clearance and β-oxidation failure [1,2]. Accordingly, carnitine supplementation in dialysis patients with carnitine insufficiency may yield clinical benefits by ameliorating several of the above-mentioned conditions.

In this review, we describe the profile of carnitine metabolism and the effects of carnitine treatment on the metabolism and function of dialysis patients. We also assess the
current findings related to the carnitine treatment of patients undergoing dialysis therapy, particularly its impact on cardiac function, ESA-resistant anemia, muscle symptoms, and malnutrition.

2. Carnitine Homeostasis

The main dietary sources of carnitine are meat products, with small amounts of carnitine found in vegetables [5,6]. About 100–400 mg per day of carnitine is provided from a normal diet. Dietary carnitine is absorbed from the intestine by both active and passive transport and meets 65–75% of daily needs. The remaining 25–35% is supplied by biosynthesis in the kidney and liver from methionine and lysine. Carnitine is found both intracellularly and extracellularly and in both non-esterified and esterified forms. The former is free carnitine, while the latter is acylcarnitines. Short-, medium-, and long-chain fatty acids are found in carnitine esters and are present in biological systems. The proportion of acylcarnitine varies widely according to physical activity, disease condition, and nutritional state. Under normal conditions in humans, acylcarnitine accounts for approximately 20% of total carnitine in serum, 10–15% of that in the liver and skeletal muscle, and 50–60% of that in urine [7–9].

Under physiological conditions, the total carnitine content in the body has been estimated to be 100 mmol. More than 90% of total body carnitine is found in skeletal muscle, with 2–3% in the liver and kidney. Thus, only 0.5–1% is present in the extracellular fluid [10]. The brain has a relatively low concentration of carnitine, despite being one of the few organs with endogenous biosynthesis capability. Carnitine cannot bind to protein and is mainly filtered at the glomeruli of the kidney. However, over 90% of filtered carnitine is reabsorbed by the proximal renal tubule in individuals with normal kidney function, and the serum excretory threshold level of free carnitine in the kidney appears to be 40 µmol/L, which is near the normal serum concentration of free carnitine [5,6]. Tubular reabsorption of free carnitine predominates. Therefore, the excretion of acylcarnitine by the kidney is 4- to 8-fold higher than that of free carnitine [5]. Plasma membrane transporters and carnitine-dependent enzymes are important for maintaining carnitine homeostasis. Together, free and acylcarnitine comprise the carnitine system.

The high-affinity Na+/carnitine cotransporter OCTN2 is the most physiologically associated plasma membrane transporter of carnitine [11]. OCTN2 is extensively found in numerous tissues, such as the heart, skeletal muscle, kidney, and placenta. OCTN2 is localized to the brush border of tubular epithelial cells in the kidney and is most active in the proximal tubules of the nephron, which is the site of approximately 65% of reabsorption and secretion [12]. The association of mutations in the OCTN2 gene with primary systemic carnitine deficiency indicates its importance [13].

Carnitine/acylcarnitine translocase (CACT) and carnitine acyltransferases are known as carnitine-dependent enzymes. CACT converts mitochondrial carnitine to cytoplasmic acylcarnitine and allows the flow of both carnitine and short-chain acyl-carnitines into and out of the mitochondria [14]. Carnitine acyltransferases exist in tissue-specific isoforms with distinct kinetic characteristics and with significant modulatory targets involved in fatty acid metabolism and coenzyme-A (CoA) release [15].

The proper function of OCTN2 and the various carnitine-dependent enzymes is needed to maintain the carnitine system. Carnitine has an important role in energy metabolism. It transports long-chain fatty acids across the inner mitochondrial membrane and modulates β-oxidation and the resulting adenosine triphosphate (ATP) production [16]. Furthermore, carnitine participates in intermediary metabolism by regulating the ratio of acyl-CoA/CoA in the cell. The main mechanisms underlying this function of carnitine are the production of short-chain acylcarnitines, which are catalyzed by carnitine acetyltransferase, and the conversion of carnitine to acylcarnitine, which is catalyzed by CACT [14,17]. Carnitine has a buffer action for accumulated acyl-CoA. The accumulation of acyl-CoA inhibits several enzymes, including acetyl CoA carboxylase, adenine nucleotide translocase, citrate synthetase, pyruvate dehydrogenase, and pyruvate carboxylase, and it induces mito-
Therefore, an accumulation of acyl groups within the mitochondria inhibits the activity of energy-producing enzymes. Acyl-CoA is restricted to the mitochondrial matrix and cannot pass the membrane. However, its acyl group is transferred from acyl-CoA to carnitine, and carnitine is metabolized into acylcarnitine. Acylcarnitine translocates from mitochondria to the extracellular fluid and is finally excreted via the urine. The detoxifying effects of carnitine are important for cell metabolism [18]. The fatty acid metabolism and functions of carnitine are shown in Figure 1.

![Figure 1. Fatty acid metabolism and metabolic functions of carnitine. CACT, carnitine acetyltransferase; CPT, carnitine palmitoyl transferase; OCTN2, organic cation/carnitine transporter 2, PCS, palmitoyl CoA synthetase.](image)

Serum carnitine concentrations are 50–60 µmol/L, which is calculated as the sum of free carnitine and acylcarnitine. When serum-free carnitine drops below 20 µmol/L, the clinical symptoms of carnitine deficiency can develop. In patients with severe hereditary metabolic diseases, acylcarnitine is found in the serum and urine. In these patients, the endogenous carnitine pool falls into a deficit to manage the crucial acyl transfer, which increases the acyl/free carnitine ratio in serum. A ratio exceeding 0.4 has been used to indicate carnitine insufficiency in clinical practice [19]. Daily urinary total carnitine excretion typically consists of 50% acylcarnitine, resulting in a urinary acyl/free carnitine ratio of about 1.0 [20]. Carnitine homeostasis is shown in Figure 2.
3. Carnitine Deficiency in Patients Who Are Undergoing Dialysis Therapy

Carnitine homeostasis is profoundly perturbed in patients with end-stage kidney disease, particularly patients on dialysis. Dietary intake of carnitine is decreased due to falls in appetite, total energy levels, and protein intake. In addition, accumulating evidence has linked inflammation to malnutrition, and chronic inflammation might also interrupt carnitine transfer in the intestine [21]. Protein-energy wasting (PEW) and inflammation are the most pivotal risk factors for morbidity and mortality in patients on dialysis [22–24]. Carnitine biosynthesis can also fall in patients on dialysis due to reduced biosynthesis in the kidney and limited compensation by the liver [25]. Furthermore, the kidney disease may itself modulate OCTN2 activity on the renal tubule [26]. Filtered carnitine in the glomerulus cannot be reabsorbed in anuric patients undergoing hemodialysis. Therefore, chronic hemodialysis treatment reduces serum and tissue levels of carnitine and can promote acylcarnitine accumulation. As a result of the low molecular weight of carnitine and its high hydrophilicity and absence of protein binding, carnitine is significantly removed by the dialyzer [27,28].

According to Japanese guidelines [29], a free carnitine level < 20 µmol/L is defined as carnitine deficiency, a high risk of carnitine deficiency is defined as a level in the range of 20–36 µmol/L, and carnitine insufficiency is defined as a serum acyl/free carnitine ratio > 0.4. Consequently, serum carnitine levels are significantly lower in patients receiving hemodialysis than in healthy individuals at 22.0 ± 5.4 µmol/L and 43.3 ± 8.6 µmol/L, respectively [30]. Serum endogenous carnitine levels are significantly negatively correlated with dialysis therapy duration, with most of the reduction occurring within the first few months of hemodialysis initiation [30]. Long-term hemodialysis (i.e., longer than 1 year) is also linked to a marked 38% reduction in muscle carnitine pools compared with those before hemodialysis initiation [30]. Another investigation also reported that the total carnitine and acylcarnitine levels in muscle were significantly decreased in patients on dialysis [31]. We recently reported the prevalence of carnitine deficiency in 150 patients on hemodialysis [32]. Of these, serum free carnitine levels were below the normal range (36–74 µmol/L) in 90% of the patients, and 25.3% of the participants met the definition of carnitine deficiency (<20 µmol/L). Furthermore, 64.7% were diagnosed as having high
risk of carnitine deficiency (acyl/free carnitine ratio > 0.4). In addition, just 13.3% of the participants \( (n = 20) \) had a normal ratio of \( \leq 0.4 \) and 86.7% of the participants \( (n = 130) \) were diagnosed with carnitine insufficiency. A longer duration of dialysis was significantly associated with lower serum carnitine levels in multivariate analysis [32].

Acylcarnitine levels are significantly higher in patients on maintenance hemodialysis than in healthy individuals. Acylcarnitine levels are significantly elevated in patients who have been receiving hemodialysis for at least 12 months [4,28]. Indeed, acylcarnitine levels account for about 50% of the total serum carnitine stores in these patients compared with just 15% in healthy individuals [4,28]. Hemodialysis procedures decrease free, short-chain, medium-chain, and dicarboxylic acylcarnitines but do not affect long-chain acylcarnitines [33]. The dialytic removal of acylcarnitine during a single hemodialysis session is significantly associated with the carbon chain length of the acyl groups, with no major removal of the 18-carbon chain esters [34]. The removal rate of acylcarnitine clearly decreases as the carbon chain length increases because it increases their molecular weight and alters their lipophilicity. Furthermore, longer-chain acylcarnitines can bind to protein [35]. Therefore, the acyl/free carnitine ratio is positively correlated with the number of months on hemodialysis treatment [30,36]. Acylcarnitines are classified according to carbon chain length. Tandem mass spectrometry can determine the details of acylcarnitines, such as whether they are short-chain, middle-chain, and long-chain acylcarnitines. Tandem mass spectrometry has revealed that a lower ratio of acetylcarnitine (C2)/(palmitoylcarnitine + octadecenoylcarnitine [C16+C18:1]), which indicates the ratio of short-chain/long-chain acylcarnitines, in patients on hemodialysis is associated with all-cause mortality [37].

4. Removal of Carnitine by Dialysis Therapy

In 2018, 339,841 patients underwent maintenance dialysis in Japan. Of these, 37.0% were receiving hemodiafiltration. Approximately 71% of patients who were receiving hemodiafiltration were treated with online hemodiafiltration and the pre-dilution method [38,39]. Compared with conventional high-flux hemodialysis, hemodiafiltration is a more effective technique; it relies on high-flux membranes that can remove both small solutes, such as urea, and low-molecular weight proteins, such as β2-microglobulin [40,41]. Serum carnitine is removed by hemodialysis. Previous work determined the percent reduction in serum-free carnitine in patients on hemodialysis with or without diabetes and without levocarnitine treatment. The reductions in plasma free carnitine were −64.7% and −66.6% in patients with or without diabetes, respectively [33]. However, the hemodialysis procedure was not described in detail (i.e., blood and dialysate flow rates, treatment time, and Kt/V). We previously investigated the reduction rate of the serum carnitine level after single sessions of hemodialysis and hemodiafiltration [32]. Hemodialysis using high-flux dialyzers was conducted at blood and dialysate flow rates of 200–240 mL/min and 500 mL/min, respectively. Hemodiafiltration using high-flux hemodiafilters was performed at blood flow, replacement fluid, and dialysate flow rates of 200–300, 200–250, and 250–300 mL/min, respectively. Although no significant differences were evident in the patients’ baseline characteristics or in the pre-dialysis serum total, free, or acylcarnitine concentrations between the hemodialysis and hemodiafiltration groups, the Kt/V values were 1.28 ± 0.27 and 1.45 ± 0.31 in the hemodialysis and hemodiafiltration groups, respectively \( (p = 0.042) \). There was a significantly greater decrease in serum total, free, and acylcarnitine levels in the hemodiafiltration group. Reduction rates of serum free carnitine of 64% ± 4% and 75% ± 7% were obtained under hemodialysis and hemodiafiltration conditions, respectively \( (p < 0.0001) \). These findings indicate the greater clearance of small molecular weight solutes by hemodiafiltration.

Patients on peritoneal dialysis exhibit a decreased serum free carnitine level and increased acyl/free carnitine ratio compared with age- and sex-matched individuals with normal kidney function [42,43]. In patients on peritoneal dialysis, the mechanism of carnitine deficiency is considered to be decreased dietary intake of carnitine-containing food, decreased renal carnitine synthesis, and decreased renal excretion of acylcarnitine [27,30].
Another contributor might be the loss of free carnitine into the peritoneal dialysis fluid [44]. The prevalences of carnitine deficiency, high risk of carnitine deficiency, and carnitine insufficiency in peritoneal dialysis patients are comparable to those of age-, sex-, and dialysis vintage-matched hemodialysis patients [45]. Lower serum-free carnitine levels are associated with a longer duration of peritoneal dialysis and an older age.

5. Carnitine Supplementation in Dialysis Patients

The association between carnitine deficiency and a decreased serum-free carnitine level may result in various cellular metabolic disorders, such as reduced mitochondrial β-oxidation of fatty acids and consequent diminished energy production and storage of toxic acylcarnitines and suppression of carnitine-related enzymes involved in metabolism [46]. These carnitine-related metabolic aberrations may induce the above-mentioned clinical disorders frequently found in patients on dialysis, which include muscle weakness and cardiomyopathy, PEW, plasma lipid abnormalities, and ESA-resistant anemia, as well as hemodialysis-associated symptoms such as hypotension and muscle cramps [2–4].

Carnitine supplementation for the treatment of dialysis-related carnitine deficiency can be performed orally or intravenously. Multiple investigations have evaluated the benefits of carnitine supplementation in patients on dialysis. Intravenously administered levocarnitine has a bioavailability of 100%. When a dose of 1–2 g levocarnitine is intravenously administered to healthy individuals, the serum carnitine levels rapidly increase to 10 times that of the threshold for renal tubular reabsorption; 70–90% is consequently excreted in an unchanged form in the urine 12–24 h after administration. Therefore, a single dose of levocarnitine does not persist in the system for a sufficient length of time for any significant amount to equilibrate into the skeletal and cardiac muscle. However, for hemodialysis patients, an intravenous dose of levocarnitine remains in the blood for a long enough time for it to be taken up into the organs or tissue compartments, with up to about 90% of the administered levocarnitine possibly moved into tissues [4]. Chronic intravenous levocarnitine administration elevates muscle carnitine levels by between 60% and 200% [47–50].

In contrast, the bioavailability of oral levocarnitine administration is low, even in healthy individuals. Only 15% of a standard 2-g dose is absorbed into the blood in healthy individuals and just 5% of an oral 6-g dose [51,52]. The bioavailability of oral levocarnitine in patients on dialysis has not yet been evaluated. The metabolism of dietary carnitine and choline produces trimethylamine N-oxide (TMAO), which directly induces atherosclerosis in rodents [53,54]. Intestinal bacteria metabolize carnitine and choline to trimethylamine, which is absorbed in the intestine. Trimethylamine is itself oxidized by hepatic flavin monooxygenase to make TMAO [55]. Under normal conditions, TMAO is rapidly removed from the circulation, largely via excretion in the urine [56,57]. Accordingly, circulating TMAO levels appear to be associated with coronary artery disease and may also be associated with mortality in patients on long-term hemodialysis [58,59]. However, no study has shown whether oral levocarnitine treatment or TMAO levels would accelerate atherosclerosis in hemodialysis patients. Thus, additional work is required to evaluate the superiority, efficacy, and safety of intravenous levocarnitine administration compared with oral administration because there is no evidence of associations between the increased levels of TMAO and atherosclerosis progression in dialysis patients.

The National Kidney Foundation has stated that the detection and diagnosis of dialysis-related carnitine deficiency, as well as the decision to treat chronic dialysis patients with levocarnitine, should be determined by clinical symptoms and signs [60]. Furthermore, proof of decreased serum-free carnitine levels or an increased acyl/free carnitine ratio is dispensable for the clinical diagnosis of dialysis-related carnitine deficiency. Serum-free carnitine levels are helpful to rule out dialysis-related carnitine deficiency. However, low concentrations of serum-free carnitine cannot be used as a predictive factor of a clinical response to levocarnitine treatment.
In addition, the National Kidney Foundation has declared that the administration of levocarnitine to dialysis patients should be considered for the following four clinical conditions [60]: (1) patients with anemia who are unable to maintain optimal hemoglobin or hematocrit levels with the use of ESA, despite adequate iron status, and with no other identifiable cause of anemia or a hypo-response to ESA; (2) patients with intradialytic hypotension and no other possible causes with repeated symptomatic intradialytic hypotensive events requiring treatment; (3) patients with cardiomyopathy who have heart failure symptoms such as New York Heart Association class III–IV or symptomatic cardiomyopathy with documented impaired left ventricular ejection fraction (LVEF) and a poor response to standard medical therapy; and (4) selected patients who have symptoms that diminish their quality of life, including skeletal muscle weakness and malaise.

6. Anemia

In patients with end-stage kidney disease, anemia is induced by decreased production of erythropoietin by the kidney or fibrosis of the bone marrow. Renal anemia is commonly treated with ESA in patients with impaired kidney function. Although renal anemia strongly influences prognosis, higher-dose ESA may increase the risk of cardiovascular events in the dialysis population [61,62]. Moreover, the dosage of ESAs to maintain target hemoglobin levels varies widely among patients on dialysis [63]. A lower hematocrit level has been associated with shorter survival [64]. However, a lower hematocrit level was not a significant predictor of mortality in multivariate analysis adjusted for age, serum albumin, and the presence of diabetes. ESA resistance, which is characterized by inflammation and malnutrition, may be a significant novel predictor of mortality [64]. Patients with target hematocrit levels (i.e., 33–36%) receiving a higher ESA dose exhibit a rate of mortality double that of patients with hematocrit levels in the same range but receiving a low ESA dose. Therefore, the use of ESAs should be minimized and ESA resistance is recognized as an important marker for improving survival in the dialysis population.

Levocarnitine administration is suggested as a potential additional therapy to ESA in the management of renal anemia. The Centers for Medicare and Medicaid Services allow intravenous levocarnitine administration to patients on hemodialysis who have ESA-resistant anemia and decreased serum carnitine levels [64]. Although the most common cause of hyporesponsiveness to ESAs is iron deficiency, carnitine deficiency is proposed to be one of the causes of ESA-resistant anemia in Japanese Society for Dialysis Therapy guidelines [65]. Serum carnitine levels have been reported to be lower in patients with severe anemia needing high-dose ESA than in patients with mild-to-moderate anemia or no anemia [66]. In patients with a lower serum carnitine level and need for higher-dose ESA, erythrocyte membranes develop osmotic fragility. This shortens the survival time of erythrocytes and lowers hematocrit levels [67–70]. However, erythrocyte stability is reported to be improved by levocarnitine therapy, and this treatment would be associated with improved survival of erythrocytes through the following mechanism: levocarnitine regulates the erythrocyte membrane lipid complex, modifies the fatty acid metabolism, enhances the Na-K pump activity of erythrocytes, reduces membrane rigidity, and decreases erythrocyte calcium levels [69,71–74].

A systematic review and recent meta-analysis found that levocarnitine treatment ameliorates renal anemia and decreases ESA requirements in hemodialysis patients [75,76]. The efficacy of levocarnitine for treating renal anemia in patients on dialysis has been investigated by multiple studies. This work is summarized in Table 1 [43,69–71,77–94]. The aim of these studies was to maintain hematocrit or hemoglobin levels in carnitine and control groups by significantly decreasing the dosage of ESA in carnitine patients. ESA resistance can be determined by measuring the erythropoietin resistance index (ERI), which is calculated as the ESA dose divided by the hemoglobin level and body weight of each patient. This index is useful for assessing the response of the body to levocarnitine. Any decrease in ESA dosage or increase in the hemoglobin level during the observation period would decrease this index. The ERI was reduced by levocarnitine treatment in several
studies, suggesting that levocarnitine improves erythropoietin efficiency versus control
groups. However, the CARNIDIAL trial found no improvement in the ERI with levocarni-
tine administration in patients with a shorter duration of hemodialysis (<6 months) and no
documented carnitine deficiency. In addition, levocarnitine treatment increased calcium
and phosphate levels and was not associated with parathyroid hormone or fibroblast
growth factor 23 [94,95].

Further studies should be conducted to determine whether levocarnitine treatment is
effective in all dialysis patients with renal anemia and whether it improves long-term out-
comes. Moreover, its dose–response profile in renal anemia has not yet been investigated.

### Table 1. Studies of the effects of levocarnitine on renal anemia in dialysis patients.

| Ref | Study Design | Subjects | Dose and Route | Treatment Duration | Findings |
|-----|--------------|----------|----------------|-------------------|----------|
| [77] | Two-way, parallel, double-blind | 29 HD patients, 29 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 6 mo | ↑ RBC survival T: 39.1 ± 1 days; T: 42.7 ± 0.05 days (p = 0.0058) → RBC survival T: 42.8 ± 1 days; T: 36.5 ± 0.05 days (NS) |
| [78] | One-way, open-label | 14 HD patients (ESA-resistant) | 500 mg/day PO | 3 mo | ↑ HT T: 24.0% ± 2.0%; T: 26.1 ± 2.0% (p = 0.003) |
| [71] | One-way, open-label | 15 HD patients | 30 mg/kg per Dx, IV | 3 mo | ↑ HT T: 30.0% ± 1.9%; T: 34.2 ± 2.4% (p < 0.0001), ↓ DeforRCs (p < 0.004) |
| [43] | One-way, open-label | 12 PD patients | 2 g/day PO | 3 mo | ↑ HT T: 35.4% ± 3.3%; T: 38.1 ± 3.4% (p < 0.03), ↓ Hb T: 11.9 ± 1.1 g/dL; T: 11.9 ± 1.1 g/dL (p < 0.01) |
| [79] | Two-way, parallel, double-blind | 28 HD patients | 20 mg/kg per Dx, IV Placebo | 6 mo | → Hb T: 34.1 ± 3.2%; T: 32.8 ± 4.0% (NS) |
| | Four-way, parallel, double-blind | 30 HD patients | 10 mg/kg per Dx, IV | 6 mo | → Hb T: 33.9 ± 3.2%; T: 35.1 ± 4.2% (NS) |
| | 33 HD patients | 30 mg/kg per Dx, IV Placebo | 6 mo | → Hb T: 33.6 ± 3.3%; T: 33.5 ± 2.7% (NS) |
| [80] | Two-way, parallel, double-blind | 48 HD patients, 65 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 6 mo | ↑ Hb T: 9.7 ± 1.1 g/dL; T: 10.8 ± 1.2 g/dL (p < 0.0001) → Hb T: 9.8 ± 1.2 g/dL; T: 9.9 ± 1.3 g/dL (NS) |
| [81] | Two-way, parallel, open label | 1 g/Dx, IV | 78 HD patients | 7 mo | ↑ Hb T: 7.5 ± 1.5 g/dL; T: 11.4 ± 1.2 g/dL (p < 0.05) ↓ ERI T: 185 ± 16 U/kg; T: 142 ± 12 U/kg (p < 0.05) → Hb T: 7.5 ± 1.4 g/dL; T: 9.2 ± 1.2 g/dL (NS) → ERI T: 185 ± 15 U/kg; T: 160 ± 12 U/kg (NS) |
| [82] | Two-way, parallel, double-blind | 18 HD patients | 15 mg/kg per Dx, IV Placebo | 6 mo | ↑ Hb T: 24.2% ± 2.2%; T: 32.5% ± 3.7% (p = 0.001) ↓ Hb T: 7.9 ± 0.8 g/dL; T: 10.3 ± 1.1 g/dL (p = 0.001) → Hb T: 27.5% ± 4.5%; T: 30.2% ± 4.0% (p = 0.1) → Hb T: 8.0 ± 0.4 g/dL; T: 8.7 ± 2.5 g/dL (p = 0.4) |
| [83] | Two-way, parallel, single-blind | 10 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 2 mo | ↑ Hb +0.89 ± 0.56 g/dL vs. -0.47 ± 0.77 g/dL (p = 0.001) |
| [84] | Double-blind, crossover, placebo-controlled | 16 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 3 mo | → ESA doses T: 8562 ± 6762 U/L; T: 8750 ± 7946 U/L (NS) → Hb T: 11.3 ± 1.9 g/dL; T: 11.5 ± 1.5 g/dL (NS) |
| [85] | Two-way, parallel, open-label | 20 HD patients | 1 g per Dx, twice a week, IV | 6 mo | ↑ Hb T: 6.8 ± 1.0 g/dL; T: 7.7 ± 1.1 g/dL (p < 0.001) ↓ ERI values not reported (p < 0.001) → Hb T: 6.7 ± 1.0 g/dL; T: 6.9 ± 1.0 g/dL (NS), → ERI (NS) |
| [86] | Two-way, parallel, open-label | 20 HD patients | 1 g/Dx, IV | 3 mo | ↑ Hb T: 7.8 ± 1.3 g/dL; T: 9.9 ± 1.9 g/dL (p < 0.05) → Hb T: 7.8 ± 1.1 g/dL; T: 8.5 ± 1.2 g/dL (NS) |
| [87] | One-way, open-label | 62 HD patients | 600 mg/day PO for 12 mo, then 1 g/Dx IV for 12 mo | 24 mo | ↑ Hb T: 10.2 ± 1.2 g/dL; T: 10.9 ± 0.9 g/dL |
| | 18 PD patients | 600 mg/day PO for 12 mo | 12 mo | → Hb T: 10.6 ± 1.1 g/dL; T: 10.6 ± 1.3 g/dL |
| [88] | Two-way, parallel, double-blind | 24 HD patients | 1 g/day, PO | 4 mo | → Hb T: 10.5 ± 2.5 g/dL; T: 11.3 ± 2.1 g/dL (NS) ↓ ESA doses T: 7250 ± 5020 U/week; T: 2500 ± 4180 U/week (p = 0.001) → Hb T: 9.5 ± 2.2 g/dL; T: 9.9 ± 2.5 g/dL (NS) ↓ ESA doses T: 8000 ± 3186 U/week; T: 6000 ± 5083 U/week (p = 0.033) |
| [89] | Two-way, parallel, open-label | 25 HD patients | 1 g/Dx, IV and 1 g/non-Dx, PO | 36 mo | ↓ ESA doses T: 5976 ± 1732 U/week; T: 391 ± 659 U/week (p < 0.001) → ESA doses T: 6100 ± 1587 U/week; T: 5519 ± 1360 U/week (NS) |
| [90] | Two-way, parallel, double-blind | 13 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 4 mo | → ESA doses T: -769 ± 1739 U/week (NS), → Hb T: -0.08 ± 0.90 g/dL (NS) → ESA doses T: +153 ± 177 U/week (NS), → Hb T: +0.26 ± 0.56 g/dL (NS) |
| [91] | Two-way, parallel, open-label | 23 HD patients | 15 mg/kg per Dx, IV No treatment | 6 mo | → ESA doses, → Ht (NS) |
7. Cardiac Function

Cardiovascular disease is a leading cause of mortality in dialysis patients [93]. Approximately 75% of end-stage kidney disease patients commencing hemodialysis treatment experience left ventricular dysfunction, represented by reduced LVEF, which is a significant risk factor for congestive heart failure [97]. Furthermore, intradialytic hypotension has been linked to mortality and is an independent predictor of mortality in this population [97–99].

The main energy source for cardiac myocytes is β-oxidation of fatty acids. Carnitine concentrations in myocytes are some of the highest of all cell types. Furthermore, the production of intracellular acylcarnitine and lactate is induced by myocardial ischemia. Thus, levocarnitine treatment might be useful for cardiac symptoms. Numerous investigations have reported the efficacy of levocarnitine treatment in terms of cardiac function; these are summarized in Table 2 [49,50,89,100–108].

The relationship between hypotensive episodes and levocarnitine treatment has also been investigated in dialysis patients. Patients who experience hypotension during hemodialysis treatment have lower serum carnitine levels than normotensive individuals [109]. Levocarnitine treatment significantly reduces intradialytic hypotension versus placebo [49,110]. Accordingly, intravenous levocarnitine supplementation is allowed for the management of dialysis-related hypotension in hemodialysis patients who have lower serum carnitine levels than normotensive individuals [49,110].

A strong correlation has been found between LVEF and serum carnitine levels in patients on dialysis. In addition, 3-month administration of levocarnitine improves LVEF, significantly so in patients with repeated hypotensive events [111]. It was suggested that patients experiencing symptomatic hypotension had a significantly lower LVEF and a higher mortality risk compared with asymptomatic patients [110]. Other studies have obtained similar results [89,103,112]. Mounting evidence favors a role for levocarnitine in the management of cardiac dysfunction. On the other hand, other studies have reported the ineffectiveness of levocarnitine treatment [50,104]; however, these findings must be interpreted with caution, because these studies included patients with normal LVEF. In our previous reports, atherosclerosis assessed by brachial-ankle pulse wave velocity and cardiac function assessed by LVEF and left ventricular mass index (LVMI) were improved by levocarnitine treatment in patients on hemodialysis [107,113]. Levocarnitine administration decreased N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and ameliorated the ERI. Furthermore, the responders to levocarnitine treatment were patients with left

### Table 1. Cont.

| Ref | Study Design | Subjects | Dose and Route | Treatment Duration | Findings a |
|-----|--------------|----------|----------------|-------------------|------------|
| [92] | Two-way, parallel, double-blind | 13 HD patients | 1 g/Dx, IV Placebo, IV | 6 mo | ↓ ERI T0: 102 ± 53 U/kg/week; T12: 63 ± 38 U/kg/week (p < 0.02) ↓ ERI T0: 79 ± 32 U/kg/week; T12: 80 ± 47 U/kg/week (NS) |
| [70] | Two-way, parallel, double-blind | 10 HD patients | 1 g/Dx, IV Placebo, IV | 6 mo | ↓ ERI T0: 135 ± 79; T12: 118 ± 108 U/kg per week per %Ht (p < 0.05) ↑ ERI T0: 136 ± 66; T12: 217 ± 204 U/kg per week per %Ht (p < 0.05) |
| [69] | Two-way, parallel, double-blind | 20 HD patients | 5 mg/kg or 25 mg/kg per Dx, IV Placebo, IV | 4 mo | ↓ ERI T0: 16.0 ± 11.0; T12: 13.6 ± 10.5 U/kg per week per gHb (p < 0.02) Values not reported |
| [86] | Two-way, parallel, double-blind | 13 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 6 mo | ↓ ERI -1.62 ± 0.91 vs. +1.33 ± 0.79 U/kg per gHb (p < 0.05) |
| [93] | Two-way, parallel, open-label | 30 HD patients | 1 g/Dx, IV Placebo, IV | 12 mo | ↓ ERI T0: 10.7 ± 7.3; T12: 6.4 ± 3.8 U/kg per gHb per week (p < 0.0001) ↓ ERI T0: 0.10 ± 7.9; T12: 9.6 ± 6.5 U/kg per gHb per week (NS) |
| [94] | Two-way, parallel, double-blind | 46 HD patients | 1 g/Dx, IV Placebo, IV | 12 mo | → ERI T0: 20.6 ± 12.8; T12: 15.6 ± 15.9 IU/kg per gHb (p = 0.10) → ERI T0: 15.8 ± 11.3; T12: 9.5 ± 5.8 IU/kg per gHb (p = 0.10) |

Dx, dialysis session; HD, hemodialysis; ERI, erythropoietin resistance index; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Ht, hematocrit; IV, intravenous injection; mo, months; NS, not significant; PO, per oral; RBC, red blood cell; Ref, reference. a The findings show no difference (→), a decrease (↓), or an increase (↑).
ventricular hypertrophy, as defined by the LVMI on echocardiography. These results suggest that levocarnitine treatment might be effective for patients with a larger baseline LVMI [107]. Therefore, these results indicate that levocarnitine treatment is beneficial for patients with left ventricular hypertrophy, reduced LVEF, or dialysis-related hypotension.

Table 2. Studies of the effect of levocarnitine on cardiac function and hypotension in dialysis patients.

| Ref | Study Design | Population | Dose and Route | Treatment Duration | Findings |
|-----|--------------|------------|----------------|-------------------|----------|
| [101] | Two-way, crossover, double-blind | 9 HD patients | 990 mg/d PO then placebo for 2 mo each | 2 mo | ↓ Hypotension (p < 0.001) |
|      |              | 9 HD patients | Placebo then 990 mg/d PO for 2 mo each |     | → Hypotension (NS) |
| [50]  | Two-way, parallel, double-blind | 14 HD patients | 2 g/Dx, IV | 6 weeks | No difference in cardiac function (NS) |
| [49]  | Two-way, parallel, double-blind | 38 HD patients | 20 mg/kg per Dx, IV Placebo | 3 mo | ↓ Hypotension (p < 0.05) |
| [49]  | One-way, open-label | 35 HD patients | No treatment | 36 mo | ↓ LV end-diastolic volume (p < 0.05) |
| [102] | One-way, open-label | 11 HD patients | 1 g/Dx, IV | 2 mo | ↑ LVEF (p < 0.05) |
| [103] | One-way, open-label | 11 HD patients | 1 g/d PO then 0.5 g/d PO for 1 mo each | 2 mo | → LVEDD, LVFS (NS) |
| [104] | One-way, open-label | 18 HD patients | 500 mg/d PO | 6 mo | ↑ LVEF (p < 0.005) |
| [105] | One-way, open-label | 11 HD patients (impaired LVEF) | 1 g/Dx, IV | 8 mo | ↑ LVEF T: 56.4 ± 0.06; T0: 48.6 ± 17.6% (p < 0.05) |
| [106] | Two-way, parallel, double-blind | 10 HD patients | 900 mg/d PO | 3 mo | ↓ Hypotension T: 42.4 ± 19.4%; T0: 48.6 ± 17.6% (p < 0.05) |
| [107] | Two-way, parallel, double-blind | 10 HD patients | 900 mg/d PO Placebo | 12 mo | No difference in cardiac function (NS) |
| [108] | Two-way, parallel, double-blind | 10 HD patients | 20 mg/kg/d PO | 12 mo | ↑ LVEF T: 53.1% ± 5.3%; T0: 58.6% ± 5.5% (p < 0.001) |
| [109] | Two-way, parallel, double-blind | 10 HD patients | 30 mg/kg/d PO before Dx, IV Placebo | 3 mo | ↓ Hypotension 9.3% vs. 33.1% (p < 0.0001) |

CTR, cardiothoracic ratio; Dx, dialysis session; HD, hemodialysis; IV, intravenous injection; LVEDD, left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; mo, months; NS, not significant; PO, per oral; Ref, reference. * The findings show no difference (→), a decrease (↓), or an increase (↑).

Myocardial fatty acid metabolism, as assessed by 123I-labeled β-methyl-p-iodophenylpentadecanoic acid (BMIPP), has been reported to be reduced in patients on long-term hemodialysis and recovered by levocarnitine therapy [102]. Tetradecyl glycidic acid (TDGA) impairs mitochondrial carnitine acyltransferase 1, and its administration induces left ventricular hypertrophy with enhanced lipid accumulation in the rat heart [111]. BMIPP washout from the myocardium is also decreased after TDGA administration [114]. Therefore, carnitine deficiency interrupts fatty acid metabolism in the myocardium and leads to myocardial lipid storage in patients on hemodialysis. A decreased free carnitine concentration results in disrupted fatty acid transfer into mitochondria; subsequently, the accumulation of acylcarnitine in the mitochondria disrupts carnitine-related enzymes involved in ATP production and transportation. Accordingly, levocarnitine treatment-induced amelioration of myocardial fatty acid metabolism and the acyl/free carnitine ratio might help to improve LVEF and decrease the LVMI.

Although levocarnitine treatment may be beneficial in improving LVEF, it is important to determine whether the treatment reduces cardiac events, hospitalizations, and mortality. To clarify the association between levocarnitine treatment and the hospitalization rate and number of hospital days, a large cohort study was conducted in patients on hemodialysis [115]. This study enrolled 2967 patients who were treated with levocarnitine for at least 3 months and had a 3-month or longer pre-levocarnitine period. The adjusted relative risk
of hospitalization significantly decreased during the levocarnitine treatment compared with the rate before the initiation of levocarnitine treatment. Compared with the baseline hospitalization rate before levocarnitine treatment initiation, levocarnitine decreased the hospitalization rate by 34% and 58% at 6–9 months and 15–18 months, respectively. Furthermore, patients with cardiovascular disease, anemia, and hypoalbuminemia prior to levocarnitine treatment benefited most from levocarnitine treatment, in whom it was associated with fewer hospitalizations [115].

Uremia alters both carnitine and fatty acid metabolism. The combination of uremia-induced left ventricular hypertrophy and carnitine deficiency impairs myocardial metabolism and cardiac function. Levocarnitine treatment might partly improve the uremic hypertrophy, besides augmenting the metabolism. Additional large-scale clinical studies must be performed to clarify whether levocarnitine treatment ameliorates cardiovascular mortality in patients on dialysis.

8. Muscle Symptoms and Quality of Life

Sarcopenia and muscle weakness are frequent in patients with chronic kidney disease. Sarcopenia is caused by the aggravation of some physiological systems and is associated with aging. Decreased muscle strength and skeletal muscle mass are related to physical function [116,117]. In the general population, sarcopenia has been linked to adverse clinical outcomes, such as mortality, disability, hospitalization, falls, decreased quality of life, and need for long-term care [116,117]. Sarcopenia has also been associated with negative outcomes in patients with end-stage kidney disease or on dialysis [118–121]. Generally, physical activity falls with age in not only the general population, but also among patients with chronic kidney disease [122]. Patients on dialysis with decreased physical function have been found to have higher mortality than those with better physical function [123]. Although the clinical importance of sarcopenia is recognized, there are no clear intervention methods for the dialysis population. The pathophysiology of this syndrome is believed to be associated with amino acid deficiency, including that of carnitine.

In addition to sarcopenia, both inflammation and PEW are significant predictors of mortality in patients receiving dialysis therapy [22–24]. A recent meta-analysis reported a 28–50% prevalence of PEW or frailty in patients receiving dialysis [124]. Another report revealed that 30% of dialysis patients had mild or moderate malnutrition and that 6–8% of patients had severe malnutrition [125–127]. Although three pathophysiologies—sarcopenia, frailty, and PEW—are distinguished, they share some components that are associated with hospitalization and mortality. In particular, malnutrition and chronic inflammation complicated with sarcopenia are important predictors of clinical outcomes in patients on hemodialysis [128,129]. In addition, elevated proinflammatory cytokine levels stimulate protein catabolism through the ubiquitin–proteasome pathway, leading to muscle weakness or wasting [130]. The production of inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, can be decreased by levocarnitine treatment [131–133].

Levocarnitine corrects insufficient energy supplies at the cellular level, alleviates long-chain fatty acid transport into mitochondria, and accelerates the removal of short- and medium-chain fatty acids stored during metabolism. Therefore, levocarnitine treatment may have beneficial effects on muscle wasting because fatty acid is the main source of energy in skeletal muscle [134]. Levocarnitine may increase the β-oxidation rate of fatty acids and maintain glycogen stores in skeletal muscle, thereby boosting ATP production [135]. Skeletal muscle function may be improved or maintained via levocarnitine-mediated augmentation of energy metabolism. Levocarnitine supplementation improves not only physical function but also mental and cognitive function in elderly individuals with normal kidney function [136,137]. Although levocarnitine supplementation fails to increase arm and leg muscle strength, it does increase the lean muscle mass of the arm and leg in elderly individuals with normal kidney function [138].

In Japan, patients receiving hemodialysis who had muscular symptoms such as cramps and asthenia have been found to have significantly lower endogenous serum carnitine
levels compared with non-symptomatic patients [139]. Thirty patients on hemodialysis with muscular weakness, fatigue, or cramps were treated with levocarnitine for 12 weeks. Some muscle symptoms were improved in approximately 70% of the patients [139]. Fourteen patients on hemodialysis were treated with levocarnitine in a double-blind crossover manner to investigate carnitine levels in muscle and serum before and after 2 months of levocarnitine treatment. Although levocarnitine treatment ameliorated symptoms such as asthenia and cramps occurring during hemodialysis, these symptoms worsened during the washout period (i.e., after levocarnitine treatment was ceased) [140]. In addition, to evaluate the efficacy of levocarnitine for muscle function, a two-way parallel controlled trial was conducted for 6 months [141]. Muscle strength was significantly improved in four of the seven patients in the levocarnitine group at the study end, whereas none of the seven controls showed a significant improvement. Thereafter, all 14 patients were treated with levocarnitine for 10 months, with muscle strength increased in nine of the 14 patients. We previously conducted a randomized control trial of 91 hemodialysis patients who had lower serum carnitine levels [142]. The participants were randomly assigned to receive intravenous levocarnitine treatment (levocarnitine group) or no treatment (control group) for 12 months. Clinical dry weight, body mass index, and serum albumin levels fell significantly in the control group. However, there were no such results in the levocarnitine group. In addition, there were significant differences in the percent changes in arm muscle area, hand grip strength, and lean body mass after 12 months between the two groups [142]. Levocarnitine treatment was beneficial in patients on dialysis, particularly in elderly patients or those with diabetes, because it was able to maintain lean body mass and muscle function.

In addition to muscle and dialytic symptoms in patients on dialysis, a significant association has been reported between the acyl/free carnitine ratio and the physical component of the 36-Item Short Form Survey (SF-36) in men. Moreover, levocarnitine treatment improves SF-36 scores compared with baseline [68]. Furthermore, to evaluate health-related quality of life from the perspective of patients on dialysis, the SF-36 score was measured. Symptoms during hemodialysis were evaluated at each dialysis session using additional questionnaires. Six months of oral levocarnitine therapy boosted general health and physical function [143]. The efficacy of levocarnitine treatment for dialysis patients in terms of muscle symptoms, physical activities, and quality of life is summarized in Table 3 [49,50,83,84,87,100,139–147].

A meta-analysis failed to identify the clinical significance of levocarnitine treatment of intradialytic hypotension and muscle function [148]. However, some major limitations were noted, such as the small number of patients in many of the studies and a low associated statistical power. Furthermore, the definitions of dialysis-related hypotension and muscle cramps were not unified. To confirm the clinical efficacy of levocarnitine treatment of intradialytic hypotension and muscle cramps, additional adequately sized randomized clinical studies are required in this population.

**Table 3.** Studies of the effect of levocarnitine on muscle symptoms and quality of life in dialysis patients.

| Ref | Study Design | Subjects | Dose and Route | Treatment Duration | Findings ± |
|-----|--------------|----------|----------------|-------------------|------------|
| [101]| Double-blind, cross-over, placebo-controlled | 18 HD patients | 990 mg/day, PO Placebo, PO | 2 mo | ↓ Cramps (p < 0.001), ↓ Asthenia (p < 0.001), ↓ Dyspnea (p < 0.001) |
| [140]| Double-blind, cross-over, placebo-controlled | 14 HD patients | 2 g/day, PO Placebo, PO | 2 mo | ↑ Exercise time (p = 0.01), ↓ Asthenia (p = 0.01), ↓ Muscle cramps (p = 0.01) |
| [50]| Two-way, parallel, double-blind | 14 HD patients | 2 g/Dx, IV Placebo, IV | 1.5 mo | No difference in muscular status (NS) |
| [144]| One-way, open-label | 6 HD patients | 2 g/day, PO | 1.5 mo | No difference in muscular function (NS) |
| [49]| Two-way, parallel, double-blind | 38 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 6 mo | ↓ Cramps (p = 0.02), ↓ Asthenia postdialysis (p = 0.04), ↑ O₂ consumption (p = 0.03) |
| [145]| One-way, open-label | 26 HD patients | 2 g/dialysate (n = 11), 2 g/day PO (n = 6), 2 g/Dx IV (n = 9) | 6 mo | ↓ Cramps (p = 0.04), ↓ Pain (p = 0.04), ↓ Isometric force (p = 0.001) |
9. Plasma Lipid Profiles and Inflammation-Related Parameters

Patients on dialysis exhibit a higher risk of atherosclerotic cardiovascular disease. Observational studies of dialysis patients have revealed a close relationship of dyslipidemia (e.g., elevated low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, elevated triglyceride, and/or elevated non-HDL cholesterol) with both atherosclerosis severity and risk of coronary artery disease [149,150]. Furthermore, dyslipidemia has a closer association with ischemic heart disease than with cerebrovascular disease. Several factors, including decreased activities of lipoprotein lipase and lecithin cholesterol acyltransferase (LCAT) and decreased hepatic lipase levels, promote dyslipidemia development in chronic kidney disease patients. The 2003 guidelines of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative recommended a triglyceride level < 150 mg/dL, an LDL cholesterol level < 100 mg/dL, and a non-HDL cholesterol level < 130 mg/dL [151].

Levcarnitine treatment may be beneficial for dyslipidemia in dialysis patients because carnitine increases the transport of free fatty acids into mitochondria and decreases the availability of free fatty acids for triglyceride synthesis. Decreased carnitine levels may be a possible contributing factor to hyperlipidemia in the dialysis population. In addition, carnitine treatment may improve dyslipidemia because carnitine stimulates the β-oxidation of long-chain fatty acids and decreases the ester bound to glycerol, even in dialysis patients [100].

Inflammation is highly prevalent in patients on hemodialysis, and elevated C-reactive protein is a predictor of all-cause and cardiovascular mortality in this population [152–156]. Inflammation can induce hepcidin overexpression and thus cause or aggravate absolute iron deficiency by inhibiting iron enteral absorption and functional iron deficiency through decreased release of stored iron from the liver and reticuloendothelial system [157]. The antioxidant and anti-inflammatory effects of levcarnitine have been described in vitro and in vivo [158,159]. Levcarnitine has also been shown to impact insulin sensitivity and protein catabolism; it has been proposed that increased levcarnitine is likely to improve nutritional status by reducing insulin resistance [160]. In one study, when patients

| Ref | Study Design | Subjects | Dose and Route | Treatment Duration | Findings * |
|-----|--------------|----------|----------------|-------------------|-----------|
| [146] | One-way, open-label | 6 HD patients | 2 g/day, PO | 2 mo | ↓ Cramps (p = 0.011), ↓ Weakness (p = 0.001), ↓ Fatigue (p = 0.05) |
| [139] | Two-way, parallel, open-label | 30 HD patients | 500 mg/day, PO | 2 mo | ↓ Weakness (p < 0.005), ↓ Fatigue (p < 0.005), ↓ Cramps/aches (p < 0.05) |
| [147] | Two-way, parallel, double-blind | 9 HD patients | 10 mg/kg per Dx, IV | 4 mo | No difference in muscle cramps, uremic pruritus, physical strength, and general well-being |
| [143] | Two-way, parallel, double-blind | 101 HD patients | 1 g/day, PO | 6 mo | ↑ SF-36 scores T2: +18.3 ± 6.4 (NS) |
| [141] | Two-way, double-blind | 7 HD patients | 2 g/Dx, IV for 6 mo, then 1 g/Dx, IV for 10 mo | 16 mo | ↑ Daily activity score T2: 3.5; T3: 2.0 (NS) |
| [84] | Double-blind, cross-over, placebo-controlled | 16 HD patients | 20 mg/kg per Dx, IV | 3 mo | No changes in muscle parameters and QOL scores |
| [86] | Two-way, parallel, double-blind | 13 HD patients | 20 mg/kg per Dx, IV | 6 mo | ↑ SF-36 scores T2: 33.9 ± 1.9; T3: 43.2 ± 3.0 (p < 0.05) |
| [83] | Two-way, parallel, single-blind | 10 HD patients | 20 mg/kg per Dx, IV | 2 mo | ↑ SF-36 scores T2: +18.3 ± 12.7 vs. −6.4 ± 16.4 (p = 0.001) |
| [142] | Two-way, parallel, open-label | 42 HD patients | 1 g/Dx, IV | 12 mo | ↑ AMA: +2.11% vs. −4.11% (p < 0.01); ↑ LBM 0.70% vs. −2.22% (p < 0.001); ↑ HGS: +1.58% vs. −2.69% (p < 0.05) |
| [147] | Two-way, parallel, open-label | 18 PD patients | 600 mg/day, PO for 12 mo | 24 mo | ↓ Muscle spasms in patients who had undergone HD for >4 years (p-value not reported) |

AMA, arm muscle area; Dx, dialysis session; HD, hemodialysis; HGS, hand grip strength; LBM, lean body mass; IV, intravenous injection; mo, months; NS, not significant; PD, peritoneal dialysis; PO, per oral; QOL, quality of life; Ref, reference; SF-36, 36-Item Short Form Survey.

* The findings showed no difference (→), or decrease (↓) or increase (↑).
were divided into two groups according to albumin level (<3.5 g/dL or \geq3.5 g/dL) before levocarnitine treatment, the higher albumin group displayed a significant increase in the prealbumin level and an improved malnutrition–inflammation score (MIS) [161]. Some clinical trials have indicated that levocarnitine supplementation can improve nutritional status in hemodialysis patients. It has been reported that oral levocarnitine supplementation tended to lower graft loss within 3 months after kidney transplantation, which might be related to the antioxidant effects of carnitine [162]. Several studies have examined the effects of levocarnitine treatment on plasma lipid levels and inflammation-related parameters in patients on maintenance dialysis. These studies are listed in Table 4 [48,80,85,86,88,90,92,131–133,161,163–173].

Multiple studies have shown that levocarnitine treatment has beneficial effects on dyslipidemia. Nonetheless, conflicting results were reported in some studies. A meta-analysis failed to identify beneficial effects of levocarnitine treatment on dyslipidemia in patients on dialysis [75,174]. However, another meta-analysis reported that levocarnitine administration decreased LDL-cholesterol levels in a subgroup of patients intravenously administered levocarnitine and with a longer interventional duration, whereas it was not associated with a reduction in total cholesterol and triglycerides levels or an increase in HDL-cholesterol levels [175]. Furthermore, meta-analyses demonstrated that levocarnitine administration decreased serum C-reactive protein levels in both statistically significant and clinically relevant manners [176] and that it increased total protein, albumin, transferrin, and prealbumin levels [177]. However, there were several limitations in previous studies, including differences among studies in plasma lipid levels and serum carnitine levels, levocarnitine dosage, administration methods, and study durations. Furthermore, research is required into specific dialysis populations with dyslipidemia, such as patients with low HDL cholesterol or high triglyceride levels.

### Table 4. Studies of the effect of levocarnitine on lipid profiles and inflammatory-related parameters in dialysis patients.

| Ref | Study Design | Subjects | Dose and Route | Treatment Duration | Findings * |
|-----|--------------|----------|----------------|-------------------|-----------|
| [163] | Two-way, parallel, open-label | 8 HD patients | 0.5 g/Dx IV for 2 mo, then 1.0 g/Dx IV for 1.5 mo Placebo, IV | 3.5 mo | ↓ TG T<sub>0</sub>: 336 ± 56 mg/dL; T<sub>1.5</sub>: 244 ± 82 mg/dL (p < 0.05) → TG T<sub>3.5</sub>: 329 ± 72 mg/dL; T<sub>1.5</sub>: 444 ± 82 mg/dL (NS) |
| [164] | Two-way, parallel, open-label | 11 HD patients | 1 g/Dx, IV for 1 mo then 2 g/Dx dialysate for 3 mo Placebo, PO for 1 mo then 4 g/Dx dialysate for 3 mo | 4 mo | ↓ TG, ↑ HDL (p-values not reported) |
| [165] | Two-way, crossover, double-blind | 9 HD patients | 1 g t.i.d. PO then placebo for 5 wk each Placebo then 1 g t.i.d. PO Placebo for 5 wk each | 5 wk | No difference in plasma lipid levels (NS) |
| [48] | Two-way, parallel, double-blind | 38 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 6 mo | No difference in plasma lipid levels (NS) |
| [166] | Two-way, parallel, double-blind | 15 HD patients | 1–1.5 g/Dx, IV Placebo, PO | 2 mo | No difference in plasma lipid levels (NS) |
| [167] | Two-way, parallel, double-blind | 11 HD patients | 100 µmol/L dialysate Placebo | 6 mo | No difference in plasma lipid levels (NS) |
| [168] | Two-way, parallel, open-label | 6 HD patients | 900 mg t.i.d. PO Placebo | 1 mo | ↑ TG T<sub>0</sub>: 180 ± 66 mg/dL; T<sub>1</sub>: 219 ± 88 mg/dL (p < 0.05) → TG T<sub>2</sub>: 222 ± 35 mg/dL; T<sub>1</sub>: 222 ± 35 mg/dL (NS) |
| [131] | Two-way, parallel, open-label | 21 HD patients | 20 mg/kg per Dx, IV Placebo, IV | 6 mo | ↓ TG T<sub>0</sub>: 1.6 ± 0.6; T<sub>1</sub>: 1.5 ± 0.7 mmol/L (p = 0.001); ↑ TP T<sub>0</sub>: 6.4 ± 0.5; T<sub>1</sub>: 6.9 ± 0.5 g/dL (p < 0.001); ↑ Alb T<sub>0</sub>: 3.6 ± 0.3; T<sub>1</sub>: 4.1 ± 0.3 g/dL (p < 0.001); ↑ Albu T<sub>0</sub>: 1.2 ± 0.2; T<sub>1</sub>: 1.6 ± 0.4 g/L (p < 0.001); ↑ BMI T<sub>0</sub>: 23.4 ± 4.0; T<sub>1</sub>: 23.7 ± 4.0 (p < 0.001) → TG, TP, Alb, BMI (NS) |
| [132] | Two-way, parallel, double-blind | 20 HD patients | 1 g/Dx, IV Placebo, IV | 6 mo | ↓ CRP T<sub>0</sub>: 2.1 ± 0.6 mg/dL; T<sub>1</sub>: 0.67 ± 0.1 mg/dL (p = 0.02) → TC, HDL, LDL, TG (NS) → CRP, TC, HDL, LDL, TG (NS) |
| [88] | Two-way, parallel, double-blind | 24 HD patients | 1 g/day, PO Placebo, PO | 4 mo | ↓ TG T<sub>0</sub>: 166 ± 71 mg/dL; T<sub>1</sub>: 138 ± 54 mg/dL (p < 0.001); ↑ HDL T<sub>0</sub>: 30 ± 7 mg/dL; T<sub>1</sub>: 34 ± 7 mg/dL (p < 0.001); ↑ TC T<sub>0</sub>: 142 ± 58 mg/dL; T<sub>1</sub>: 151 ± 48 mg/dL (p < 0.029) → HDL |
| [92] | Two-way, parallel, double-blind | 13 HD patients | 1 g/Dx, IV Placebo, IV | 6 mo | → TC, HDL, TG (NS) → TC, HDL, TG (NS) |
Table 4. Cont.

| Ref | Study Design | Subjects | Dose and Route | Treatment Duration | Findings * |
|-----|--------------|----------|----------------|--------------------|------------|
| [169] | Two-way, parallel, double-blind | 32 HD patients | 600 mg/Dx, IV | 12 mo | ↑ MDA T<sub>0</sub>: 2.2 ± 0.7 μmol/mL; T<sub>3</sub>: 1.5 ± 0.7 μmol/mL (p < 0.001); ↑ ABI T<sub>0</sub>: 0.71 ± 0.06; T<sub>3</sub>: 0.78 ± 0.08 (p < 0.001); ↑ MDA T<sub>0</sub>: 1.94 ± 0.5 μmol/mL; T<sub>3</sub>: 1.9 ± 0.7 μmol/mL (p < 0.001); ↑ ABI T<sub>0</sub>: 0.75 ± 0.08; T<sub>3</sub>: 0.72 ± 0.01 (p < 0.001) |
| [168] | Two-way, parallel, open-label | 20 HD patients | 1 g/Dx, twice a week, IV | 6 mo | ↑ TC (p < 0.001); ↑ HDL(p < 0.001), ↓ TG (p < 0.001) |
| [170] | Two-way, parallel, open-label | 18 HD patients | 1 g/Dx, PO | 3 mo | ↓ TLB T<sub>0</sub>: 190 ± 69 mg/dL; T<sub>3</sub>: 179 ± 51 mg/dL (p < 0.05); ↓ LDL 119 ± 21 mg/dL; T<sub>3</sub>: 98 ± 19 mg/dL (p < 0.05); ↓ CRP T<sub>0</sub>: 20.8 ± 1.7 μM; T<sub>3</sub>: 16.5 ± 1.3 μM (p < 0.05) |
| [171] | Two-way, parallel, open-label | 18 HD patients | 1 g/Dx, PO | 3 mo | ↓ SAA T<sub>0</sub>: −32% (p < 0.001) |
| [172] | Two-way, parallel, open-label | 17 HD patients | 1 g/Dx, PO | 3 mo | ↓ SAA (NS) |
| [173] | Two-way, parallel, open-label | 20 HD patients | 1 g/Dx, PO | 2 mo | → Alb T<sub>0</sub>: 3.37 ± 0.40 g/dL; T<sub>3</sub>: 3.38 ± 0.43 g/dL (NS) |
| [180] | Two-way, parallel, double-blind | 48 HD patients | 20 mg/kg per Dx, IV | 6 mo | ↑ CRP T<sub>0</sub>: 1.8 ± 1.2 μg/L; T<sub>3</sub>: 1.2 ± 0.2 (p < 0.002), ↑ Alb T<sub>0</sub>: 3.6 ± 0.1 g/dL; T<sub>3</sub>: 3.9 ± 0.4 g/dL (p < 0.0001), ↑ BMI T<sub>0</sub>: 20.5 ± 0.1; T<sub>3</sub>: 21.2 ± 0.5 (p < 0.0001) |

ABI, ankle brachial index; Alb, albumin; BMI, body mass index; CRP, C-reactive protein; Dx, dialysis session; HD, hemodialysis; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; MDA, malondialdehyde; IV, intravenous injection; mo, months; NS, not significant; PO, per oral; Ref, reference; SAA, serum amyloid A; TC, total cholesterol; Tf, transferrin; TG, triglyceride; TP, total protein.

* The findings showed no difference (→), or decrease (↓) or increase (↑).

10. Conclusions

The number of patients being treated with dialysis therapy is increasing worldwide. Patients with end-stage kidney disease who are receiving dialysis therapy frequently experience carnitine system dysfunction. Carnitine deficiency and uremic syndrome complicate the already complex pathophysiology of patients on dialysis. Furthermore, a dysfunctional fatty acid metabolism induces surplus production of free radicals and undesired apoptosis. Regarding carnitine deficiency, levocarnitine treatment positively affects pathologic processes in patients on dialysis. There are four principal indications for levocarnitine treatment in dialysis patients with carnitine deficiency according to the American National Kidney Foundation: (1) ESA-resistant anemia that has not responded to the standard ESA dosage; (2) recurrent symptomatic hypotension during hemodialysis; (3) symptomatic cardiomyopathy or confirmed cardiomyopathy with reduced LVEF; and (4) fatigability and muscle weakness that undermine quality of life. However, there were some limitations in the previous studies regarding levocarnitine treatment in the dialysis population, including sample size, adequacy of study design, and definition of target diseases. Furthermore, research has not been able to identify a dose–response relationship and the optimal administration route for levocarnitine treatment. Therefore, additional adequately sized clinical trials are required to determine whether levocarnitine treatment improves survival in patients on dialysis.

Author Contributions: Conceptualization M.A. and T.M.; methodology, H.T.; software, M.A.; validation: H.T.; investigation, T.M. and H.T.; resources: M.A.; data curation, M.A. and T.M.; writing—original draft preparation, M.A.; writing—review and editing, H.T. and T.M.; visualization, M.A.;
supervision, M.A.; project administration, T.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: M.A. and T.M. chair courses endowed by Nikkiso Co., Ltd., NIPRO Corporation, Otsuka Pharmaceutical Co., Ltd., and Terumo Corporation. The other authors declare that they have no conflict of interest.

References

1. Golper, T.A.; Ahmad, S. L-carnitine administration to hemodialysis patients: Has it times come? Semin. Dial. 1992, 5, 94–98. [CrossRef]
2. Hiatt, W.R.; Koziol, B.J.; Shapiro, J.L.; Brass, E.P. Carnitine metabolism during exercise in patients on chronic hemodialysis. Kidney Int. 1992, 41, 1613–1619. [CrossRef] [PubMed]
3. Guarnieri, G.; Situlin, R.; Biolo, G. Carnitine metabolism in uremia. Am. J. Kidney Dis. 2001, 38, S3–S7. [CrossRef] [PubMed]
4. Evans, A.M.; Faull, R.; Fornasini, G.; Lemanowicz, E.F.; Longo, A.; Pace, S.; Nation, R.L. Pharmacokinetics of L-carnitine in patients with end-stage renal disease undergoing long-term hemodialysis. Clin. Pharmacol. Ther. 2000, 68, 238–249. [CrossRef] [PubMed]
5. Borum, P.R. Carnitine. Annu. Rev. Nutr. 1983, 3, 233–259. [CrossRef]
6. Moorthy, A.V.; Rosenblum, M.; Rajaram, R.; Shug, A.L. A comparison of plasma and muscle carnitine levels in patients on peritoneal or hemodialysis for chronic renal failure. Am. J. Nephrol. 1983, 3, 205–208. [CrossRef]
7. Rebouche, C.J.; Chenard, C.A. Metabolic fate of dietary carnitine in human adults: Identification and quantification of urinary and faecal metabolism. J. Nutr. 1991, 121, 539–546. [CrossRef]
8. Lopaschuk, G.D.; Belke, D.D.; Gamble, J.; Itoi, T.; Schönekess, B.O. Regulation of fatty acid oxidation in the mammalian heart in health and disease. Biochem. Biophys. Acta 1994, 1213, 263–276. [CrossRef]
9. Marzo, A.; Martelli, E.A.; Urso, R.; Rochetti, M.; Rizza, V.; Kelly, J.G. Metabolism and disposition of intravenously administered acetyl-L-carnitine in healthy volunteers. Eur. J. Clin. Pharmacol. 1989, 37, 59–63.
10. Matare, M.; Bellinghieri, G.; Costantino, G.; Santoro, D.; Calvani, M.; Savica, V. History of L-Carnitine: Implications for renal disease. J. Ren. Nutr. 2003, 13, 2–14. [CrossRef]
11. Tamai, I.; Ohashi, R.; Nezu, J.; Yabuuchi, H.; Oku, A.; Shimane, M.; Sai, Y.; Tsuji, A. Molecular and functional identification of sodium-dependent high affinity human carnitine transporter OCTN2. J. Biol. Chem. 1998, 273, 20378–20382. [CrossRef]
12. Tamai, I.; China, K.; Sai, Y.; Kobayashi, D.; Nezu, J.; Kawahara, E.; Tsuji, A. Na (+)-coupled transporter of L-carnitine and its subcellular localization in kidney. Biochim. Biophys. Acta 2001, 1512, 273–284. [CrossRef]
13. Koizumi, A.; Nozaki, J.; Ohura, T.; Kayo, T.; Wada, Y.; Nezu, J.; Ohashi, R.; Tamai, I.; Shoji, Y.; Takada, G.; et al. Genetic epidemiology of the carnitine transporter OCTN2 gene in a Japanese population and phenotypic characterization in Japanese pedigrees with primary systemic carnitine deficiency. Hum. Mol. Genet. 1999, 8, 2247–2254. [CrossRef] [PubMed]
14. Pande, S.V.; Murthy, M.S.R. Carnitine-acylcarnitine translocase deficiency: Implications in human pathology. Biochim. Biophys. Acta 1994, 1226, 269–276. [CrossRef]
15. McCurry, J.D.; Brown, N.F. The mitochondrial carnitine palmitoyltransferase system: From concept to molecular analysis. Eur. J. Biochem. 1997, 244, 1–14. [CrossRef]
16. Zammit, V.A. Carnitine acyltransferase: Functional significance of subcellular distribution and membrane topology. Prog. Lipid Res. 1999, 38, 199–244. [CrossRef]
17. Biber, L.L. Carnitine. Annu. Rev. Biochem. 1988, 57, 261–283. [CrossRef] [PubMed]
18. Shimabukuro, M.; Zhou, Y.T.; Levi, M.; Unger, R.H. Fatty acid-induced beta cell apoptosis: A link between obesity and diabetes. Proc. Natl. Acad. Sci. USA 1998, 95, 2498–2502. [CrossRef]
19. Winter, S.C.; Zorn, E.M.; Vance, W.H. Carnitine deficiency. Lancet 1990, 335, 981–982. [CrossRef]
20. Suzuki, Y.K.; Tokuyama, K.; Kinoshita, M. Urinary profile of L-Carnitine and its derivatives in starved normal persons and ACTH injected patients with myopathy. J. Nutr. Sci. Vitaminol. 1983, 29, 303–312. [CrossRef]
21. Kanda, E.; Kato, A.; Masakane, I.; Kanno, Y. A new nutritional risk index for predicting mortality in hemodialysis patients: Nationwide cohort study. PLoS ONE 2019, 14, e0214524. [CrossRef] [PubMed]
22. Kalantar-Zadeh, K.; Kopple, J.D.; Block, G.; Humphreys, M.H. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am. J. Kidney Dis. 2001, 38, 1251–1263. [CrossRef] [PubMed]
23. Fouque, D.; Kalantar-Zadeh, K.; Kopple, J.; Cano, N.; Chauveu, P.; Cuppari, L.; Franch, H.; Guarnieri, G.; Ikizler, T.A.; Kayser, G.; et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* 2008, 73, 391–398. [CrossRef] [PubMed]

24. Abe, M.; Kalantar-Zadeh, K. Haemodialysis-induced hypoglycaemia and glycaemic disarrays. *Nat. Rev. Nephrol.* 2015, 11, 302–313. [CrossRef]

25. Tein, I. Carnitine transport: Pathophysiology and metabolism of known molecular defects. *J. Inherit. Metab. Dis.* 2003, 26, 147–169. [CrossRef] [PubMed]

26. Kernber, J.; Hoppel, C. Genetic disorders of carnitine metabolism and their nutritional management. *Annu. Rev. Nutr.* 1998, 18, 179–206. [CrossRef]

27. Evans, A.M. Dialysis-related carnitine disorder and levocarnitine pharmacology. *Am. J. Kidney Dis.* 2003, 42 (Suppl. 4), S13–S26. [CrossRef]

28. Evans, A.M.; Fornaini, G. Pharmacokinetics of L-carnitine. *Clin. Pharm.* 2003, 42, 941–967. [CrossRef]

29. Japan Pediatric Society. Available online: http://www.jpeds.or.jp/modules/guidelines/index.php?option=com_content&id=2 (accessed on 21 September 2018).

30. Evans, A.M.; Faull, R.J.; Nation, R.L.; Prasad, S.; Elias, T.; Reuter, S.E.; Fornaini, G. Impact of haemodialysis on endogenous plasma and muscle carnitine levels in patients with end-stage renal disease. *Kidney Int.* 2004, 66, 1527–1534. [CrossRef] [PubMed]

31. Spagnoli, L.G.; Palmieri, G.; Mauriello, A.; Vacha, G.M.; D’Iddio, S.; Giorgelli, G.; Corsi, M. Morphometric evidence of the trophic effect of L-carnitine on human skeletal muscle. *Nutr. Res.* 1990, 15, 55–62. [CrossRef]

32. Hatanaka, Y.; Higuchi, T.; Akiya, Y.; Horikami, T.; Tei, R.; Furukawa, T.; Takashima, H.; Tomita, H.; Abe, M. Prevalence of carnitine deficiency and decreased carnitine levels in patients on hemodialysis. *Blood Purif.* 2019, 47, 1–7. [CrossRef] [PubMed]

33. Sotirakopoulos, N.; Athanasiou, G.; Tsitsios, T.; Mavromatidis, K. The influence of L-carnitine supplementation on hematocrit and hemoglobin levels in patients with end stage renal failure on CAPD. *Ren. Fail.* 2000, 24, 505–510. [CrossRef]

34. Grzegorzewska, A.E.; Mariak, I.; Dobrowolska-Zachwieja, A. Continuous ambulatory peritoneal dialysis (CAPD) adequacy influences serum free carnitine level. *Int. Urol. Nephrol.* 1999, 31, 533–540. [CrossRef]

35. Shimizu, S.; Takahama, H.; Tei, R.; Furukawa, T.; Okamura, M.; Kitai, M.; Nagura, C.; Maruyama, T.; Higuchi, T.; Abe, M. Prevalence of carnitine deficiency and decreased carnitine levels in patients on peritoneal dialysis. *Nutrients* 2019, 11, 2645. [CrossRef]

36. Schreiber, B. Levocarnitine and dialysis: A review. *Nutr. Clin. Pract.* 2005, 20, 218–243. [CrossRef] [PubMed]

37. Reuter, S.E.; Evans, A.M.; Faull, R.J.; Chace, D.H.; Fornaini, G. Impact of haemodialysis on individual endogenous plasma acylcarnitine concentrations in end-stage renal disease. *Ann. Clin. Biochem.* 2005, 42, 387–393. [CrossRef]

38. Marzo, A.; Arrigoni Martelli, E.; Mancinelli, A.; Cardace, G.; Corbelletta, C.; Bassani, E.; Solbiati, M. Protein binding of L-carnitine family components. *Eur. J. Drug Metab. Pharmacokinet.* 1991, 3, 364–368.

39. Debska-Sliżen, A.; Kawecka, A.; Wojnarowski, K.; Pras, J.; Malgorzewicz, S.; Kunicka, D.; Zdrojewski, Z.; Walęsiak, S.; Lipinski, J.; Rutkowski, B. Correlation between plasma carnitine, muscle carnitine and glycogen levels in maintenance hemodialysis patients. *Int. J. Artif. Organs* 2000, 23, 90–96. [CrossRef] [PubMed]

40. Penne, E.L.; van der Weerd, N.C.; Blankstijn, P.J.; van den Dorpel, M.A.; Grooteman, M.P.; Nubé, M.J.; Ter Wee, P.M.; Lèvesque, R.; Bots, M.L.; CONTRAST investigators. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. *Clin. J. Am. Soc. Nephrol.* 2010, 5, 80–86. [CrossRef]

41. Kamei, Y.; Kamei, D.; Tsuchiya, K.; Mineshima, M.; Nitta, K. Association between 4-year all-cause mortality and carnitine profile in maintenance hemodialysis patients. *PLoS ONE* 2018, 13, e0201591. [CrossRef] [PubMed]

42. Masakane, I.; Kikuchi, K.; Kawanishi, H. Evidence for the clinical advantages of predilution on-line hemodiafiltration. *Contrib. Nephrol.* 2017, 189, 17–23.

43. Penne, E.L.; van der Weerd, N.C.; Blankstijn, P.J.; van den Dorpel, M.A.; Grooteman, M.P.; Nubé, M.J.; Ter Wee, P.M.; Lèvesque, R.; Bots, M.L.; CONTRAST investigators. Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. *Clin. J. Am. Soc. Nephrol.* 2010, 5, 80–86. [CrossRef]

44. Maduell, F.; Moreso, F.; Pons, M.; Ramos, R.; Mora-Macià, J.; Carreras, J.; Soler, J.; Torres, F.; Campistol, J.M.; Martinez-Castelao, A.; et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J. Am. Soc. Nephrol.* 2013, 24, 487–497. [CrossRef] [PubMed]

45. Constantin-Teodosiu, D.; Kirby, D.P.; Short, A.H.; Burden, R.P.; Morgan, A.G.; Greenha, P.L. Free and esterified carnitine in continuous ambulatory peritoneal dialysis patients. *Kidney Int.* 1996, 49, 158–162. [CrossRef] [PubMed]

46. Sotirakopoulos, N.; Athanasiou, G.; Tsitsios, T.; Mavromatidis, K. The influence of L-carnitine supplementation on hematocrit and hemoglobin levels in patients with end stage renal failure on CAPD. *Ren. Fail.* 2002, 24, 505–510. [CrossRef]

47. Grzegorzewska, A.E.; Mariak, I.; Dobrowolska-Zachwieja, A. Continuous ambulatory peritoneal dialysis (CAPD) adequacy influences serum free carnitine level. *Int. Urol. Nephrol.* 1999, 31, 533–540. [CrossRef]

48. Shimizu, S.; Takahama, H.; Tei, R.; Furukawa, T.; Okamura, M.; Kitai, M.; Nagura, C.; Maruyama, T.; Higuchi, T.; Abe, M. Prevalence of carnitine deficiency and decreased carnitine levels in patients on peritoneal dialysis. *Nutrients* 2019, 11, 2645. [CrossRef] [PubMed]

49. Schreiber, B. Levocarnitine and dialysis: A review. *Nutr. Clin. Pract.* 2005, 20, 218–243. [CrossRef] [PubMed]

50. Brass, E.P. Pharmacokinetic considerations for the therapeutic use of carnitine in hemodialysis patients. *Clin. Ther.* 1995, 17, 176–185. [CrossRef] [PubMed]

51. Golper, T.A.; Wolfson, M.; Ahmad, S.; Hirschberg, R.; Kurtin, P.; Katz, L.A.; Nicora, R.; Ashbrook, D.; Kopple, J.D. Multicenter trial of L-carnitine in maintenance dialysis patients. I. Carnitine concentrations and lipid effects. *Kidney Int.* 1990, 38, 904–911. [CrossRef] [PubMed]
49. Ahmad, S.; Robertson, H.T.; Golper, T.A.; Wolfson, M.; Kurtin, P.; Katz, L.A.; Hirschberg, R.; Nicora, R.; Ashbrook, D.W.; Koppel, J.D. Multicenter trial of L-carnitine in maintenance hemodialysis patients. II. Clinical and biochemical effects. Kidney Int. 1990, 38, 912–918. [CrossRef]

50. Fagher, B.; Cederblad, G.; Eriksson, M.; Monti, M.; Moritz, U.; Nilsson-Ehle, P.; Thysell, H. L-carnitine and haemodialysis: Double blind study on muscle function and metabolism and peripheral nerve function. Scand. J. Clin. Lab. Investog. 1985, 45, 169–178. [CrossRef]

51. Sahajwalla, C.G.; Helton, E.D.; Purich, E.D.; Hoppe, C.L.; Cabana, B.E. Comparison of L-carnitine pharmacokinetics with and without baseline correction following administration of single 20-mg/kg intravenous dose. J. Pharm. Sci. 1995, 84, 634–639. [CrossRef]

52. Segre, G.; Bianchi, E.; Corsi, M.; D’Iddio, S.; Ghirardi, O.; Macciari, F. Plasma and urine pharmacokinetics of free and of short-chain carnitine after administration of carnitine in man. Arzneimittelforschung 1988, 38, 1830–1834.

53. Koeth, R.A.; Wang, Z.; Levinson, B.S.; Buffa, J.A.; Org, E.; Sheehy, B.T.; Britt, E.B.; Fu, X.; Wu, Y.; Li, L.; et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat. Med. 2013, 19, 576–585. [CrossRef] [PubMed]

54. Wang, Z.; Klipfell, E.; Bennett, B.J.; Koeth, R.; Levinson, B.S.; Dugar, B.; Feldstein, A.E.; Britt, E.B.; Fu, X.; Chung, Y.M.; et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011, 472, 57–63. [CrossRef]

55. Lang, D.H.; Yeung, C.K.; Peter, R.M.; Ibarra, C.; Gasser, R.; Itagaki, K.; Philpot, R.M.; Rettie, A.E. Isoform specificity of trimethylamine N-oxygenation by human flavin-containing monoxygenase (FMO4) and P450 enzymes: Selective catalysis by FMO3. Biochem. Pharmacol. 1998, 56, 1005–1012. [CrossRef]

56. Al-Waiz, M.; Mitchell, S.C.; Idle, J.R.; Smith, R.L. The metabolism of 14C-labelled trimethylamine and its N-oxide in man. Xenobiotica 1987, 17, 551–558. [CrossRef] [PubMed]

57. Mitchell, S.C.; Zhang, A.Q.; Noblet, J.M.; Gillespie, S.; Jones, N.; Smith, R.L. Metabolic disposition of [14C]-trimethylamine N-oxide in rat: Variation with dose and route of administration. Xenobiotica 1997, 27, 1187–1197. [CrossRef] [PubMed]

58. Wilson, W.H.; Wang, Z.; Kennedy, D.J.; Wu, Y.; Buffa, J.A.; Agatia-Boyle, B.; Li, X.S.; Levinson, B.S.; Hazen, S.L. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ. Res. 2015, 116, 448–455.

59. Stubbs, J.R.; House, J.A.; Ocque, A.J.; Zhang, S.; Johnson, C.; Kimber, C.; Schmidt, K.; Gupta, A.; Wetmore, J.B.; Nolin, T.D.; et al. Serum trimethylamine-N-oxide is elevated in CKD and correlates with coronary atherosclerosis burden. J. Am. Soc. Nephrol. 2016, 27, 305–313. [CrossRef]

60. Eknoyan, G.; Latos, D.L.; Lindberg, J. Practice recommendations for the use of L-carnitine in dialysis-related carnitine disorder. National Kidney Foundation Carnitine Consensus Conference. Am. J. Kidney Dis. 2003, 41, 868–876. [CrossRef]

61. Parfrey, P.S.; Foley, R.N.; Wittreich, B.H.; Sullivan, D.J.; Zagari, M.J.; Frei, D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J. Am. Soc. Nephrol. 2005, 16, 2180–2189. [PubMed]

62. Palmer, S.C.; Navaneethan, S.D.; Craig, J.C.; Johnson, D.W.; Tonelli, M.; Garg, A.X.; Pellegrini, F.; Ravani, P.; Jardine, M.; Perkovic, V.; et al. Meta-analysis: Erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann. Intern. Med. 2010, 153, 23–33. [CrossRef] [PubMed]

63. Zhang, Y.; Thamer, M.; Stefanik, K.; Kaufman, J.; Cotter, D.J. Epoetin requirements predict mortality in hemodialysis patients. Am. J. Kidney Dis. 2004, 44, 866–876. [CrossRef]

64. Gunnell, J.; Yeun, J.Y.; Depner, T.A.; Kaysen, G.A. Acute-phase response predicts erythropoietin resistance in hemodialysis and peritoneal dialysis patients. Am. J. Kidney Dis. 1999, 33, 63–72. [CrossRef]

65. Yamamoto, H.; Nishi, S.; Tomo, T.; Masakane, I.; Saito, K.; Nangaku, M.; Hattori, M.; Suzuki, T.; Morita, S.; Ashida, A.; et al. 2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in Chronic Kidney Disease. Ren. Replace. Ther. 2017, 3, 36. [CrossRef]

66. Kooistra, M.P.; Struyvenberg, A.; Vanes, A. The response to recombinant human erythropoietin in patients with the anemia of end-stage renal disease is correlated with serum carnitine levels. Nephron 1991, 57, 127–128. [CrossRef]

67. Matsumura, M.; Hatakeyama, S.; Kon, I.; Mabuchi, H.; Muramoto, H. Correlation between serum carnitine levels and erythrocyte osmotic fragility in hemodialysis patients. Nephron 1996, 72, 574–578. [CrossRef]

68. Steiber, A.L.; Weatherspoon, L.J.; Spry, L.; Davis, A.T. Serum carnitine concentrations correlated to clinical outcome parameters in chronic hemodialysis patients. Clin. Nutr. 2004, 23, 27–34. [CrossRef]

69. Kletzmayr, J.; Mayer, G.; Legenstein, E.; Heinz-Peer, G.; Leitha, T.; Hörl, W.H.; Kovarik, J. Anemia and carnitine supplementation in hemodialyzed patients. Kidney Int. Suppl. 1999, 55, S93–S106. [CrossRef]

70. Caruso, U.; Leone, L.; Cravotto, E.; Nava, D. Effects of L-carnitine on anemia in aged hemodialysis patients treated with recombinant human erythropoietin: A pilot study. Dial. Transplant. 1998, 27, 498–506.

71. de los Reyes, B.; Perez-García, R.; Liras, A.; Arenas, J. Reduced carnitine palmitoyl transferase activity and altered acyl-trafficking in red blood cells from hemodialysis patients. Biochim. Biophys. Acta 1996, 1315, 37–39. [CrossRef]

72. Arduini, A.; Rossi, M.; Mancinelli, G.; Belfiglio, M.; Scurti, R.; Radatti, G.; Shoheif, S.B. Effect of L-carnitine and acetyl-L-carnitine on the human erythrocyte membrane stability and deformability. Life Sci. 1990, 47, 2395–2400. [CrossRef]
74. Hörl, W.H. Is there a role for adjuvant therapy in patients being treated with epoetin? *Nephrol. Dial. Transplant.* **1999**, *14*, 50–60. [CrossRef]
75. Hurot, J.M.; Cuchernet, M.; Haugh, M.; Fouque, D. Effects of L-carnitine supplementation in maintenance hemodialysis patients: A systematic review. *J. Am. Soc. Nephrol.* **2002**, *13*, 708–714.
76. Zhu, Y.; Xue, C.; Ou, J.; Xie, Z.; Deng, J. Effect of L-carnitine supplementation on renal anaemia in patients on hemodialysis: A meta-analysis. *Int. Urol. Nephrol.* **2021**, [CrossRef] [PubMed]
77. Arduini, A.; Bonomini, M.; Clutterbuck, E.J.; Laffan, M.A.; Pusey, C.D. Effect of L-carnitine administration on erythrocyte survival in haemodialysis patients. *Nephrol. Dial. Transplant.* **2006**, *21*, 2671–2672. [CrossRef] [PubMed]
78. Matsumoto, Y.; Amano, I.; Hirose, S.; Tsutara, Y.; Hara, S.; Murata, M.; Imai, T. Effects of L-carnitine supplementation on renal anaemia in poor responders to erythropoietin. *Blood Purif.* **2001**, *19*, 24–32. [CrossRef] [PubMed]
79. Bräss, E.P.; Adler, S.; Sietsema, K.E.; Haß, W.R.; Orlando, A.M.; Amato, A. Intravenous L-carnitine increases plasma carnitine, reduces fatigue, and may preserve exercise capacity in haemodialysis patients. *Am. J. Kidney Dis.* **2001**, *37*, 1018–1028. [CrossRef]
80. Savica, V.; Santoro, D.; Mazzaglia, G.; Ciolino, F.; Monardo, P.; Calvani, M.; Bellinghieri, G.; Kopple, J.D. L-carnitine infusions may suppress serum C-reactive protein and improve nutritional status in maintenance haemodialysis patients. *J. Ren. Nutr.* **2005**, *15*, 225–230. [CrossRef] [PubMed]
81. Cui, H.X.; Wu, E.L. Effect of levocarnitine/iron saccharate combination on renal anaemia and oxidative stress in patients undergoing haemodialysis. *Trop. J. Pharm. Res.* **2016**, *15*, 2269–2274. [CrossRef]
82. Mitwalli, A.H.; Al-Wakeel, J.S.; Alam, A.; Tarif, N.; Abu-Aisha, H.; Rashed, M.; Al Nahed, N. L-carnitine supplementation in haemodialysis patients. *Saudi J. Kidney Dis. Transplant.* **2005**, *16*, 17–22.
83. Rathod, R.; Naik, M.S.; Khandelwal, P.N.; Kulkarni, S.G.; Gade, P.R.; Siddiqui, S. Results of a single blind, randomized, placebo-controlled clinical trial to study the effect of intravenous L-carnitine supplementation on health-related quality of life in Indian patients on maintenance haemodialysis. *Indian J. Med. Sci.* **2006**, *60*, 143–153.
84. Semeniuk, J.; Shalansky, K.F.; Taylor, N.; Jastrzebski, J.; Cameron, E.C. Evaluation of the effect of intravenous L-carnitine on quality of life in chronic haemodialysis patients. *Clin. Nephrol.* **2000**, *54*, 470–477.
85. Singh, H.; Jain, D.; Bhaduri, G.; Gupta, N.; Sangwan, R. Study on effects of L-carnitine supplementation on anaemia with erythropoietin hypersensitivity and lipid profile in chronic kidney disease patients on maintenance haemodialysis. *Indian J. Basic Appl. Med. Res.* **2020**, *9*, 224–232.
86. Fu, R.G.; Wang, L.; Zhou, J.P.; Ma, F.; Liu, X.D.; Ge, H.; Zhang, J. The effect of levocarnitine on nutritional status and lipid metabolism during long-term maintenance haemodialysis. *Acad. J. Xi’an Jiaotong Univ.* **2010**, *22*, 203–207.
87. Kuwasawa-Iwasaki, M.; Io, H.; Muto, M.; Ichikawa, S.; Wakabayashi, K.; Kanda, R.; Nakata, J.; Nohara, N.; Tomino, Y.; Suzuki Y. Effects of L-carnitine supplementation in patients receiving erythropoiesis or peritoneal dialysis. *Nutrients* **2020**, *12*, 3371. [CrossRef] [PubMed]
88. Emami Naini, A.; Moradi, M.; Mortazavi, M.; Amini Harandi, A.; Hadizadeh, M.; Shirani, F.; Basir Ghafoori, H.; Emami Naini, P. Effects of oral L-carnitine supplementation on lipid profile in chronic kidney disease patients on maintenance haemodialysis. *Clin. Nephrol.* **2016**, *85*, 199–208. [CrossRef] [PubMed]
89. Matsumoto, Y.; Amano, I.; Hirose, S.; Tsutara, Y.; Hara, S.; Murata, M.; Imai, T. Effects of L-carnitine supplementation on urinary anaemia in poor responders to erythropoietin. *Blood Purif.* **2001**, *19*, 24–32. [CrossRef] [PubMed]
90. Vaux, E.C.; Taylor, D.J.; Altmann, P.; Rajagopalan, B.; Graham, K.; Cooper, R.; Bonomo, Y.; Styles, P. Effects of carnitine supplementation on muscle metabolism by the use of magnetic resonance spectroscopy and near-infrared spectroscopy in end-stage renal disease. *J. Nutr. Metab.* **2012**, *510483*. [CrossRef]
91. Mercadal, L.; Coudert, M.; Prié, D. Effects of L-carnitine on mineral metabolism in the multicentre, randomized, double blind, placebo-controlled CARNIDIAL trial. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 1836–1842. [CrossRef]
92. Mercadal, L.; Tézenas du Montcel, S.; Chonchol, M.B.; Debure, A.; Depreneuf, H.; Fumeron, C.; Servais, A.; Bassiliös, N.; et al. L-carnitine treatment in incident haemodialysis patients: The multicenter, randomized, doubleblind, placebo-controlled CARNIDIAL trial. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 1836–1842. [CrossRef]
93. Steiber, A.L.; Davis, A.T.; Spry, L.; Strong, J.; Buss, M.L.; Ratkiewicz, M.M.; Weatherspoon, L.J. Carnitine treatment improved quality-of-life measure in a sample of Midwestern hemodialysis patients. *JPEN J. Parenter. Enteral. Nutr.* **2006**, *30*, 10–15. [CrossRef] [PubMed]
94. Reuter, S.E.; Faull, R.J.; Evans, A.M. L-carnitine supplementation in the dialysis population: Are Australian patients missing out? *Nephrology* **2008**, *13*, 3–16. [CrossRef]
98. Fotiadou, E.; Georgiannos, P.I.; Chourdakis, M.; Zebekakis, P.E.; Liakopoulous, V. Eating during the Hemodialysis Session: A Practice Improving Nutritional Status or a Risk Factor for Intradialytic Hypotension and Reduced Dialysis Adequacy? *Nutrients* 2020, 12, 1703. [CrossRef]

99. Shoji, T.; Tsubakihara, Y.; Fuji, M.; Imai, E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int. 2004, 66*, 1212–1220. [CrossRef]

100. Casciani, C.U.; Caruso, U.; Cravotto, E.; Corsi, M.; Maccari, F. Beneficial effects of L-carnitine in post-dialysis syndrome. *Curr. Ther. Res. 1982, 32*, 116–127.

101. van Es, A.; Henny, F.C.; Kooistra, M.P.; Lobo, H.; Scholte, H.R. Amelioration of cardiac function by L-carnitine administration in patients on haemodialysis. *Contrib. Nephrol. 1992, 98*, 28–35. [PubMed]

102. Sakurabayashi, T.; Takaesu, Y.; Haginoshita, S.; Takeda, T.; Aotoke, I.; Miyazaki, S.; Koda, Y.; Yusa, Y.; Sakai, S.; Suzuki, M.; et al. Improvement of myocardial fatty acid metabolism through L-carnitine administration to chronic hemodialysis patients. *Am. J. Nephrol. 1999, 19*, 480–484. [CrossRef]

103. Matsumoto, Y.; Sato, M.; Ohashi, H.; Tadokoro, M.; Osumi, Y.; Ito, H.; Morita, H.; Amano, I. Effects of L-carnitine supplementation on cardiac morbidity in hemodialyzed patients. *Am. J. Nephrol. 2000, 20*, 201–207. [CrossRef] [PubMed]

104. Sakurabayashi, T.; Miyazaki, S.; Yuasa, Y.; Sakai, S.; Suzuki, M.; Takahashi, S.; Hirasawa, Y. L-carnitine supplementation decreases the left ventricular mass in patients undergoing hemodialysis. *Circ. J. 2008, 72*, 926–931. [CrossRef]

105. Sabry, A.A. The role of oral L-carnitine therapy in chronic hemodialysis patients. *Saudi J. Kidney Dis. Transplant. 2010, 21*, 454–459.

106. Kudoh, Y.; Aoyama, S.; Torii, T.; Chen, Q.; Nagahara, D.; Sakata, H.; Nozawa, A. Hemodynamic stabilizing effects of L-carnitine in chronic hemodialysis patients. *Cardiorenal Med. 2013, 3*, 200–207. [CrossRef]

107. Higuchi, T.; Abe, M.; Yamazaki, T.; Okawa, E.; Ando, H.; Hotta, S.; Oikawa, O.; Kikuchi, F.; Okada, K.; Soma, M. Levocarnitine Improves Cardiac Function in Hemodialysis Patients with Left Ventricular Hypertrophy: A Randomized Controlled Trial. *Am. J. Kidney Dis. 2016, 67*, 260–270. [CrossRef] [PubMed]

108. Ibarra-Sifuentes, H.R.; Del Cueto-Aguilera, A.; Gallegos-Arguijo, D.A.; Castillo-Torres, S.A.; Vera-Pineda, R.; Martinez-Granados, R.J.; Atliano-Diaz, A.; Cuellar-Monterrubio, J.E.; Pezina-Cantú, C.O.; Martinez-Guevara, E.J.; et al. Levocarnitine decreases intradialytic hypotension episodes: A randomized controlled trial. *Ther. Apher. Dial. 2017, 21*, 459–464. [CrossRef] [PubMed]

109. Riley, S.; Rutherford, S.; Rutherford, P.A. Low carnitine levels in hemodialysis patients: Relationship with functional activity status and intra-dialytic hypotension. *Clin. Nephrol. 1997, 48*, 392–393. [CrossRef] [PubMed]

110. Poldermans, D.; Man in’t Veld, A.J.; Rambaldi, R.; Van Den Meiracker, A.H.; Van Den Dorpel, M.A.; Rocchi, G.; Boersma, E.; Bax, J.J.; Weimar, W.; Roelandt, J.R.; et al. Cardiac evaluation in hypotension-prone and hypotension-resistant hemodialysis patients. *Kidney Int. 1999, 56*, 1905–1911. [CrossRef]

111. Litwin, S.E.; Raya, T.E.; Gay, R.G.; Bedotto, J.B.; Bahl, J.J.; Anderson, P.G.; Goldman, S.; Bressler, R. Chronic inhibition of fatty acid oxidation: New model of diastolic dysfunction. *Am. J. Physiol. 1990, 258*, 51–56. [CrossRef] [PubMed]

112. Romagnoli, G.F.; Naso, A.; Carraro, G.; Liedestri, V. Beneficial effects of L-carnitine in dialysis patients with impaired left ventricular function: An observational study. *Curr. Med. Res. Opin. 2002, 18*, 172–175. [CrossRef]

113. Higuchi, T.; Abe, M.; Yamazaki, T.; Mizuno, M.; Okawa, E.; Ando, H.; Oikawa, O.; Kikuchi, F.; Okada, K.; Soma, M. Effects of levocarnitine on brachial-ankle pulse wave velocity in hemodialysis patients: A randomized controlled trial. *Nutrients 2014, 6*, 5992–6004. [CrossRef] [PubMed]

114. Fujibayashi, Y.; Som, P.; Yonekura, Y.; Knapp, F.F., Jr.; Tamaki, N.; Yamamoto, K.; Konishi, J.; Yokoyama, A. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analog, [125I] (p-iodophenyl)-3-(R, S)-methylpentadecanoic acid (BMIPP), and correlation to ATP concentration–II. Studies in salt-induced hypertensive rats. *Nucl. Med. Biol. 1982*, 9, 32–38. [CrossRef]

115. Kazmi, W.H.; Obdair, G.T.; Sternberg, M.; Lindberg, J.; Schreiber, B.; Lewis, V.; Pereira, B.J. Carnitine therapy is associated with decreased hospital utilization among hemodialysis patients. *Am. J. Nephrol. 2005, 25*, 106–115.

116. Cruz-Jentoft, A.J.; Landi, F.; Topinkova, E.; Michel, J.P. Understanding sarcopenia as a geriatric syndrome. *Curr. Opin. Clin. Nutr. Metab. Care 2010, 13*, 1–7. [PubMed]

117. Muscaritoli, M.; Anker, S.D.; Argilés, J.; Aversa, Z.; Bauer, J.M.; Biolo, G.; Boirie, Y.; Bosaeus, I.; Cederholm, T.; Costelli, P.; et al. Consensus definition of sarcopenia, cachexia and precachexia: Joint document elaborated by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting diseases” and “nutrition in geriatrics”. *Clin. Nutr. 2010, 29*, 154–159. [CrossRef]

118. Fielding, R.A.; Vellas, B.; Evans, W.J.; Bauer, J.M.; Newman, A.B.; Abellan van Kan, G.; Andrieu, S.; Bauer, J.; Breuille, D.; et al. Sarcopenia: An undiagnosed condition in older adults. Current consensus definition: Prevalence, etiology, and consequences. *International Working Group on Sarcopenia. J. Am. Med. Dir. Assoc. 2011, 12*, 249–256. [CrossRef]

119. Ikižler, T.A.; Cano, N.J.; Franch, H.; Fouque, D.; Himmelfarb, J.; Kalantar-Zadeh, K.; Kuhlmann, M.K.; Stenvinkel, P.; TerWee, P.; Teta, D.; et al. International Society of Renal Nutrition and Metabolism. Prevention and treatment of protein energy wasting in chronic kidney disease patients: A consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int. 2013, 84*, 1096–1107. [CrossRef] [PubMed]

120. Kim, J.C.; Kalantar-Zadeh, K.; Kopple, J.D. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J. Am. Soc. Nephrol. 2013, 24*, 337–351. [CrossRef]
121. Carrero, J.J.; Stenvinkel, P.; Cuppari, L.; Ikizler, T.A.; Kalantar-Zadeh, K.; Kaysen, G.; Mitch, W.E.; Price, S.R.; Wanner, C.; Wang, A.Y.; et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: A consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNMM). *J. Ren. Nutr.* 2013, 23, 77–90. [CrossRef]

122. Johansen, K.L.; Chertow, G.M.; Ng, A.V.; Mulligan, K.; Carey, S.; Schoenfeld, P.Y.; Kent-Braun, J.A. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int.* 2000, 57, 2564–2570. [CrossRef] [PubMed]

123. Stack, A.G.; Martin, D.R. Association of patient autonomy with increased transplantation and survival among new dialysis patients in the United States. *Am. J. Kidney Dis.* 2005, 45, 730–742. [CrossRef] [PubMed]

124. Carrero, J.J.; Thomas, F.; Nagy, K.; Arogundade, F.; Avesani, C.M.; Chan, M.; Chmielewski, M.; Cordeiro, A.C.; Espinosa-Cuevas, A.; Fiaccadori, E.; et al. Global Prevalence of Protein-Energy Wasting in Kidney Disease: A meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism. *J. Ren. Nutr.* 2018, 28, 380–392. [CrossRef] [PubMed]

125. Johansen, K.L. The frail dialysis population: A growing burden for the dialysis community. *Blood Purif.* 2015, 40, 288–292. [CrossRef] [PubMed]

126. Johansen, K.L.; Chertow, G.M.; Jin, C.; Kutner, N.G. Significance of frailty among dialysis patients. *J. Am. Soc. Nephrol.* 2007, 18, 2960–2967. [CrossRef]

127. Bellinghieri, G.; Santoro, D.; Calvani, M.; Savica, R. Role of carnitine in modulating acute-phase protein synthesis in hemodialysis patients. *J. Ren. Nutr.* 2005, 15, 13–17. [CrossRef]

128. Stenvinkel, P.; Heimbürger, O.; Lindholm, B.; Kaysen, G.A.; Bergström, J. Are there two types of malnutrition in chronic renal failure? Evidence for relationship between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol. Dial. Transplant.* 2000, 15, 953–960. [PubMed]

129. Kalantar-Zadeh, K.; Block, G.; McAllister, C.J.; Humphreys, M.H.; Kopple, J.D. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am. J. Clin. Nutr.* 2004, 80, 299–307. [CrossRef] [PubMed]

130. Bistrian, B.R.; Schwartz, J.; Istfan, N.W. Cytokines, muscle proteolysis, and the catabolic response to infection and inflammation. *Proc. Soc. Exp. Biol. Med.* 1992, 200, 220–223. [CrossRef]

131. Duranay, M.; Akay, H.; Yilmaz, F.M.; Senes, M.; Tekeli, N.; Yücel, D. Effects of L-carnitine infusions on inflammatory and nutritional markers in haemodialysis patients. *Nephrol. Dial. Transplant.* 2006, 21, 3211–3214. [CrossRef] [PubMed]

132. Suchitra, M.M.; Ashalatha, V.L.; Sailaja, E.; Rao, A.M.; Reddy, V.S.; Bitla, A.R.; Sivakumar, V.; Rao, P.V. The effect of L-carnitine supplementation on lipid parameters, inflammatory and nutritional markers in maintenance hemodialysis patients. *Saud J. Kidney Dis. Transpl.* 2011, 22, 1155–1159. [PubMed]

133. Kalantar-Zadeh, K.; Block, G.; McAllister, C.J.; Humphreys, M.H.; Kopple, J.D. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am. J. Clin. Nutr.* 2004, 80, 299–307. [CrossRef] [PubMed]

134. Bistrian, B.R.; Schwartz, J.; Istfan, N.W. Cytokines, muscle proteolysis, and the catabolic response to infection and inflammation. *Proc. Soc. Exp. Biol. Med.* 1992, 200, 220–223. [CrossRef]

135. Malaguarnera, M.; Cammalleri, L.; Gargante, M.P.; Cristaldi, E.; Colonna, V.; Motta, M. L-Carnitine treatment reduces severity of physical and mental fatigue, and increases cognitive functions in centenarians: A randomized and controlled clinical trial. *Am. J. Clin. Nutr.* 2003, 41, 4–12. [CrossRef]

136. Malaguarnera, M.; Cammalleri, L.; Gargante, M.P.; Cristaldi, E.; Colonna, V.; Motta, M. L-Carnitine treatment reduces severity of physical and mental fatigue, and increases cognitive functions in centenarians: A randomized and controlled clinical trial. *Am. J. Clin. Nutr.* 2003, 78, 1738–1744. [CrossRef]

137. Badrasawi, M.; Shahar, S.; Zahara, A.M.; Nor Fadilah, R.; Singh, D.K. Efficacy of L-carnitine supplementation on frailty status and physical and mental fatigue and increases cognitive functions in centenarians: A randomized and controlled clinical trial. *Nutr. Metab.* 2017, 14, 7. [CrossRef] [PubMed]

138. Malaguarnera, M.; Gargante, M.P.; Cristaldi, E.; Colonna, V.; Messano, M.; Koverech, A.; Neri, S.; Vacante, M. Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. *Arch. Gerontol. Geriatr.* 2008, 46, 181–190. [CrossRef] [PubMed]

139. Sakurai, T.; Matsumoto, Y.; Shinzato, T.; Takai, I.; Nakamura, Y.; Sato, M.; Nakai, S.; Miwa, M.; Morita, H.; Miwa, T.; et al. Effects of L-carnitine supplementation on muscular symptoms in hemodialyzed patients. *Am. J. Kidney Dis.* 1998, 32, 258–264. [CrossRef] [PubMed]

140. Bellinghieri, G.; Savica, V.; Mallamace, A.; Di Stefano, C.; Consolo, F.; Spagnoli, L.G.; Villaschi, S.; Palmieri, G.; Corsi, M.; Maccari, F. Correlation between increased serum and tissue L-carnitine levels and improved muscle symptoms in healthy older adults: A randomized, double-blind placebo-controlled study. *Nutr. Metab.* 2017, 14, 7. [CrossRef] [PubMed]

141. Malaguarnera, M.; Gargante, M.P.; Cristaldi, E.; Colonna, V.; Messano, M.; Koverech, A.; Neri, S.; Vacante, M. Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. *Arch. Gerontol. Geriatr.* 2008, 46, 181–190. [CrossRef] [PubMed]

142. Johansen, K.L.; Chertow, G.M.; Ng, A.V.; Mulligan, K.; Carey, S.; Schoenfeld, P.Y.; Kent-Braun, J.A. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int.* 2000, 57, 2564–2570. [CrossRef] [PubMed]

143. Johansen, K.L.; Chertow, G.M.; Ng, A.V.; Mulligan, K.; Carey, S.; Schoenfeld, P.Y.; Kent-Braun, J.A. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int.* 2000, 57, 2564–2570. [CrossRef] [PubMed]

144. Carrero, J.J.; Thomas, F.; Nagy, K.; Arogundade, F.; Avesani, C.M.; Chan, M.; Chmielewski, M.; Cordeiro, A.C.; Espinosa-Cuevas, A.; Fiaccadori, E.; et al. Global Prevalence of Protein-Energy Wasting in Kidney Disease: A meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism. *J. Ren. Nutr.* 2018, 28, 380–392. [CrossRef] [PubMed]

145. Johansen, K.L. The frail dialysis population: A growing burden for the dialysis community. *Blood Purif.* 2015, 40, 288–292. [CrossRef] [PubMed]
170. Hakeshzadeh, F.; Tabibi, H.; Ahmadinejad, M.; Malakoutian, T.; Hedayati, M. Effects of L-Carnitine supplement on plasma coagulation and anticoagulation factors in hemodialysis patients. Ren. Fail. 2010, 32, 1109–1114. [CrossRef]

171. Tabibi, H.; Hakeshzadeh, F.; Hedayati, M.; Malakoutian, T. Effects of l-carnitine supplement on serum amyloid A and vascular inflammation markers in hemodialysis patients: A randomized controlled trial. J. Ren. Nutr. 2011, 21, 485–491. [CrossRef]

172. Ahmadi, S.; Banadaki, S.D.; Mozaffari-Khosravi, H. Effects of oral L-carnitine supplementation on leptin and adiponectin levels and body weight of hemodialysis patients: A randomized clinical trial. Iran. J. Kidney. Dis. 2016, 10, 144–150. [PubMed]

173. Alattiya, T.N.; Jaleel, N.A.; Al-Sabbag, M.S.; Jamil, N.S.; Mohammed, M.M. Effect of oral L-carnitine supplementation on the mortality markers in hemodialysis patients. Int. J. Pharm. Sci. Rev. Res. 2016, 14, 64–69.

174. Yang, S.K.; Xiao, L.; Song, P.A.; Xu, X.; Liu, F.Y.; Sun, L. Effect of L-carnitine therapy on patients in maintenance hemodialysis: A systematic review and meta-analysis. J. Nephrol. 2014, 27, 317–329. [CrossRef]

175. Huang, H.; Song, L.; Zhang, H.; Zhang, H.; Zhang, J.; Zhao, W. Influence of L-carnitine supplementation on serum lipid profile in hemodialysis patients: A systematic review and meta-analysis. Kidney Blood Press Res. 2013, 38, 31–41. [CrossRef]

176. Chen, Y.; Abbate, M.; Tang, L.; Cai, G.; Gong, Z.; Wei, R.; Zhou, J.; Chen, X. L-Carnitine supplementation for adults with end-stage kidney disease requiring maintenance hemodialysis: A systematic review and meta-analysis. Am. J. Clin. Nutr. 2014, 99, 408–422. [CrossRef]

177. Zhou, J.; Yang, T. The efficacy of L-carnitine in improving malnutrition in patients on maintenance hemodialysis: A meta-analysis. Biosci. Rep. 2020, 40, BSR20201639. [CrossRef] [PubMed]