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ROLE OF LEVOCARNITINE IN SYSTEMIC TREATMENT OF PATIENTS OF DIVERSE PROFILE AND PATIENTS ON CHRONIC HEMODYALISIS

L-carnitine (Lat. *levocarnitinum*, other names – l-carnitine, levocarnitine, vitamin B_T, vitamin B_{11}) is a natural substance related to B complex vitamins.

Unlike vitamins, the carnitine is synthesized in the human body, therefore it is sometimes called a vitamin-like-substance [1].

The carnitine has an immediate impact on metabolism of fatty acids, facilitating their intake into mitochondria of cells and thus providing the substrate for oxidation processes and energy generation. These processes are links of the Krebs cycle which represents a key stage of cellular respiration [2].

The fatty acids are used as a substrate of energy generation in all tissues except for the brain. In case of an excessive intake of fatty acids, the carnitine facilitates and intensifies their disposal. In simple words, the carnitine is a substance that helps the body to transform fat into energy. Normally it is produced in liver and kidneys and accumulated in skeletal muscles, heart, brain and sperm [3].

The levocarnitine synthesis requires participation of vitamins C, B_3, B_6, B_9, B_{12}, of iron, lysine, methionine and a number of ferments. Normally the body is able to independently ensure the required carnitine level, however, there are several pathological conditions and congenital defects in which the level of carnitine production by the body is reduced. In these cases carnitine medications are used to correct the metabolic disorders.

Among congenital metabolic disorders with primary and secondary deficiency of carnitine are glutaric aciduria, methylmalonic aciduria, propionic acidemia, deficiency of acyl-CoA dehydrogenase etc. The primary deficiency is inherited according to the autosomal recessive pattern and manifests itself in the hepatic encephalopathy, disorders of cardiac functions, suppression of higher nervous activity. The secondary carnitine deficiency accounts for various myopathies. Both options can lead, directly or indirectly, to development of renal insufficiency.

The acquired carnitine deficiency can arise through disorder of the body's synthetic abilities – owing to liver or kidney diseases, poor nutrition, increased expenditure (stress, intoxication, physical exertion, pregnancy), increased excretion (loss during hemodialysis), digestion disorders (pancreatic deficiency).

Carnitine intake with food is possible during consumption of meet, poultry, fish, and dairy products.

The recommended daily dose of L-carnitine is:

— for adults – up to 300 mg;
— for children from 7 to 18 years – 100-300 mg.

The carnitine deficiency is revealed using a biochemical method by extremely low concentration of the free carnitine in plasma less than 20 μmol/l one week after drug intake and it can manifest itself simultaneously by low concentrations in tissues and/or urine.

The carnitine is applied, as an auxiliary remedy, for the growth of muscle mass (anabolic action) and lipid exchange activation, as an antihypoxic and antioxidant agent. The carnitine activates decomposition of fats, stimulates oxidation of fatty acids, participates in their transport into mitochondria, in such a way decreases accumulation of fat in tissues and contributes to reduction in cholesterol level in the body. The anabolic action of carnitine makes itself evident in the amino acids synthesis and exchange of phospholipids, it improves endurance, recovery abilities of the body and stimulates growth of muscular tissue.

Another important function of the substance is detoxification. The carnitine helps the body to get rid of waste emerging during the oxidative decomposition of complex substances (including lipids).

The substance's antioxidant action contributes to detoxification of xenobiotics having particular significance for the body's intoxication and malfunction of liver or/and kidneys.

The carnitine has a wide range of uses in various fields of medicine acting both as a food additive and a supplement to the existing treatment.

Application areas:

— general: contributes to the body's growth and development, decreases the feeling of hunger and weakness, weight reduction due to intensified fat consumption, anabolic effect (muscle mass growth), energy increase, enhancement of the body resistance, antioxidant action, slowing down of bone demineralization:

— cardiology: supplementation to the treatment regimen of angina pectoris, coronary heart disease, cardiac insufficiency, recovery after ischemic events;

— gastroenterology: chronic liver impairment, liver cirrhosis, fatty hepatosis, anacid and hypoacid gastritis; adipose degeneration;

— nephrology/urology: chronic renal insufficiency, toxic syndrome, additional therapy for patients on

hemodialysis, adipose kidney degeneration, spermatogenesis disorders;

— endocrinology: diabetes mellitus, diabetic nephropathy, adiposity, thyrotoxicosis, metabolic syndrome, growth disorders in children;

— neurology: brain hemorrhage, encephalopathy, Alzheimer disease, polyneuropathy;

— surgery: pre-surgical preparation and post-operative recovery;

— vital functions: immune system reinforcement, cognitive function enhancement, an intensive physical exertion, exhaustion, chronic fatigue syndrome, abstinence syndrome etc.

A series of clinical trials has been conducted which proves decline of the carnitine level in the body in various diseases.

Various trials have shown that in case of a cardiac insufficiency the total carnitine level in myocard decreases from 60% to 42% of the norm. The decrease in carnitine level manifested itself by decreased heart function, oxidative stress and an increased glycolysis level. Treatment with carnitine made it possible to enhance the glycolysis and, as a consequence, to restore the heart function and decrease the events of an oxidative stress. Other trials have demonstrated that levocarnitine decreases the degree of damage of myocard after ischemia and improves reperfusion by means of reducing the toxic effect of high level of free fatty acids (emerges as a consequence of ischemia) as well as by means of improving the glycometabolism. Apart from increase in the level of fatty acids' transport into mitochondria, the levocarnitine reduces the intramitochondrial acetyl CoA and free CoA ratio, thus enhancing the oxidative activity. Delivery of the carnitine and saturation of myocard with it allows to prevent the loss of high-energy phosphate compounds, reduce the events of ischemic damage and eventually improve the recovery of myocard.

The carnitine has shown clinically the anti-ischemic, anti-angiospastic and anti-anginal properties. The mechanism of these improvements has been revealed after assessment of biochemical blood tests of 472 patients.

The mechanism of reduction of ischemic and reperfusion implications includes several stages, and it can be projected to the majority of human organs and systems:

— prevention of accumulation of a long-chain acyl-CoA contributing to production of free radicals by mitochondria damaged as a result of hypoxia;

— improvement of the recovery mechanisms of membrane phospholipids damaged as a result of an oxidative stress;

— suppression of arrhythmia;

— reduction of the apoptosis triggered by ischemia.

— reduction of the carnitine level in myocard in patients with dilated cardiomyopathy has been proven [4-6].

Development of a **hepatic steatosis** is attributed to the carnitine insufficiency which is also related to dysfunction of mitochondria. There are trials on the use of L-carnitine as a new supplementation to the treatment of a nonalcoholic steatohepatitis. A randomized controlled trial with participation of 80 patients with a clinical diagnosis of a nonalcoholic steatohepatitis was conducted. The result was an improvement of blood chemistry values: liver enzyme values (proven reduction of AST (P=0,000), ALAT (P=0,000), GGT values (P=0,007) compared to the initial indices and the group "placebo + diet"), the lipid pattern (24 weeks after the start of the trial, a proven reduction in the total cholesterol level occurred (P=0,000) and in cholesterol of the low-density lipoproteins), also a proven reduction in the glycemia level (P=0,000) was registered as well as that of insulin resistance (P=0,000), C-reactive protein (P=0,004) and TNF-α (P=0,000) in the group "L-carnitine + diet" compared to the initial indices and the group "placebo + diet" [7].

Other trials have shown the results as a significant reduction in the level of serumal ammonia and hepatic encephalopathy events [8].

There are also trials confirming the positive effect of carnitine when treating poisonings with the valproic acid (an antiepileptic, myorelaxing and sedative medication) and hepatotoxicity induced by this medication when treating bipolar affective disorders [9].

The carnitine's efficiency is also indicated in case of a **peripheral neuropathy** including the diabetic and alcoholic ones.

The influence of carnitine on the cure of physical and mental fatigue in elderly persons was studied separately. It was a double-blind placebo-controlled randomized study with participation of 66 patients. The patients from the carnitine group demonstrated improved values of the fat mass reduction ($P < 0,01$), the improved muscle mass gain ($P < 0,01$), and the improved values of a long-chain acylcarnitine and a short-chain carnitine of the blood plasma ($P < 0,001$) [10].

All studies independently underline the fact that the subsequent hydrolysis of the acyl-CoA compounds to the free acids is the cause of the acidosis which can endanger the patient's life. The levocarnitine neutralizes the acyl-CoA compounds by transforming it into acylcarnitine which is rapidly removed from the body. Thus, the carnitine is efficient in various kinds of intoxication (drug, alcoholic intoxication, intoxication with xenobiotics).

The carnitine increases resistance to the oxidative stress by suppressing a ferment which activates the DNA damage of the cell [11].

Taking into account all possible positive carnitine's effects, special attention should be paid to consideration of its role in treatment of patients with the chronic kidney disease (CKD), in particular, of patients on hemodialysis (HD).

Since the carnitine is produced by kidneys, kidney diseases can lead to depletion of its natural reserves in the body. For patients with CKD staying on HD, this event is inevitable. Except for the carnitine's positive influence on the healthy body, there are a number of HD complications during correction of which the medication can be used as an adjuvant therapy.

The complications of hemodialysis fall into two groups:

— treatment-related: hypotension, muscle cramps, nausea and vomiting, flush, headache, itch, chest pain, fever etc.;

— hemodialysis apparatus-related: air embolism, hemolysis, hyper- and hypothermia, blood loss, disorders of nervous conductivity.

Multiple studies were conducted that examined the carnitine status in patients with CKD staying on HD [12]. It has been proven that except for reduction in carnitine production during CKD, also its loss at HD occurs since it passes freely through the dialysis membrane. As this takes place, the losses amounted to 27% - 68% which is equal to 190-2100 mmol a session. The analysis took into account the difference of plasma/serum carnitine level in patients before and after the HD [13].

The next study confirms that in 49% of patients on HD the carnitine level in the blood plasma is below the normal level, and ratio "acylcarnitine – free carnitine" exceeds 0,4 in 47% of patients.

The time spent on HD correlates with the reduction of the carnitine level in blood plasma and its concentration in muscles, although, prior to HD, the carnitine levels in blood serum are elevated due to its disturbed excretion [14]. There are data on correlation between the level of total blood plasma carnitine with the level of creatinine from protein intake with food [15, 16].

In the new studies, a positive influence of carnitine on the hemodynamic status of patients on chronic HD was observed. A blind placebo-controlled randomized study with control of the heart function after three months has shown that the concentration of free carnitine and acylcarnitine was substantially elevated – from 22,3 ± 7,1 up to 140,3 ± 57,5 mmol/l, and from 15,8 ± 2,8 up to 94,8 ± 50,4 mmol/l respectively in the group of patients who received carnitine. The ejection fraction was also substantially elevated – from 61,8 ± 16,0 up to 64,4 ± 13,8 % ($P < 0,05$) in the carnitine group, although, according to echography data, there was no significant difference in two patient groups – those who received carnitine and those who did not. The frequency of hypotension episodes also reduced credibly – from 4,0 ± 1,7 to 1,3 ± 0,9 times in a month ($p < 0,05$) [17].

The carnitine has shown a good effect in the study that examined complications related to the HD procedure – hypotension and muscle cramps. The results of a placebo-controlled randomized study in patients with terminal CKD on HD were published. The study was conducted in several stages, and in conclusion the carnitine demonstrated a positive influence on muscle cramps frequency (DI 95%, $P = 0.05$) [18].

Another study demonstrated that the plasma carnitine levels in patients with CKD do not correlate with the carnitine levels in skeletal muscles [19]. It was found that the concentration of total and free carnitine in muscles decreased but the ratio of total and free carnitine remained in a norm; a correlation between the reduction of total and free carnitine levels and the dialysis duration was revealed; absence of interrelation of the carnitine's concentration in blood plasma and muscles.

Examinations of the carnitine's influence on correction of anemia as one more complication of CKD began after emergence of erythropoietin (EPO) medications because of the fact that certain authors assumed that the reduction of the carnitine plasma level decreases patients response to the EPO therapy [20, 21].

Multiple studies (Hurot et al.) revealed an increase in EPO consumption and more successful anemia correction in patients with CKD on HD during the use of carnitine, and a positive impact on the lipid profile: reduction of the total cholesterol level, of high density lipoproteins and low-density lipoproteins ratio, improvement of myocardial function, reduction in syndromes of arrhythmia and asthenia, muscle weakness.

No influence on weight reduction was proven in these studies [21].

In 2003 the National Kidney Foundation conducted a conference dedicated to a consensus on carnitine (the Carnitine Consensus Conference) the results of which were published in American Journal of Kidney Disease [22]. The following conclusions can be drawn from the conference's results:

— in spite of a relatively small number of studies dedicated to examination and proving of the carnitine effect in patients with CKD on HD, the specialists are increasingly inclined to prescribe the medication to these patients, taking into account numerous positive effects on HD complications and reduction of undesirable HD effects in patients with CKD;

— many studies proving a substantial reduction of an undesirable hypotensive effect in patients with CKD on HD;

— it is recommended to assess the level of improvements as a result of application of this medication every three months during treatment of patients with CKD on HD.

Although K-DOQI guidelines do not declare recommendations as to prescription of the carnitine for patients with CKD on HD, its application as a supplementation therapy can be promising, due to multiple positive influences on HD complications [24].

The patients staying on HD can receive carnitine both via the peroral and intravenous route. The carnitine levels in muscle tissues are increased by 60-200% after 6 weeks of application. No data on toxicity were published [15].

Thereby, the carnitine's application as a medicinal product affecting various links of metabolism and possessing an anabolic, anti-oxidant and antihypoxic action, is justified and indicated for treatment of patients with chronic kidney insufficiency.

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Received on 12.01.2014