

# Effectiveness of copper and zinc supplementation in patients treated by nutrition therapy

## *Skuteczność suplementacji miedzią i cynkiem u chorych leczonych żywieniowo*

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Medical Studies/Studia Medyczne 2016; 32 (4): 240–247

DOI: 10.5114/ms.2016.64696

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**Key words:** malnutrition, nutrition therapy, zinc, copper.

**Słowa kluczowe:** niedożywienie, leczenie żywieniowe, cynk, miedź.

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### Abstract

**Introduction:** Parenteral nutrition (PN) therapy may be effective only provided that the organism is supplied with all the indispensable components. In clinical practice, the treatment of an undernourished patient requires the introduction of substitution of various nutrients, including such elements as copper and zinc.

**Aim of the research:** An evaluation of the effectiveness of copper and zinc supplementation in patients receiving short-term parenteral nutrition therapy – lasting up to 10 days, and long-term therapy – for more than 10 days.

**Material and methods:** The study was conducted in the Clinical Department of Surgery at the Regional Polyclinical Hospital in Kielce. Two study groups were distinguished: group 1 – PN with supplementation up to 10 days, into which were qualified 35 patients (16 females and 19 males; median age 66 years); group 2 – PN with supplementation lasting for more than 10 days, into which were qualified 34 patients (15 females and 19 males, median age 59 years), and two control groups. Control group 1 were 20 healthy individuals selected at random from among the medical staff. Control group 2 were patients qualified for planned surgical procedure of gallbladder removal. In order to evaluate the concentration of copper and zinc in patients in the study groups, venous blood was collected prior to the introduction of nutrition, and within 7-day intervals during the parenteral nutrition.

**Results:** No statistically significant differences were observed between the concentrations of zinc in the blood of patients in study groups 1 and 2. This means that, irrespective of the time of measurement, the zinc concentration in blood was similar. In study group 1, the mean concentration of copper was higher in the measurement performed after 7 days of PN (88.48 µg/dl), compared to the measurement prior to PN (82.45 µg/dl) ( $p = 0.028$ ). The lowest mean concentration of copper in blood in study group 2 was observed in the measurement prior to the introduction of PN (71.17 µg/dl) and, at the same time, it was lower than the measurements performed after 14 (98.16 µg/dl), 21 (96.33 µg/dl), and 28 (100.03 µg/dl) days. A significant increase in the concentration of copper and zinc was observed after 14 days of PN.

**Conclusions:** based on the results of the analysis performed, it was found that zinc and copper administration in standard PN doses is sufficient. The concentration of copper remains within reference values; however, it is higher after PN therapy.

### Streszczenie

**Wprowadzenie:** Leczenie żywieniowe pozajelitowe (PN) może być skuteczne tylko pod warunkiem dostarczenia organizmowi wszystkich niezbędnych składników. W praktyce klinicznej terapia niedożywionego chorego wymaga włączenia substytucji różnych substancji odżywczych, w tym mikroelementów, takich jak miedź i cynk.

**Cel pracy:** Ocena skuteczności suplementacji miedzią i cynkiem u chorych leczonych PN w krótkim (do 10 dni) i długim (powyżej 10 dni) okresie.

**Materiał i metody:** Badania przeprowadzono w Klinice Chirurgii Wojewódzkiego Szpitala Zespołowego w Kielcach. Wyodrębniono dwie grupy badane: 1 – PN z suplementacją do 10 dni, do której zakwalifikowano 35 chorych (16 kobiet, 19 mężczyzn, mediana wieku: 66 lat), 2 – PN z suplementacją powyżej 10 dni, do której włączono 34 chorych (15 kobiet, 19 mężczyzn, mediana wieku: 59 lat), oraz dwie grupy kontrolne.

**Wyniki:** W grupie badanej 1 średnie stężenie miedzi było większe po 7 dniach PN (88,48 µg/dl) w porównaniu ze stężeniem przed włączeniem PN (82,45 µg/dl) ( $p = 0,028$ ). Najmniejsze średnie stężenie miedzi we krwi w grupie badanej 2 stwierdzono przed wprowadzeniem PN (71,17 µg/dl) i jest ono mniejsze od stężenia oznaczonego po 14 (98,16 µg/dl), 21 (96,33 µg/dl) i 28 (100,03 µg/dl) dniach PN. Istotny wzrost stężenia miedzi i cynku zaobserwowano po 14 dniach PN.

**Wnioski:** Na podstawie przeprowadzonej analizy stwierdzono, że suplementacja PN cynkiem i miedzią w standardowych dawkach jest wystarczająca. Stężenie miedzi mieści się w granicach wartości referencyjnych, ale jest większe po leczeniu PN.

## Introduction

Malnutrition is observed in approximately 30–50% of hospitalised patients, and a considerable number of these patients are already undernourished at admission to hospital [1–3]. In the majority of cases it further deepens during hospitalisation [4, 5]. Malnutrition is defined as a deficiency of supply of energy, proteins, and other nutrients, which exerts a clear, negative effect on the body composition, its functions, and the clinical course of the disease [6, 7]. The consequences of malnutrition may concern both mental and somatic disorders [8, 9], prolonged periods of hospitalisation, and increasing costs [10, 11], as well as increasing mortality [12, 13].

During the perioperative period, metabolism usually increases by 10% [14]. Attempts to identify the factors which, during the perioperative period, cause an intensification of stress reactions resulted in reports in which the researchers indicated that even 12-hour starvation before surgery brings about metabolic changes that prolong the period of convalescence after non-complicated surgical procedures [15, 16]. Parenteral nutrition therapy is an important preparation for surgery, and during the post-operative period it enables a quicker transition from the anabolic to the catabolic phase, considerably reducing the possibility of occurrence of severe post-operative complications [17–19]. Parenteral nutrition may be effective only provided that the organism is supplied with all the indispensable components. These are: amino acids, glucose, fat emulsion, electrolytes – sodium (Na), potassium (K), calcium (Ca), magnesium (Mg), phosphorus (P), trace elements, vitamins, and water [20, 21]. Vitamins and trace elements are important components of all modes of nutrition because they act like co-enzymes and co-factors in many metabolic processes [22–26]. The consequences of severe deficiency of microelements are not perceived instantly because the full clinical image develops over many weeks. Biochemical disorders are manifested within 3–5 days. The syndrome of biological deficiency is observed even earlier. Copper and zinc belong to the group of nutritional microelements, the administration of which is associated with many health benefits. The majority of recommendations concerning the supply of zinc and copper are based on the demand calculated for a healthy individual [27, 28]. There is a lack of studies comparing the demand for microelements in undernourished patients compared to those who are well nourished. For obvious ethical reasons,

no randomised studies have been conducted to evaluate the administration of PN with and without the addition of microelements. The supply of a complete kit of microelements constitutes an integral element of nutritional support [29, 30].

Zinc (Zn) is a necessary trace element, a structural and functional component of approximately 120 enzymes that regulate the basic life processes, including, among others: metabolism of carbohydrates, fats, proteins, amino acids, collagen, and functions of the cell membrane [31]. Its amount in the body of a healthy individual is 2–4 g, of which about 75% is contained in erythrocytes, muscles, bones, and skin.

In natural conditions, zinc loss takes place mainly with the pancreatic juice into the gastrointestinal tract, from where it is excreted with faeces. Another route is excretion with urine and sweat. The concentration of zinc in serum decreases in acute inflammatory states and after injuries, because of the presence of fistulas, as well as in patients suffering from diarrhoea and cirrhosis of the liver. Zinc deficiency causes typical eczematous changes in the skin, hair loss, impairment of wound healing, and immune disorders [32–35]. Exposure to high doses has a toxic effect. Apart from acute intoxication, long-lasting supplementation of high doses of zinc impairs the absorption of copper. An excess of zinc may cause toxic symptoms: acute – nausea and vomiting, and chronic – in the form of iron deficiency [36, 37].

Copper (Cu) is the component of some proteins, cytochrome oxidase, ceruloplasmin, and other enzymes. It has an anti-oxidative effect. The human body contains 80–200 mg of copper, mainly in the liver, which regulates its distribution, processing, and excretion. Among the symptoms of copper deficiency are mentioned: ischaemia, neutropaenia, cardiac arrhythmia, degenerative changes in the nervous system, and pseudo-scurvy [38–40]. Among the circumstances leading to the accumulation of an excess of copper is impairment of bile flow [41]. Copper shows even greater toxicity than zinc and iron. Its overdosing leads to disorders in the absorption of zinc and iron, as well as other metals. Among the symptoms of acute intoxication are mentioned: nausea, vomiting, acute abdominal pain, diarrhoea, and in chronic intoxication: pharyngitis, bronchitis, and intestinal colic [42].

## Aim of the research

The objective of the study was an evaluation of the effectiveness of copper and zinc supplementation in

patients receiving short-term parenteral nutrition therapy lasting from 7 to 10 days, and long-term parenteral nutrition therapy for a period longer than 10 days.

## Material and methods

Into the study were qualified patients of both genders who received nutritional therapy in the Clinic of Surgery. The criteria of inclusion into the study with administration of parenteral nutrition were as follows:

- age 18 – 85 years, nutritional therapy for > 7 days;
- high obstruction of the gastrointestinal tract (cancer-related stricture of the oesophagus);
- external gastrointestinal fistulas;
- short bowel syndrome;
- acute pancreatitis;
- inflammatory bowel diseases and multi-organ injury.

Criteria for exclusion:

- age under 18 and over 85 years;
- nutritional therapy for < 7 days;
- terminal period of a cancerous disease, patients receiving nutritional support.

In all the patients who qualified for the study, the state of nutrition was evaluated, and a kit of measurements of the somatic state was performed: body height, weight, and body mass index (BMI) calculated according to the following formula:  $BMI = \text{body weight (kg)}/\text{body height (m}^2\text{)}$ .

In each patient, the nutritional status was evaluated using the Nutritional Risk Screening (NRS) 2002, which allows assessment of the four basic factors: dynamics of weight loss, disorders in dietary intake, current body mass index, and the degree of intensification of the disease. Prior to the introduction of nutritional therapy, the following laboratory blood tests were performed: levels of Na, K, Ca, Mg, Cl, P, glucose, total protein and albumin, urea, creatinine, triglycerides, cholesterol, bilirubin, C-reactive protein, and the activity of: aspartate aminotransferase, alanine aminotransferase,  $\gamma$ -glutamyl transferase, and complete blood count. The monitoring of nutrition was carried out by daily clinical examination of the patient, measurement of temperature, fluid balance, assessment of the site of peripheral venous catheter insertion and central venous catheter insertion, and the results of laboratory tests, the frequency of performance of these tests being dependent on the state of the patient and the progress in treatment. During the first days of nutritional therapy the examinations were performed every second day, while during the period of stabilisation – twice a week. In all patients the material for tests – venous blood – was collected prior to the implementation of nutrition, and at 7-day intervals during nutritional therapy.

The duration of parenteral nutrition constituted a determinant to select two basic groups of patients: The patients were divided as follows: group 1 – PN

from 7–10 days, 35 patients; group 2 – PN more than 10 days, 34 patients.

According to the adopted criteria, into study group 1 were qualified 35 patients (16 females and 19 males, median age: 66 years). Into study group 2 were qualified 34 patients (15 females and 19 males, median age: 59 years). Control group 1 included 20 healthy, normally nourished individuals (13 females and 7 males, median age: 36 years). Control group 2 were patients qualified for planned surgical procedure of gallbladder removal (27 females and 11 males, median age: 35 years).

The tests were performed in the Diagnostic Laboratory at the Regional Polyclinical Hospital.

In order to determine the concentration of zinc in this procedure, the colorimetric method 5-Br-PAPS was applied without deproteinisation of the sample. The concentrations of zinc 68–107  $\mu\text{g}/\text{dl}$  were adopted as reference values.

Determination of the concentration of copper in serum was done using colorimetric method without deproteinisation of the sample. The concentrations of copper 70–155  $\mu\text{g}/\text{dl}$  were adopted as reference values.

## Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics software. Basic descriptive statistics were analysed and the following tests were performed: *t*-Student test for dependent samples, and one-way single factor analyses for dependent and independent samples. The *p*-values < 0.05 were considered statistically significant.

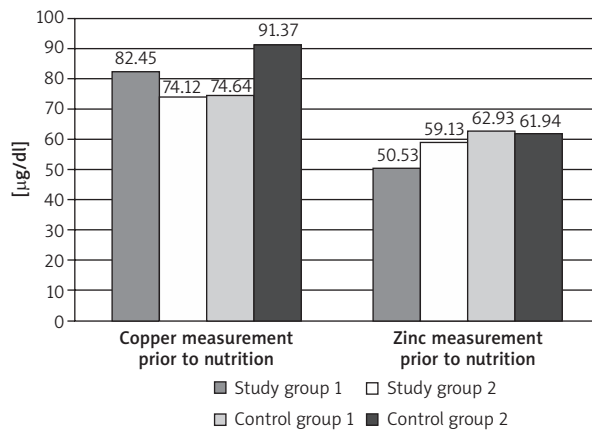
## Results

Two study groups and two control groups were distinguished in the study. In study group 1, the patients received parenteral nutrition (PN) for up to 10 days, 35 patients (16 females and 19 males, median age: 66 years). In study group 2, PN was applied for longer than 10 days, 34 patients (15 females and 19 males, median age: 59 years). Control group 1 were 20 healthy, normally nourished individuals selected at random from among the medical staff of the Clinic. Control group 2 included 38 patients qualified for planned surgical procedure of gallbladder removal.

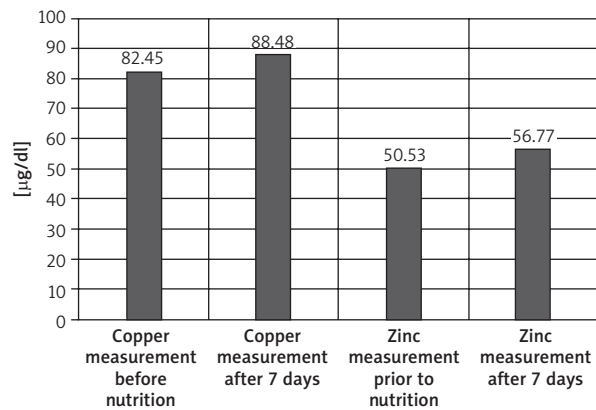
In the first measurement of the concentration of copper, no significant differences were observed ( $p > 0.05$ ), between study group 1 (82.45  $\mu\text{g}/\text{dl}$ ), study group 2 (74.12  $\mu\text{g}/\text{dl}$ ), and control group 1 (74.64  $\mu\text{g}/\text{dl}$ ).

In control group 2 the mean concentration was the highest (91.37  $\mu\text{g}/\text{dl}$ ) ( $p = 0.030$ , Figure 1).

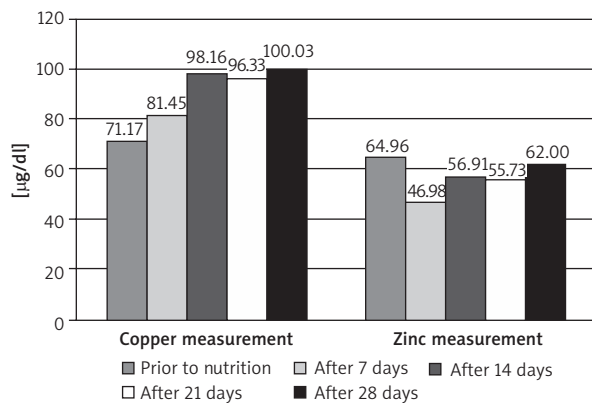
In study group 1 the patients receiving parenteral nutrition for up to 10 days, the concentration of copper was higher in the second measurement (88.48  $\mu\text{g}/\text{dl}$ ), after the implementation of PN, compared to the first measurement (82.45  $\mu\text{g}/\text{dl}$ ), prior to the implementation of parenteral nutrition ( $p = 0.028$ ). Cohen's *d* val-



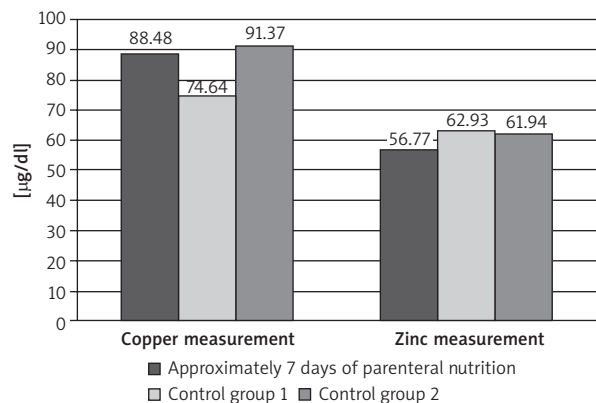
**Figure 1.** Comparison of mean concentration of copper and zinc in blood of examined patients in the first measurement in study group 1 and 2, and in control group 1 and 2



**Figure 2.** Comparison of mean concentration of copper and zinc in blood of patients examined. Study group 1 in measurement prior to parenteral nutrition, and after 7 days of parenteral nutrition



**Figure 3.** Comparison of mean concentration of copper and zinc in blood in patients in study group 2, in measurement before parenteral nutrition, and after 7, 14, 21, and 28 days of parenteral nutrition



**Figure 4.** Comparison of mean concentration of copper and zinc in blood of patients in study group 1 and control group 1 and 2

ue (0.395) shows that the strength of the effect of the differences was moderate (Figure 2).

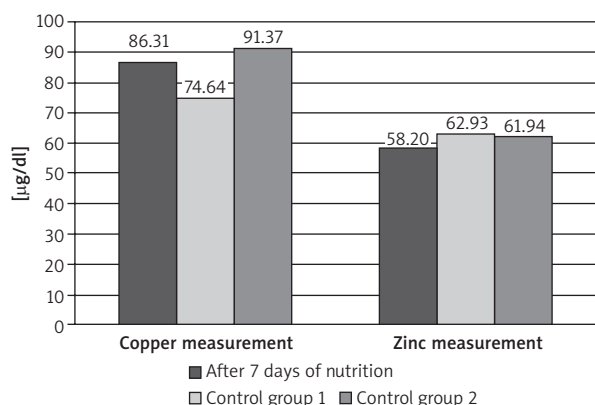
In study group 2 patients who received PN for longer than 10 days, the mean concentration of copper in blood differed between the first measurement prior to the implementation of PN, and measurements after 14, 21, and 28 days of parenteral nutrition, with the mean values of copper concentrations in measurements performed after 14, 21, and 28 days being similar.

The lowest mean concentration of copper in blood in study group 2 was observed in the measurement prior to the implementation of PN (71.17  $\mu\text{g}/\text{dl}$ ) and was simultaneously lower than the measurements after 14 (98.16  $\mu\text{g}/\text{dl}$ ), 21 (96.33  $\mu\text{g}/\text{dl}$ ), and 28 (100.03  $\mu\text{g}/\text{dl}$ ) days. The concentration of copper significantly increased after 14 days of PN ( $p = 0.013$ ) (Figure 3).

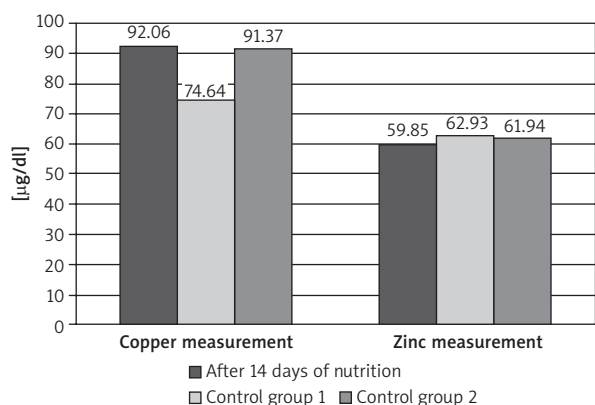
The concentration of zinc in patients' blood in the first measurement before implementation of paren-

teral nutrition was similar in all groups (Figure 1). In study group 1, receiving parenteral nutrition for a period up to 10 days, no differences were noted in the measurements of zinc concentration ( $p = 0.276$ ). This means that the patients in study group 1 had a similar concentration of zinc in blood before PN (50.53  $\mu\text{g}/\text{dl}$ ), and after 10 days of parenteral nutrition (56.77  $\mu\text{g}/\text{dl}$ ) (Figure 2). In study group 2, in patients who received PN for longer than 10 days, no statistically significant differences were observed between the measurements of zinc levels in blood. This means that irrespective of the measurement time, the concentration of zinc in blood was comparable ( $p = 0.528$ ) (Figure 3).

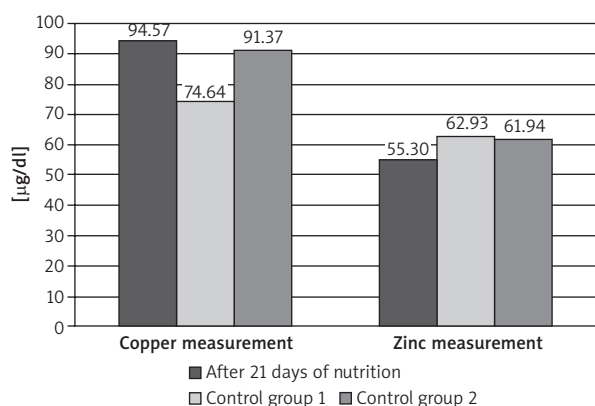
No statistically significant differences in the concentrations of copper and zinc in blood were found in study groups 1 and 2, compared to control groups 1 and 2, and individual measurements after 7, 14, and 21 days (Figures 4–7) ( $p > 0.05$ ).



**Figure 5.** Comparison of mean concentration of copper and zinc in blood of patients from study group 2 after 7 days, and control groups 1 and 2



**Figure 6.** Comparison of mean concentration of copper and zinc in blood of patients from study group 2 after 14 days and control groups 1 and 2



**Figure 7.** Comparison of mean concentration of copper and zinc in blood of patients from study group 2 after 21 days and control group 1 and 2

## Discussion

In parenteral nutrition, trace elements are usually administered in standard doses [43, 44], irrespective of body weight or the rate of metabolism. The sup-

ply of trace elements in PN is managed in two ways. Complex preparations are administered in mixtures that contain in their composition all trace elements that cover the daily demand. Microelements cooperate in the body; therefore, a change in the content of a single component causes a disturbance of balance. The principle of applying a kit of microelements instead of single elements is based on the observation of biochemical mechanisms of the effect of the endogenous antioxidant network [45]. With the second method of supplying inorganic micro-components single-component preparations, corrective with individual elements, are administered in the case of detection of deficiency [46–48]. This requires more time, incurs higher costs, and also increases the risk of making mistakes while determining doses. At present, in many countries it is not possible to determine a balanced supplementation scheme of products containing single compounds. It is important to develop new basic preparations that contain many components, to which additional microelements could be attached in the case of patients with an increased loss, e.g. of zinc. The demand for trace elements reported by various researchers shows considerable differences, and is subject to constant corrections in the course of closer recognition of their importance, metabolism, routes of excretion, etc.

The majority of preparations containing microelements for PN have been prepared for patients in a stable state. These solutions transpire to be properly balanced for chronically ill patients from the aspect of the majority of microelements.

In light of the results obtained, the effectiveness of zinc supplementation for PN in standard doses was successfully confirmed. No differences were found in the mean concentration of zinc in blood prior to and after the introduction of PN. While analysing the results in study group 1 and 2, the effectiveness of zinc supplementation in standard doses was observed, which was confirmed by the studies of Howard *et al.* [46]. These studies evaluated the concentration of iron, zinc, copper, manganese, chromium, and selenium in tissues collected during the post-mortem examination of 8 persons with short bowel syndrome, in whom the mean duration of PN was 14 years. The results showed normal values of selenium, iron, and zinc, but elevated values of manganese, copper, and chromium. The introduction of parenteral nutrition provided the researchers with a rare opportunity to recognise and understand the role of individual trace elements. The syndromes and diseases as a consequence of their deficiency have been described, and doses indispensable for any human deprived of normal nutrition have been determined. Deficit of micro-components may lead to clear clinical consequences [49]. Trace elements are very important in parenteral nutrition, although the deficiency of some of them manifest after many

months, or even years, of administration of PN deprived of an individual element. This, however, does not concern the deficiency of zinc and copper, which manifest as early as within the first weeks of nutrition and are of a great clinical importance [50]. The demand during the period of disease, stress, and after injury is difficult to establish because the majority of recommendations concerning the supply are based on the demand calculated for a healthy individual. The supply of trace elements should enable the maintenance of an optimum function of tissues, and prevent deficiencies. In the case of total parenteral nutrition there is a consensus that the daily supplementation of microelements should be applied [51, 52]. According to the guidelines by the American Agency for Food and Drug Administration (FDA), the daily demand for zinc and copper administered parenterally to adults is: for copper 0.3–0.5 mg, and for zinc 2.5–5 mg [53]. The dosing of trace elements in PN should be individualised and adjusted to the clinical state of an individual patient [54–56]. The importance of microelements for health is undisputed, e.g. zinc is indispensable in the form of catalytic ion in structural and regulatory proteins. Their importance for health is increasingly appreciated, and deficiency may play an important role in the development of a disease [57, 58]. Preparations designed for PN do not contain microelements due to the stability of the solution, which requires separate prescribing of these substances, while they are omitted in as many as 50% of patients receiving parenteral nutrition [59]. The basic feature of a necessary trace element is that its lack or inadequate supply in a diet are associated with repeatable structural or biochemical changes, which are reversed after its supplementation. The determination of an optimum supply of nutritional micro-components is far from being perfect. It is possible to perform a complex evaluation of individual demand based on the demand in the state of health. It has been proven that the supplementation of trace elements in the case of application of preparations currently available on the market, in the majority of situations, is sufficient to prevent the development of the states of deficiency. However, determination of the amount of supply of microelements that would provide an optimum functioning of tissues remains imprecise. The lowest mean concentration of copper in blood in study group 2 was observed in the measurement performed prior to the introduction of PN. The concentration of copper significantly increased after 14 days of PN. The results of studies indicate that the mean concentration of copper remained on a constant level after 14, 21, and 28 days. Such a supplementation of microelements transpired to be adequately balanced for patients from study group 1 and 2, from the aspect of copper. In turn, Chen *et al.* [60] evaluated changes in the concentrations of zinc and copper in 17 patients who received PN for up to 89 days. The

mean concentration of zinc in serum considerably decreased after 4 weeks of treatment in the group without zinc supplementation, compared to the level before treatment, and in the second group. The concentration of copper significantly decreased in both groups. These results show that the decrease in the content of zinc and copper in serum is commonly observed in PN while applying solutions without supplementation of trace elements. In the study by Itokawa [61], the symptoms of deficiency of trace elements developed in patients receiving long-term PN not containing zinc occurred in the form of a wet dermatitis. In this case, the concentration of zinc was very low. The response to intravenous treatment with zinc was striking. The deficiencies of copper in the form of anaemia and neutropaenia disappeared after the supplementation with this element.

In clinical practice the treatment of a severely undernourished patient requires the administration of various nutritional substances, including such microelements as zinc and copper. Their deficiency, as well as excess, are dangerous for a patient [62]; hence, an evaluation of the effectiveness of supplementation during nutritional therapy of severely ill patients is very important. Even the slightest deficiency of one nutrient may be perceived as a failure in nutritional care, which should satisfy the total and obvious demands of each organism [63–65]. Ethical reasons do not allow the performance of randomised studies that would evaluate the use of PN with and without the addition of microelements.

In the literature there are a wide variety of views concerning the composition of preparations for PN. The presented study confirmed that the supplementation of microelements in standard doses is justified in the case of zinc and copper. This is an important therapeutic management because it enables the balance or reduction of deficiency of nutrients, and allows an attempt to restore normal concentrations.

These solutions transpired to be adequately balanced from the aspect of content of zinc and copper in the examined group of patients, which was confirmed in the study evaluating the concentration of zinc in study group 1 and 2. In both groups, no significant increase in the concentrations of copper and zinc were obtained.

## Conclusions

The results of the presented study allow the drawing of the following conclusions: 1) substitution of zinc in nutritional therapy is sufficient because the mean concentrations remain within the range of reference values; 2) an upward tendency was observed in concentrations of copper within short- and long-term PN; however, it remained within the range of reference values, which indicated the necessity for the modification of supplementation.

## Conflict of interest

The authors declare no conflict of interest.

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