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The influence of nickel on intestinal microbiota disturbances

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ABSTRACT

Introduction: Over the last decade, there has been an increased interest in the role of nickel as a cause of allergic reactions and as an element affecting the intestinal microbiota. Its presence can cause dysbiosis, i.e., an increase in the number of harmful microorganisms at the expense of probiotic bacteria. The disturbed microbiota affects the organism's metabolism and increases the risk of developing certain diseases.

This study aims to analyze the available scientific literature on nickel and its effect on the disturbances in the intestinal microbiota.

Materials and methods: The PubMed database and the Cochrane Library were used to find scientific articles with the following combinations of keywords: 'nickel', 'nickel and microbiota', 'nickel and allergy', 'nickel and health', 'microbiota', and 'microbiota disturbances'. Scientific publications from the last 20 years were analyzed.

Results: Nickel is an essential element for certain biochemical reactions that allow microorganisms (both beneficial and harmful) to grow and develop. Some strains of bacteria seem to have the ability to reduce the host's exposure to this heavy metal. Excess nickel intake contributes to the disturbance of the proper composition of intestinal microflora, especially in patients diagnosed with systemic nickel allergy syndrome. This may have adverse health effects, possibly contributing to obesity.

Conclusions: The wide use of nickel in consumer products, as well as its widespread presence in water and food, increases the probability of human contact with this metal. Further research on the influence of nickel on the human body and its microbiota should be conducted.

Keywords: nickel; microbiota; human health; dysbiosis; diet.

INTRODUCTION

Over the last decade, there has been an increased interest in the role of nickel not only as a cause of allergic reactions but also as an element affecting intestinal microbiota [1]. Intestinal microbiota have numerous beneficial functions for the health of the organism, e.g., taking part in immune response, regulating metabolic processes, and protecting against pathogens [2]. Microbiota affect the nervous system, and disturbances in its composition may adversely affect brain function, mood, or stress response [3].

Nickel is a heavy metal with the atomic number 28. It is the 5th most common element on Earth, and naturally occurs mainly as an oxide, sulfide, and silicate. Nickel is widely used in industry but it is also found in food [1]. Human contact with nickel occurs mainly through inhalation, ingestion, or skin absorption [4, 5]. Exposure to nickel compounds has many detrimental effects on humans. The immune reaction to nickel, as a form of dermatitis, is one of the most common allergies in the modern world. Chronic exposure to nickel can cause serious respiratory, cardiovascular, and kidney diseases, and also contributes to the development of occupational diseases [6]. Relevant exposure to occupational toxicity include inhalation for mining, metallurgy, and refinery workers, and skin contact for cashiers or hairdressers [7]. Some nickel compounds, e.g., nickel sulfate – $NiSO_4$, nickel oxide – NiO, and nickel hydroxides, have been classified as carcinogenic substances. They can damage DNA by breaking their strands or producing free oxygen radicals [8].

Apart from its harmful effects, nickel plays a fundamental biological role for fungus, bacteria, archaea, and unicellular eukaryotes [9]. Nickel is an essential component for the catalysis of biochemical reactions in the active site of several key metalloenzymes (e.g., urease, hydrogenase, CO-dehydrogenase) in bacteria and lower eukaryotes [6, 9]. The importance of nickel for these microorganisms is probably related to the role Ni_2^{+-} dependent enzymes play in the intestinal microflora. Under the influence of nickel, dysbiosis can occur, i.e., an increase in the number of harmful microorganisms at the expense of probiotic bacteria. The disturbed state of the microbiota affects the host's metabolism and is responsible for various metabolic and cardiovascular diseases [9].

This study aims to analyze the available scientific literature on nickel and its effect on disturbances in the intestinal microbiota.

MATERIALS AND METHODS

The PubMed database and the Cochrane Library were used to find scientific articles alongside the following combinations of keywords: 'nickel', 'nickel and microbiota', 'nickel and allergy', 'nickel and health', 'microbiota', and 'microbiota disturbances'. The exclusion criteria were: case reports, conference materials,

meta-analyses, as well as papers in any language other than Polish or English. Scientific publications from the last 20 years were analyzed. Based on the adopted criteria and keywords, 59 scientific publications qualified for the review.

RESULTS

Nickel

Nickel is classified as heavy metal. Due to its durability, it is widely used in many industries (production of stainless steel, automobiles, laboratory equipment, coins, and jewelry, as a catalyst and dye), as well as in medicine (orthodontics, surgery, component of contrasts, and dialysis fluids) [10, 11]. As a micronutrient necessary for the proper functioning of the human body, it increases hormonal activity and is involved in lipid metabolism. Nickel enters the human body through the respiratory tract, the digestive tract, or the skin [4, 5, 11]. Recent reports have shown that various metal objects intended to have short-term but repeated contact with the skin can lead to an accumulation of nickel on the skin over time [1, 12]. Inhalation is considered to be the most dangerous method of exposure to nickel. Long term exposure may contribute to the development of asthma, pneumoconiosis, chronic rhinitis, or inflammation of the respiratory tract. In the worst case, this can also lead to cancer of the lungs, sinuses, throat, or nasal cavity [10]. An increase in immunoglobulins G, A, and M and an increased activity of proteins involved in immune reactions have been observed in people professionally exposed to nickel [13].

Nickel absorbed by the lymphatic system often damages it [14]. Nickel nanoparticles contribute to the increased production of reactive oxygen species while reducing the activity of enzymes that protect against them [8, 15].

Ultimately, nickel damages DNA molecules in the body in 3 main ways: through reactive oxygen species, damage of the DNA repair system, and breaking DNA strands [8, 10, 15].

Nickel can cause allergies and it is estimated that up to 10–20% of the population may be allergic to nickel. This condition affects many more women than men, and the symptoms of the allergy can be caused by contact with, among others, buttons, belts, jewelry, kitchen utensils, orthodontic appliances and electronics [16]. The most common form of nickel allergy is contact dermatitis. In addition, conjunctivitis, asthma, or rhinitis can occur. There have also been reports of people with baboon syndrome [17].

For the average person, food is the main source of exposure to nickel. Nickel is consumed mainly from foods such as: hazelnuts, cocoa, soybeans, giblets, seafood, whole grains, mushrooms, fruits (almonds, dates, figs, pineapple, plums, raspberries), leafy vegetables, legumes, tomatoes, beer, wine, coffee, and tea [18]. Nickel is found naturally in drinking water and various foods and is thus difficult to avoid in our diet [1]. The nickel content in products varies depending on the element content in the soil where the food was produced. In addition, the release of nickel from cookware can increase total nickel intake [1, 19]. The usual diet is estimated to result in the consumption of <300 μg of nickel per day [1, 20]. Nickel deficiency in humans has never been recorded because overall nickel consumption significantly exceeds the nutritional recommendations that have been estimated between 5–50 μg per day [7]. According to European Food Safety Authority (EFSA), a tolerable daily intake (TDI) of nickel is 2.8 μg Ni/kg body weight per day [21]. However, "the current chronic dietary exposure raises health concerns for all age groups and that the acute exposure is of concern for nickel-sensitized individuals" [21]. Nickel is not regulated in food, but a max. of 20 μg of nickel per L of drinking water is allowed in the European Union [20]. The level of nickel in drinking water is approx. 1–10 μg/L [22]. In particularly sensitive groups of the population, after consuming the above-mentioned products, skin lesions may develop or worsen. Additionally, there may be extra-cutaneous symptoms: diarrhea, nausea, vomiting, headaches, chronic fatigue. The comorbidity of the above-mentioned symptoms is referred to as systemic nickel allergy syndrome (SNAS) [23]. Moreover, nickel supplied with food significantly affects intestinal microbiota [18].

Microbiota

The human body is assumed to have 10 times more probiotics than human cells. The set of all microorganisms living in a specific environment (the human organism – the host), i.e., bacteria, fungi, viruses, and archaea, is called the microbiota [2, 24].

Theoretically, we are born with a sterile gastrointestinal tract (although the theory of 'sterile uterus' has recently been questioned). However, colonization of the intestine occurs during delivery and the first hours of a newborn's life [2, 25]. Maternal factors can influence the composition of the baby's microbiota. The type of delivery and feeding method (natural or artificial) has a decisive influence on the colonization of the baby's intestines. Having siblings also positively influence the diversification of the gut microbiota [26]. The process of differentiating the composition and number of microorganisms in the human body is most intense in the first 2 years of life, although this may change at any time [27]. There is evidence from animal studies that stress during the first years of life can bring about disturbances of the gut microflora. For example, when a baby rat is exposed to stress factors during the first years of life (e.g., separation from the mother), its microbiota changes (reducing the number of beneficial *Lactobacillus* bacteria) and this may be a factor in the development of stress-related diseases in adulthood [28].

Although the composition of microbiota is unique for each individual, it can be assumed that the bacteria of the phyla Firmicutes, Bacteroidetes, Proteobacteria, Verrucomicrobia, Fusobacteria, and Actinobacteria are the main components of our microbiota [24]. The microbiota of the upper and lower gastrointestinal tract consists mostly of anaerobic bacteria (there are about 2–3 times more of them than aerobic bacteria) [2]. In people over the age of 70, digestion, nutrient absorption changes, immune activity weakness, and a monotonous diet influence gut microbiota [29]. In the elderly, the composition of microbiota is dominated by *Clostridium*, *Eubacterium,*

and *Fusobacterium* due to the change in intestinal pH to the approx. value of 7.0–7.5 [29, 30]. A decrease in anaerobic bacteria such as *Bifidobacterium* spp. may contribute to low systemic inflammatory status and malnutrition. The content of adipose tissue also influences the composition of the microbiota. Children with increased body weight have relatively low proportions of *Bifidobacterium vulgatus* and high concentrations of *Lactobacillus* spp. [29]. What is more, obesity is associated with elevated levels of Firmicutes such as *Ruminococcaceae* and decreased levels of Bacteroidetes such as *Bacteroidaceae* and *Bacteroides* [29, 31]. The differences in the composition of microorganisms inhabiting the human body also depend on diet (the Western diet contributes to the growth of *Ruminococcus* bacteria), geographical area (African microbiota is dominated by bacteria of the *Bacteroides* type, Europeans by *Enterobacteriaceae*), and age [24].

Regardless of the country of origin, age, or skin color, intestinal microbiota affects many aspects of physiology in human beings. The main functions of probiotic bacteria include [32]:

- participation in metabolic processes (mainly in the decomposition of complex compounds into simple ones),
- development of the mucosa and improvement of peristalsis,
- protective effect on the intestinal epithelium against pathogens, as well as reducing the permeability of the epithelium,
- limiting the development of unfavorable bacteria by competition for an ecological niche,
- influence on the immune system,
- breakdown of dietary fiber,
- metabolism of some drugs and harmful substances [26].

Microbiota also plays a vital role in digestive processes. Indigestible nutrients can be broken down by probiotic organisms. The mucosa of the large intestine is nourished by short-chain fatty acids, which are formed endogenously in the lumen of the gastrointestinal tract as a product of anaerobic bacterial fermentation of the dietary fiber and resistant starch. Short-chain fatty acids also have other functions: stimulating the development of peripheral tissues and liver cells, regulating intestinal pH, and increasing the absorption of calcium, magnesium, and iron [33, 34]. Moreover, probiotic bacteria can synthesize vitamins (mainly from group B and vitamin K), to produce free amino acids, and to digest lactose (mainly *Lactobacillus* and Enterobacteriaceae) [35].

By their presence in the intestine, probiotic organisms prevent unfavorable bacteria from anchoring. They also produce bacteriocins and organic acids that inhibit the development of pathogens, and by creating a biofilm, they have a protective effect, preventing direct contact of the intestinal mucosa with substances derived from food [35].

In health, all microorganisms, including bacteria, are in a state of equilibrium, which is known as eubiosis. Disruption of this balance results in dysbiosis. While in a state of dysbiosis, pro-inflammatory endotoxins are produced, which enter the bloodstream and are transported throughout the body. Dysbiosis also leads to the formation of pro-inflammatory cytokines, unsealing of the intestinal barrier, and leaky gut syndrome [36]. Currently, the correlation between dysbiosis and the occurrence of obesity, allergies, autoimmune diseases, inflammatory bowel diseases, irritable bowel syndrome, or depression is increasingly emphasized [2].

The influence of nickel (and other heavy metals) on the gut microbiota

As already mentioned, the composition of the gut microbiota can be influenced by different factors such as diet, stress, or genetic predisposition. In addition, there are reports on the adverse effects of toxic substances from the environment, such as heavy metals, air pollution, or nanoparticles [37].

Nickel, in the active site of several enzymes, is responsible for the catalysis of important biological reactions, such as urea hydrolysis, hydrogen metabolism, methane formation, superoxide metabolism, and methylglyoxal detoxification. For many bacteria, archaea, and unicellular eukaryotes, these nickel-dependent processes enable the colonization of inhospitable and hostile environments. These include human and animal organisms in which these nickel-binding pathogens grow and survive through nickel catalysed reactions. Consequently, some nickel-dependent enzymes (e.g., urease, hydrogenase, CO-dehydrogenase) are virulence factors for pathogenic organisms. Catalyzed nickel-dependent processes and nickel delivery mechanisms to specific enzymes can be viewed and used as possible selective targets to control the pathogenesis of nickel-binding organisms [6].

On the one hand, it seems that due to the existence of a wide group of Ni2+-dependent metalloenzymes, both among prokaryotes and eukaryotes, nickel is necessary for the proper functioning of the microbiota. Several species of bacteria with pro-health effects found in the human and animal intestines show constant urease activity, for the proper functioning of which nickel cations are necessary (e.g., bacteria of the genus *Bifidobacterium*: *B. bifidum* and *B. longum*, or *Lactobacillus*: *L. fermentum*) [6, 38]. On the other hand, the available research results indicate that intestinal microbiota has a certain protective effect against the adverse effects of heavy metals as it may reduce their toxicity [39]. For example, some strains of lactic acid bacteria (e.g. *L. fermentum*) consume nickel ingested with food and thus play a role in its detoxification [40]. The possibility of analyzing the composition of the microbiota as a determinant of exposure to heavy metals is also considered [39].

There are many studies on the influence of heavy metals (nickel, cadmium, lithium, arsenic) on the microbiota in available literature [41, 42, 43, 44]. Studies in animal models showed that chickens fed with nickel-enriched fodder had higher amounts of *Escherichia coli* and *Enterococcus* in the microbiota composition. However, in their intestines, smaller amounts of probiotic *Bifidobacterium* and *Lactobacillus* were found [45]. In various studies that used other heavy metals, similar results were reported – an increase in the number of unfavorable bacteria. Cadmium supplementation caused the growth of Verrucomicrobia in mice [46], and lithium – Lachnospiraceae [47]. The rat microbiota, after oral nickel compound loading, was characterized by a reduced amount of

Verrucomicrobia and some representatives of the Bacteroidetes [39]. In mice, an increased amount of *B. fragilis* and *Interstinimonas* and a decreased amount of Firmicutes were noted, resulting in a disturbed ratio of Firmicutes to Bacteroides. The ratio of the 2 types of bacteria is often used to assess the overall health of the gut microbiota. A study by Zhou et al. also found increased amounts of bacteria from the Bacteroidales *S24-7*. The authors of the study suggested that this bacterium may be involved in the immune response induced by nickel supply [48]. Another study involving the analysis of bacterial composition in animals included representatives of the Bufo toads living in an environment heavily contaminated with heavy metals. These toads were characterized by an increased amount of bacteria of the Bacteroidetes type, and those occupying areas distant from industrial pollution – by a large number of *Tenericutes*. In addition, animals from contaminated areas had a disturbed proportion of Firmicutes to Bacteroidetes [37].

Nickel exposure may lead to dysbiosis

Changes in the composition of the microbiota under the influence of nickel ions are also observed in humans. This is confirmed by a study carried out on a group of women with a diagnosed nickel allergy. It was noticed that with a high supply of nickel, dysbiotic microbiota developed which contained a reduced amount of Enterobacteriaceae and increased *Bacillaceae* and *Clostridiaceae*, i.e., microorganisms highly resistant to nickel [40]. Also, people diagnosed with SNAS are very often characterized by a state of intestinal dysbiosis. It could be one of the extra-cutaneous symptoms of this condition. Among people diagnosed with SNAS, bacterial overgrowth in the small intestine (fermentation dysbiosis) was reported in most cases. In these cases, the patients were given probiotics containing bacteria from the *Lactobacillus*. In studies involving people with diagnosed SNAS, a low-nutrient diet was also introduced and its effect on skin symptoms and the condition of microbiota was observed. This diet resulted not only in the relief of skin symptoms reported by patients but also relief from extra-cutaneous symptoms (including reduction of intestinal dysbiosis) [23, 49, 50, 51, 52]. Therefore, it is possible to consider the supply of probiotics during the exacerbation of SNAS considering the connection with their influence on immune response.

In addition, some nickel-dependent prokaryotic and eukaryotic microorganisms infect the human body as intracellular parasites. The most important eukaryotic pathogens are Trypanosomatides, such as *Trypanosoma cruzi* and *Leishmania* spp., which are protozoa causing Chagas disease and leishmaniasis [6]. Nickel is necessary for the colonization and growth of intracellular fungi that cause meningitis, e.g., *Cryptococcus*, and some bacterial strains such as *Staphylococcus*, *Clostridium*, *Vibrio*, *Mycobacterium*, *Yersinia*, *Escherichia*, *Proteus*, *Ureaplasma*, *Klebsiella*, *Pseudomonas*, *Providencia*, and *Morganella* [9].

Nickel free-diet enhances the *Helicobacter pylori* eradication

The use of a low-nickel diet seems to be beneficial as an additional therapy during the eradication of *Helicobacter pylori*, which is one of the most common bacterial infections in the world [53, 54]. *Helicobacter pylori* is a Gram-negative bacterium and the main causative agent of many acute and chronic pathologies of the stomach, including peptic ulcers. As the human stomach is a hostile environment for this bacterium, it has developed several adaptive mechanisms that allow it to survive. The key determinants for bacterial colonization are 2 nickel enzymes, i.e., Ni_2^{+-}dependent urease, which enables the buffering of the acidic environment of the stomach, and [NiFe]-hydrogenase, which provides the free use of energetic hydrogen available in the stomach niche. Moreover, *H. pylori* are probably able to accumulate Ni_2^+ when relatively high exogenous concentrations of this ion are available [6]. Based on the provided information, it can be concluded that, since *H. pylori* belong to the bacteria that need nickel to survive, its restriction in the diet should limit the growth and development of bacteria [55, 56].

Nickel exposure and the development of obesity

Recent studies also suggest the possible influence of nickel on the development of obesity. On the one hand, the probability of the existence of *Lactobacillae* strains resistant to nickel in the digestive system of obese people, which shape their phenotypes, is considered [40]. On the other hand, it has been proven that unfavorable changes in the intestinal microbiota may be a factor in the development of excess body weight. Nickel-induced dysbiosis, as well as the associated disturbance of the intestinal mucosa and the immune response, may be a basis for the metabolic and inflammatory changes observed in people with excess body weight. Another important issue is the observed beneficial effect of probiotic therapy in the treatment of obesity [57, 58, 59, 60, 61, 62, 63]. The percentage of obese people with a nickel allergy is higher (about 60%) than in the general population (12.5%) [58, 64]. Moreover, the implementation of a normal caloric diet with a reduced amount of nickel contributed to a decrease in body mass index and a decrease in waist circumference [64].

CONCLUSIONS

The wide use of nickel in many consumer products, as well as its widespread presence in water and food, increases the probability of human contact with this metal [6, 9]. The negative effects of excessive exposure to nickel are well known [6, 9].

Apart from inducing an allergic response (mild or more developed), when ingested with food, nickel may directly influence gastrointestinal microbiota [39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52]. Some strains of bacteria exerting beneficial effects on health show the ability to neutralize this metal, e.g., representatives of *Lactobacillus* [40].

Nevertheless, excess nickel intake contributes to the disturbance of the appropriate composition of the intestinal microflora, especially in people with diagnosed SNAS [23, 49, 50, 51, 52]. This may entail further adverse health effects, including a possible contribution to the development of obesity [40, 64].

Further research on the influence of nickel on the human body and the probiotic microorganisms that live in it should be conducted. In particular, the potential possibility of alleviating nickel allergy exacerbations by introducing appropriate probiotic therapy should be investigated.

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