The Role of Cobalt in Human Health: A Brief Overview

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Abstract
Cobalt is a crucial trace element for the human body. It serves as an essential component of vitamin B12 and plays a pivotal role in the synthesis of amino acids and select proteins within nerve cells, as well as in the synthesis of neurotransmitters vital for the proper functioning of the body. Both excess and deficiency of cobalt can have detrimental effects on the human body. Notwithstanding the paramount significance of cobalt as a trace element, comprehensive studies are necessary to evaluate its role in physiological processes.

Keywords: cobalt, human health, trace element, vitamin B12, physiological processes

1. Introduction
Cobalt is an indispensable trace element for the human body, and it can be found in both organic and inorganic forms. The organic form is a vital component of vitamin B\textsubscript{12}, serving a pivotal role in the synthesis of amino acids and specific proteins within the nerve cells, as well as in the production of neurotransmitters essential for the proper functioning of the body. An excess or deficiency of cobalt can have adverse effects on human health. The objective of our review is to examine the scientific literature regarding the role of cobalt in human health. The primary function of cobalt in humans is predicated on its role in cobalamin. Cobalamin acts as a cofactor for two enzymes, namely, methylmalonyl-CoA mutase and methionine synthase within the human body [1].

Cobalt is widely distributed in the natural environment and can be generated as a result of anthropogenic activities. Cobalt salts have been employed in medicine for the treatment of anemia and, in sports, as an appealing alternative to traditional doping practices such as blood transfusions. Inorganic forms of cobalt, when present in ionic form, exhibit toxicity to the human body, and the longer they persist in the body, the greater the cellular changes they induce. Cobalt enters the body through several...
avenues: (i) through food consumption, (ii) via inhalation through the respiratory system, (iii) by skin contact, and (iv) as a component of biomaterials [2].

2. Cobalt and its Vital Role in Human Health: Implications for Growth, Cardiovascular Function, and Development

While cobalt plays a crucial role, the human body typically contains only about 2 mg of it. Vitamin $\text{B}_{12}$ (cobalamin) molecules are integral to various biological processes, particularly in the transfer of methyl groups, such as in DNA. The average recommended daily intake for an individual is typically a few micrograms (mcg). The entire cobalamin molecule must be obtained from the dietary sources. In the digestive tract, specific proteins have the capability to selectively absorb vitamin B12 from food, and carrier proteins are involved in its distribution. Typically, the vitamin is associated with a gastric factor. In the ileum, a specific receptor complex is formed by two proteins, namely, amnionless and cubilin [3].

An imbalance of trace elements, including cobalt, in children's bodies can lead to delays in physical, mental, and sexual development, decreased immunity, and the onset of chronic diseases. In the maintenance of the structure and function of the entire cardiovascular system, a critical role is attributed to approximately 25 to 45% of all macro- and microelements that are integral components of protein molecules, hormones, and enzymes. Even minor fluctuations in the levels of these microelements can trigger the development of cardiovascular diseases. The physiologically active form of cobalt is vitamin B12, and a deficiency of cobalt in the body essentially translates to a deficiency of vitamin B12, characterized by symptoms such as megaloblastic anemia. Cobalt directly participates in numerous processes associated with growth, development, and the proper functioning of the cardiovascular and other systems, rendering the investigation of this highly pertinent issue. Studies have revealed reduced cobalt levels in the hair of 89% of examined girls aged 7–8 years experiencing health problems. Cobalt deficiency in the body detrimentally affects lung capacity and growth. Maintaining an adequate cobalt level in the body plays a crucial role in influencing heart rate and diastolic blood pressure [4].

3. Cobalt’s Multifaceted Role in Human Health: Thyroid Function, Carcinogenic Properties, and Metabolic Implications

Cobalt plays a role in the metabolism of thyroid hormones. It is understood that a deficiency of cobalt in the body hinders the enzymatic reactions involved in thyroxine
synthesis, resulting in reduced activity of tyrosine iodi

Based on both experimental and epidemiological data, it is established that cobalt compounds exhibit genotoxic and carcinogenic properties. The primary pathways of exposure to cobalt compounds include inhalation through the respiratory system and endogenous exposure from alloys containing cobalt, which are utilized in endoprostheses. A growing body of evidence suggests that chronic inhalation of cobalt compounds may lead to the development of localized tumors within the airways. Nevertheless, there is no substantiated evidence indicating systemic carcinogenicity resulting from inhalation, oral ingestion, or endogenous exposure [6].

In a study investigating the role of cobalt in the development of dyslipidemia, hypertension, and diabetes, it was observed that elevated blood cobalt concentrations were linked to a reduced risk of dyslipidemia. Nevertheless, no significant associations were detected between blood cobalt concentrations and the risks of hypertension or diabetes [7].

Another study examined plasma cobalt concentrations during and after coronary artery bypass surgery under cardiopulmonary bypass. Cobalt concentration was significantly reduced on the first day after surgery (0.35±0.19 vs. 0.26±0.13 μg/L, p<0.01) and on the fourth day (0.35±0.19 vs. 0.23±0.11 μg/L, p<0.001) [8].

4. Cobalt’s Interplay in Human Biology: Competition with Iron, Athletic Serum Levels, and Pregnancy-Related Impacts

Cobalt is an indispensable trace element found in both prokaryotes and eukaryotes, although it is less prevalent in metalloproteins compared to other transition metals. This reduced prevalence is attributed to its competition with iron, which serves crucial biological functions in processes such as respiration and photosynthesis. Cobalt’s significant biological role is associated with its involvement in iron utilization [9].

When evaluating serum cobalt levels in athletes, it was observed that cobalt concentrations in aerobic-anaerobic athletes were significantly lower (p<0.01) compared to those in the control group. These findings suggest that long-term daily physical training may lead to variations in the serum concentrations of certain essential elements in athletes when compared to untrained individuals [10].
Women tend to accumulate more cobalt than men at comparable levels of exposure, a phenomenon possibly linked to increased metabolic losses of iron. Notably, during pregnancy, these losses become notably pronounced, yet their impact on cobalt intake has not been thoroughly investigated. In a study by Fort M. et al. in 2015, the relationship between alterations in hemoglobin levels and urinary cobalt excretion during pregnancy was examined. The study involved the collection of 391 pairs of urine and blood samples from pregnant women at 12 and 32 weeks of pregnancy, which were subsequently analyzed for cobalt and hemoglobin levels. Mean urinary cobalt concentrations were found to be 0.73 and 1.6 µg/g creatinine during the first and third trimesters, respectively (p<0.001). Significantly, 84% of pregnant women exhibited higher cobalt levels in the third trimester compared to the first. Furthermore, cobalt concentrations were inversely correlated with hemoglobin levels in the third trimester (p<0.05). Women who experienced a more substantial reduction in iron levels between the two trimesters demonstrated a significant increase in cobalt levels during this period. Notably, this correlation extended to a statistically significant difference in mean third-trimester cobalt concentrations between women with and without anemia, measuring 1.8 and 1.5 µg/g creatinine, respectively (p < 0.05), although no such differences were observed during the first trimester. These findings were employed in the development of generalized additive models, which encompassed both normal and anemic women. The robust association identified between fluctuations in iron status and urinary cobalt levels in pregnant women may be attributed to the enhanced intestinal absorption of cobalt that occurs when iron stores are depleted, particularly during late pregnancy when iron demands are heightened [11].

5. Cobalt Exposure and its Multifaceted Health Implications: Dose-Response Relationships, Systemic Toxicity, and Cancer Associations

Cobalt and its compounds are widely distributed in nature and are associated with numerous anthropogenic activities. Sources of cobalt exposure can be categorized into four conditions: occupational, environmental, dietary, and medical. The highest systemic cobalt concentrations are typically observed with oral cobalt supplementation and internal exposure from metal-on-metal hip implants. The resulting systemic health consequences manifest as a complex clinical syndrome, primarily encompassing neurological issues (e.g., hearing and visual impairment), cardiovascular complications, and endocrine deficits. Recently, a biokinetic model has been introduced to elucidate the dose-response relationship and the effects of chronic exposure. According to this model, health effects are improbable at blood cobalt concentrations below 300 µg/L (or
100 µg/L with a safety factor of 3) in healthy individuals. Hematological and endocrine dysfunction are identified as the principal health endpoints in the model, and it further suggests that chronic exposure within acceptable doses does not pose a substantial health risk [12].

Adverse health effects resulting from cobalt exposure, including conditions like cardiomyopathy and impairments in vision or hearing, have been reported at peak blood cobalt concentrations typically exceeding 700 µg/L (over a duration of 8–40 weeks). In humans, reversible hypothyroidism has been observed at cobalt levels around 300 µg/L and higher, along with instances of polycythemia. The mechanism behind systemic toxicity is directly linked to the interaction of free Co (II) ions with various receptors, ion channels, and biomolecules. Notably, these effects are generally reversible. Certain deviations from the typical dose-response pattern in cobalt toxicity may be attributed to rare medical conditions that reduce the systemic binding of Co (II) ions to blood proteins. Based on the available information, in most individuals with ostensibly elevated serum cobalt levels, such as users of dietary supplements and patients with hip implants, over 90% of the cobalt is bound to albumin, which possesses significant excess capacity for binding Co (II) ions. Given the existing data, it may be advisable to monitor implant patients for signs of hypothyroidism and polycythemia, particularly when their blood or serum cobalt concentrations exceed 100 µg/L [13].

Essential elements play a crucial role in the regulation of carcinogenesis. In a study investigating the association between essential elements and kidney tumors, comprising 72 healthy individuals and 100 patients with kidney tumors, it was found that levels of cobalt, chromium, iron, manganese, nickel, and zinc were markedly lower in patients with kidney tumors. The Kaplan-Meier curve analysis demonstrated that patients with reduced levels of cobalt, selenium, and zinc experienced lower progression-free survival rates [14].

The available literature highlights the role of cobalt in fostering hypoxic tolerance by activating hypoxia-inducible factor 1 (HIF-1), which may partly elucidate its significance during physical activity [15]. It has been demonstrated that children with limited functional reserves often exhibit cobalt deficiency, further underscoring the importance of this element for overall bodily functions [16].

6. Unraveling the Complex Interplay of Cobalt Toxicity and Trace Element Metabolism: Implications for Systemic Health and Metal Transport Mechanisms

Conversely, excessive intake of cobalt compounds into the body can lead to toxicity through various mechanisms, including pro-oxidant and pro-inflammatory effects. Cobalt
toxicity has been linked to pathological conditions affecting the cardiovascular, nervous, and endocrine systems [17, 18].

Furthermore, cobalt metabolism has been found to be intertwined with the metabolism of other essential trace elements. For instance, ferroportin, an iron transporter, is capable of transporting cobalt ions. Similarly, specific zinc transporters have the ability to transport cobalt. Moreover, excessive cobalt exposure in vitro can interfere with the metabolism of zinc and magnesium through competitive inhibition of their binding to transport proteins [19–21].

In a study conducted by Glukhcheva Y. in 2019, the impact of perinatal cobalt exposure on the metabolism of copper, iron, manganese, and zinc in ICR mice during early development was investigated using inductively coupled plasma mass spectrometry. The data obtained indicated a substantial influence of cobalt intake on the levels of this metal in various organs and tissues of the animals. Specifically, a significant increase in cobalt content was observed, amounting to 68-fold in the kidneys, 3.8-fold in the spleen, 11.3-fold in muscle, 41.3-fold in the liver, and 162-fold in erythrocytes. The introduction of cobalt chloride (CoCl2) into the animals' bodies also led to notable alterations in the metabolism of essential metals. Animals exposed to cobalt exhibited a significant increase in iron content in the kidney and liver by 27% and 15%, respectively. There was a trend towards increased iron content in the spleen of the laboratory animals (approximately +69%), though it did not reach statistical significance. Furthermore, exposure to CoCl2 resulted in a significant 24% rise in copper levels within the spleen parenchyma relative to control values. Simultaneously, a more than twofold increase in copper concentration in the erythrocytes of the laboratory animals was noted. Perinatal cobalt exposure was shown to enhance the availability of essential metals in ICR mice, including iron, copper, manganese, and zinc. It is postulated that the impact of cobalt on the metabolism of these metals, along with selenium, may be mediated through the cobalt-induced stimulation of hypoxia-inducible factor 1 (HIF-1), subsequently influencing the activity of metal transporters (e.g., DMT-1, ferroportin), possibly via the modulation of hepcidin production. Considering the role of these metals in the body's functioning and the link between cobalt deficiency and reduced functional reserves, it is suggested that the modulation of metal metabolism may be one of the factors influencing the physiological effects of cobalt [22].

7. Influence of Cobalt Exposure on Trace Element Distribution, Pediatric Iron Status, Respiratory Health, and Occupational Risk Assessment

The impact of cobalt on the tissue distribution of iron, copper, manganese, and zinc, as well as on serum hepcidin levels in immature animals, was examined. Pregnant
mice were subjected to a regimen of cobalt chloride at a dose of 75 mg/kg body weight, commencing three days prior to parturition and continuing through lactation. When evaluated in the offspring, a time- and tissue-dependent increase in cobalt levels was observed in the kidneys, spleen, liver, muscle, red blood cells, and serum, with assessments conducted at 18, 25, and 30 days of age. Concomitant with the rise in cobalt levels, exposure to CoCl2 led to a significant accumulation of copper, iron, manganese, and zinc in the examined tissues, with the most pronounced effects observed in 25-day-old mice. Notably, cobalt exposure resulted in a substantial increase in serum hepcidin levels only in the 18-day-old mice. These findings imply that cobalt exposure has the potential to influence the metabolism of copper, iron, manganese, and zinc [23].

Among children residing in an industrialized area, a noteworthy inverse correlation was established between urine cobalt levels and venous blood ferritin concentrations. In children diagnosed with iron deficiency anemia, cobalt concentrations were markedly higher compared to those in the control group. The authors ascribed these findings to an augmented expression of DMT1, a divalent metal transporter that becomes more active in response to elevated iron levels associated with states of iron deficiency. This transporter, albeit nonspecific, captures not only iron but also other divalent metals, including cobalt. The presence of cobalt in children with iron deficiency anemia may represent an additional health consideration that warrants attention during treatment [24].

A Swedish study investigated the association between inhaled dust, cobalt, respiratory symptoms, lung function, as well as exhaled nitric oxide. The study involved 72 workers in the carbide industry, with mean respirable dust and cobalt concentrations measuring 0.079 and 0.0017 mg/m³, respectively. The results suggested an exposure-response relationship concerning cumulative inhalation exposure to cobalt [25].

When evaluating cobalt exposure in industrial settings in Italy, it was revealed that the majority of adverse exposures occurred during the production of fabricated metal products (50%) and among operators of metalworking, electroplating, and varnishing machines (42%). The study estimated that a total of 30,401 workers were potentially exposed to cobalt, with over 72% of them being men. The average concentration of cobalt in the workplace air was approximately 0.33 µg/m³ [26].

8. Conclusion

Cobalt constitutes an essential trace element for the human body, serving as a vital component of vitamin B₁₂ and playing a critical role in the synthesis of amino acids and specific proteins within nerve cells, as well as in the generation of neurotransmitters essential for the proper functioning of the body. Both an excess and a deficiency of cobalt can have adverse effects on the human body. Despite the pivotal role that cobalt
plays, there is a paucity of research, and further studies are needed to comprehensively evaluate its role in physiological processes within the human body.

References


