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IODINE DEFICIENCY AND CARDIOVASCULAR DISEASES: A DEEP ANALYSIS

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Abstract
Iodine deficiency can lead to a decrease in myocardial contractility, increased peripheral vascular resistance, and lipid metabolism disorders. To determine iodine deficiency as a risk factor for cardiovascular diseases, 42 patients (mean age 65 ± 13 years, 16 males) were studied. Patients were divided into 5 subgroups based on the presence of hypertension, heart failure, cardiomyopathy, coronary dysfunction, and arrhythmia. Urinary iodine concentration (5.29 ± 4.52 mcg/dl) was determined using the Sandell-Kolthoff colorimetric reaction. The greatest decrease in urinary iodine concentration was observed in subgroups with arrhythmia and heart failure (4.7 ± 4.94 mcg/dl and 4.9 ± 4.81 mcg/dl, respectively). In 3 patients, an elevated level of thyroid-stimulating hormone was detected (5.3 ± 1.4 mME/l). In subgroups without arrhythmia, an increase in lipid (cholesterol, triglycerides) levels was noted. Thus, iodine deficiency is common in cardiovascular diseases. Iodine supplements may prevent the worsening of cardiovascular system status under conditions of iodine deficiency.

Introduction

Worldwide, the incidence, disability, and mortality rates from cardiovascular diseases (CVD) are increasing every year [1]. According to various studies, the rise in CVD is mainly due to the increase in incidence among younger individuals [2]. The results of the multi-center collaborative study (PDAY) on the pathobiological determinants of atherosclerosis in youth indicated that the degree of atherosclerotic changes in coronary arteries among individuals aged 15-34 is associated with dyslipidemia (DLP), arterial hypertension (AH), obesity, and blood glucose concentration. This study demonstrated that the process of atherosclerosis begins as early as adolescence and progresses with age when risk factors are present [15].

In recent years, significant attention has been given to cases of iodine deficiency. The role of iodine in the normal functioning of the body is that this micronutrient is a structural component of thyroid hormones, and its deficiency is the main cause of thyroid hormone synthesis disruption. The impact of thyroid function on the cardiovascular system (CVS) has been known for a long time—over 200 years ago, the first descriptions of hyperthyroidism and thyrotoxicosis appeared. In conditions of iodine deficiency (ID), even with normal thyroid function, various stress situations may lead to its temporary hypofunction or subclinical hypothyroidism, and if iodine deficiency persists for a long time, clear hypothyroidism may develop. In the studies of A. Hak and colleagues [3], it was proven that the risk of aortic atherosclerosis in subclinical hypothyroidism increases by 1.7 times, and the risk of myocardial infarction increases by 2.3 times.

Thyroid hormones are necessary for the binding of low-density lipoprotein (LDL) cholesterol to their receptors. In hypothyroidism, a decrease in the density of LDL receptors in fibroblasts, liver, and other tissues has been identified, which leads to the accumulation of LDL cholesterol in the

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blood. Patients with reduced thyroid function often exhibit hypercholesterolemia (HC), which results from increased cholesterol reabsorption in the intestines and decreased lipogenic activity in the liver. In subclinical hypothyroidism, HC and hypertriglyceridemia (HTG) are frequently observed together. Additionally, elevated levels of apolipoprotein A (ApoA) and apolipoprotein E, and a decrease in high-density lipoprotein cholesterol (HDL-C) levels in the blood, have been identified [4].

Several studies have shown that in conditions of iodine deficiency, when thyroid function is reduced, there is a change in peripheral blood vessel tone, particularly a decrease in endothelial-dependent vasodilation mediated by nitric oxide, a decrease in the elasticity of the blood vessel wall, and an increased risk of CVD. Iodine, as a micronutrient necessary for thyroid hormone synthesis, plays an important role in regulating various physiological processes, including cardiovascular function. Iodine deficiency, a global health problem, is increasingly linked to the pathogenesis of cardiovascular diseases. This review explores the complex mechanisms connecting iodine deficiency with CVD.[5]

Research Objective:

To evaluate the impact of iodine deficiency on cardiovascular risk in young men and to develop corrective methods for the early prevention of metabolic disorders.

Research Methods:

The study was aimed at identifying risk factors, studying the cardiovascular system (CVS), thyroid gland (TG), blood serum lipid profile, free radicals, and antioxidant systems, as well as the status of microelements.

Evidence from Population Studies

Numerous epidemiological studies have demonstrated a significant association between iodine deficiency and an increased risk of cardiovascular diseases (CVDs). These studies have shown that:

- **Low urinary iodine levels** are associated with an increased risk of coronary artery disease (CAD), stroke, and heart failure, even in individuals without overt hypothyroidism. This means that even when the thyroid gland is functioning normally, low iodine levels can still contribute to heart problems.
- **Iodine supplementation** can improve cardiovascular risk factors, such as lipid profiles and blood pressure, in individuals with subclinical hypothyroidism. This indicates that increasing iodine intake can have beneficial effects on heart health, especially for people with mildly underactive thyroid glands.
- **Populations with higher iodine intake** tend to have lower rates of CVD. This suggests a strong correlation between adequate iodine intake and reduced cardiovascular risk.[5]

Additional Considerations:

- **Causation vs. Correlation:** While these studies demonstrate a strong association between iodine deficiency and CVDs, they do not necessarily prove causation. Other factors may also contribute to the observed relationship.
- **Individual Variability:** The effects of iodine supplementation may vary depending on individual factors such as age, gender, and overall health status.

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• **Public Health Implications:** These findings highlight the importance of public health programs aimed at preventing iodine deficiency, such as iodized salt fortification.

Urinary Iodine as a Biomarker

Urinary iodine content is a quantitative and direct indicator of iodine sufficiency. While literature suggests that iodine concentration in an individual can fluctuate throughout the day and may not accurately reflect an individual's iodine status, the method of determining iodine concentration in urine is recommended for epidemiological studies. However, numerous studies have shown that urinary iodine concentration correlates with the level of iodine in 24-hour urine [8].

According to the literature, about 90% of dietary iodine is excreted in the urine [5, 7, 13, 17], and urinary iodine concentration can serve as an indicator that adequately reflects iodine intake. In the group of young men examined, the median urinary iodine was 112 mcg/L. This value indicates that there is no iodine deficiency in this population. The recommended physiological daily intake of iodine for an adult is 150 mcg [75]. Considering these data, the median urinary iodine obtained in the study indicates a reduced iodine intake. In this case, the median urinary iodine in the study group should correspond to 135 mcg/L, meaning that iodine intake in these young men is reduced by 18%.

The study of only one indicator of iodine concentration in urine does not allow for an accurate determination of the severity of iodine deficiency. For a more in-depth analysis of urinary iodine, an additional criterion for assessing urinary iodine was used - the frequency distribution indicator, i.e., the number of variants in 4 classes of the variation series: < 20 mcg/L, 20-49 mcg/L, 50-99 mcg/L, > 100 mcg/L [3, 4, 6, 7, 15]. In our study, the indicators of urinary iodine in young men were distributed across two classes of the variation series (Table 3.1.1). Of all the young men examined, iodine deficiency was detected in 63 people (26.6%), with a median urinary iodine of 91.8 mcg/L, which corresponds to mild iodine deficiency.

Explanation:

This passage discusses the use of urinary iodine concentration as a biomarker for assessing iodine status in a population. The key points are:

• **Urinary iodine is a reliable indicator of iodine intake:** Despite daily fluctuations, urinary iodine concentration is a good measure of overall iodine status, especially when used in epidemiological studies.

• **Iodine deficiency was observed in the study population:** The median urinary iodine concentration was lower than the recommended daily intake, indicating a reduced iodine intake in the young men studied.

• **Frequency distribution analysis:** By categorizing urinary iodine levels into different ranges, the researchers were able to identify a significant proportion of individuals with mild iodine deficiency.

Key terms and concepts:

• **Urinary iodine:** The amount of iodine excreted in urine.

• **Iodine sufficiency:** The state of having adequate iodine intake to meet the body's needs.

• **Epidemiological studies:** Studies that examine patterns of disease occurrence in populations.

• **Iodine deficiency:** A condition where the body does not have enough iodine.

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• **Subclinical hypothyroidism:** A condition where the thyroid gland is underactive but not enough to cause symptoms.

Frequency distribution of urinary iodine levels and goiter prevalence in young men. Tab.1

Urinary Iodine Level (mcg/L)	Number of Individuals	Median Urinary Iodine (mcg/L)	Frequency of Goiter (%)
> 100 (No Iodine Deficiency)	174	121	44
50-99 (Mild Iodine Deficiency)	63	91,8	6

While goiter is a common manifestation and criterion for iodine deficiency (ID), it's important to note that goiter prevalence reflects past, rather than current, iodine status. Goiters develop over 3-4 years in conditions of ID, and it takes time for the thyroid gland to normalize in size when iodine intake is adequate [3, 4, 6]. Therefore, goiter prevalence is an additional criterion to urinary iodine testing.

In Primorsky Krai, iodine deficiency of varying severity has been established, ranging from mild to moderate. Assessment of the dynamics of endemic goiter prevalence among children and adolescents in Primorsky Krai indicates an increasing severity of goiter endemicity [6, 83, 100, 129]. Upon palpation of the thyroid gland in 50 individuals (37.3%), diffuse goiter was detected. According to WHO criteria, ID is absent if goiter prevalence in the population is less than 5%; if the goiter frequency is 5-29.9%, this prevalence corresponds to a mild degree; with a goiter prevalence of 20-29.9%, it is moderate severity, and more than 30% is severe ID [23].

In 49 individuals with diffuse goiter, the goiter size corresponded to the 1st degree; in one person, the goiter size corresponded to the 2nd degree - this young man had previously been treated (taking iodine preparations for 1 year) for diffuse goiter.

Of the 50 people who had diffuse goiter, only 6 (2.5%) young men were found to have ID. This is consistent with the literature, which indicates that goiter prevalence does not depend on the level of iodine deficiency [16, 10, 16].

To assess the functional state of the thyroid gland, the level of hormones in serum is determined: TSH, fT4, fT3, and oT4. Currently, the diagnostic algorithm for studying thyroid function consists of the following stages: at the initial stage of the diagnostic search and in epidemiological studies, TSH is determined, at the second stage, fT4 is examined, and at the third level, fT3 is determined [11, 22].

Tab.2 **Thyroid hormone levels in the serum of young men.**

Hormone	Reference Range	Mean in Study Group
TSH (mIU/L)	0.23-3.4 (mean: 1.71)	1.38 ± 0.04
fT3 (nmol/L)	1.0-3.0 (mean: 2.00)	1.64 ± 0.02
fT4 (nmol/L)	56-172 (mean: 114)	80 ± 0.67
TT4 (pmol/L)	10-25 (mean: 17.5)	13.87 ± 0.15

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Variables:

- **TSH (Thyroid-stimulating hormone):** This hormone stimulates the thyroid gland to produce thyroid hormones.
- **fT3 (Free triiodothyronine):** An active form of thyroid hormone.
- **FT4 (Free thyroxine):** Another active form of thyroid hormone.
- **TT4 (Total thyroxine):** The total amount of thyroxine in the blood, including both the free and bound forms.

To determine the functional state of the thyroid gland in young men, the content of TSH, fT3, fT4, and TT4 in serum was determined (Table 2). The thyroid hormone T3 is the main biologically active thyroid hormone [18, 14, 18, 12]. The average values of thyroid hormones in the study group were within the normal range (Table 2).

TSH is the most important indicator for assessing thyroid function. Even latent or transient thyroid dysfunction can be detected by deviations in this hormone, when the serum levels of T3 and T4 have not yet changed. It is known that in subclinical hypothyroidism, TSH levels increase [5, 7, 20, 26, 16]. An analysis of the hormonal status revealed that in young men with iodine deficiency, TSH levels were higher compared to the level of this hormone in a young man without iodine deficiency, but the indicator remained within the normal range (Table 3).

Tab.3 **Thyroid hormone levels in young men**

Hormone	Reference Range	Mean in Group with ID (n=63)	Mean in Group without ID (n=174)	p-value
fT3 (nmol/L)	1.0-3.0	1.48 ± 0.04	1.68 ± 0.02 ***	<0.001
fT4 (nmol/L)	56-172	76.37 ± 1.38	82.48 ± 0.95 ***	<0.001
TT4 (pmol/L)	10-25	12.94 ± 0.28	14.12 ± 0.24 ***	<0.001
TSH (mIU/L)	0.23-3.4	1.43 ± 0.06	1.35 ± 0.56	<0.001
(fT3+fT4)/TSH	51.41-248	62.72 ± 2.66	67.81 ± 3.85	<0.001

$p<0.001$ indicates a statistically significant difference between the two groups.

There may be brief periods of thyroid deficiency under additional increased loads (psychological, physical) against a background of iodine deficiency, but the condition is compensated for by the pituitary-thyroid system, and thyroid gland function is considered 'normal'. The levels of fT3, fT4, and TT4 in the blood serum of the group of young men with iodine deficiency were significantly lower ($p<0.01$) than in the group of young men without iodine deficiency (but their indicators were also within the normal range), which is characteristic of normal thyroid hormone production, but with a slight tendency to decrease under conditions of mild iodine deficiency.

When analyzing the frequency distribution of thyroid hormone levels in young men, it was found that 4 individuals with a thyroid hormone level of TT4 below the norm had iodine deficiency. Other authors [3, 4] also noted a decrease in T4 with iodine deficiency. This is explained by the accelerated conversion of T4 to T3 and is considered a compensatory reaction against the background of iodine deficiency. At the lower limit of the norm, the TT4 indicator in the group of young men with iodine deficiency (20.6%) was 14 times higher than in the group without iodine deficiency (1.4%). The hormones fT3 and fT4, whose numerical values were at the lower limit of

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the norm, were also more common in the group with iodine deficiency - fT3 (11.1%), fT4 (6.3%) of cases, and in the group of young men without iodine deficiency (0.6%) and (1.3%), respectively. The integrated thyroid index or thyroid index (T3+T4)/TSH assesses the state of the thyroid gland itself. In our study, this indicator was used for an in-depth characterization of the functional activity of the thyroid gland in young men with iodine deficiency. With a frequency analysis of young men with iodine deficiency in 25.6% (42.07±2.07) and in young men without iodine deficiency in 26.3% (41.30±1.64) cases, the level of the thyroid index indicated thyroid hypofunction. The use of the integrated thyroid index made it possible to reveal latent thyroid deficiency in a part of young men in the group with iodine deficiency, as well as in young men without iodine deficiency. As is known, reduced thyroid function in young men can be against the background of iodine deficiency, and the tendency to reduce thyroid function in the group of young men without iodine deficiency may occur in the presence of autoimmune antibodies to thyroglobulin, which requires further examination of this contingent [1, 8, 9]. The average level of the thyroid index in both groups was within the normal range, but was slightly lower in the group with iodine deficiency.
Thus, among the young men examined, iodine deficiency of a mild degree was revealed in 26.6% of people. When studying the hormonal status, normal functioning of the thyroid gland was noted in young men, but with a tendency to decrease against the background of iodine deficiency. Using the integrated thyroid index, latent thyroid deficiency was revealed in a part of the examined subjects - in 25.6% of cases with iodine deficiency and in 26.3% - without iodine deficiency, which requires further research. The level of the thyroid index in the group of young men with iodine deficiency was lower than in the group of young men without iodine deficiency, which may indicate a transient but compensated by the pituitary-thyroid system, insufficient function of the thyroid gland against the background of mild iodine deficiency.

Beyond Hypothyroidism: Cardiovascular Risk Mechanisms While hypothyroidism is a clear consequence of iodine deficiency, existing evidence suggests that even subclinical iodine deficiency, without overt hypothyroidism, can contribute to CVD risk. The mechanisms are multifaceted and include:

- **Dyslipidemia:** Iodine deficiency can lead to dyslipidemia, characterized by elevated levels of low-density lipoprotein (LDL) cholesterol ("bad" cholesterol) and triglycerides, and reduced levels of high-density lipoprotein (HDL) cholesterol ("good" cholesterol"). These lipid abnormalities contribute to the development of atherosclerosis, where plaque builds up inside the arteries.
- **Oxidative Stress and Inflammation:** Iodine deficiency can increase oxidative stress and systemic inflammation, which are major drivers of atherosclerosis. Reduced thyroid hormone levels can impair antioxidant defense mechanisms, leading to increased oxidative damage to blood vessels. Additionally, iodine deficiency can disrupt the balance of immune cells, promoting a pro-inflammatory state.
- **Autonomic Dysfunction:** Iodine deficiency can affect the autonomic nervous system, which regulates heart rate, blood pressure, and vascular tone. This can lead to increased sympathetic nervous system activity, resulting in elevated blood pressure and heart rate.
- **Insulin Resistance and Diabetes:** Iodine deficiency can contribute to insulin resistance, where the body's cells become less responsive to insulin. Insulin resistance is a major risk factor for type 2 diabetes, which is strongly linked to CVD risk.

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• **Vascular Stiffness:** Iodine deficiency can lead to arterial stiffness, making blood vessels less flexible and more prone to damage. This can contribute to high blood pressure and increased risk of stroke.[25,26]

Future Research Directions To better understand the causal relationship between iodine deficiency and CVD risk, large-scale, well-designed studies are needed. Mechanistic studies are needed to explore the specific molecular pathways linking iodine deficiency to cardiovascular dysfunction. Intervention trials are required to evaluate the efficacy of iodine supplementation in reducing CVD risk in diverse populations, including those with subclinical hypothyroidism and those without overt hypothyroidism.

Conclusion

Iodine deficiency is a serious public health problem for cardiovascular health. Beyond its well-established role in thyroid hormone synthesis, iodine deficiency can contribute to CVD risk through various mechanisms, including dyslipidemia, oxidative stress, inflammation, autonomic dysfunction, and insulin resistance. Addressing iodine deficiency through public health measures such as iodized salt fortification and dietary diversification may be a promising approach to reduce the global burden of CVD.

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