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Research Article

Dependence Between Hormonal Status And Pathology In Women Exposed To Radioactive Iodine During Pregnancy As A Result Of The Chernobyl Disaster.

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Abstract

A study of the hormonal status of pregnant women exposed to radioactive iodine (I-131) as a result of the Chernobyl nuclear power plant accident revealed variability in the levels of T4, T3, thyroid-stimulating hormone, and free T4. T4 and T3 levels were highest in women with diseases of the eye and its adnexa and lowest in those with diseases of the blood, hematopoietic organs, and certain disorders involving the immune mechanism, as well as endocrine diseases. T3 has been proved to be more labile than T4. The same can be noted for thyroid-stimulating hormone. The dominant pathologies in women with high T4 concentrations included cardiovascular and nervous system diseases (G98), and genitourinary diseases (N39), which were absent in those with low T4 levels. In contrast, women with low thyroxine levels predominantly suffered from mental pathology and behavioral disorders (F45). A roughly similar pattern was observed after analysis of the distribution of disease incidence based on T3 hormone levels. Low T4 levels were associated with higher absorbed doses by the thyroid gland. For triiodothyronine, the dose relationship was inverse and not very pronounced. The obtained data are considered in terms of the relationship between thyroid irradiation levels due to I-131 on the genetic apparatus of thyrocytes altering levels of excreted hormones, and the incidence of various pathologies.

Keywords: radioactive iodine, Chernobyl disaster, hormones, thyroid gland, morbidity.

INTRODUCTION

In a series of previous studies, we examined the effect of exposure to radioactive iodine (I-131) on the subsequent primary morbidity of women with various groups of pathologies who were pregnant at the time of the Chernobyl disaster. The analysis covered the entire 30-year period up to 2016. Cardiovascular pathology was dominant, mainly in the form of primary hypertension [1,2]. These data are consistent with the results of Japanese researchers who found an increased risk of cardiovascular diseases in survivors of the atomic bombings in Hiroshima and Nagasaki [3]. A similar picture, which depended on the action of the radiation factor, also concerned an increased incidence of diseases of the respiratory, nervous and genitourinary systems [4-6]. However, no such dependence was found for the gastrointestinal tract and endocrine system [7,8].

Approximately the same picture was observed in children irradiated in utero [9]. The incidence of disease in women over the 30-year observation period was characterized by a fluctuating course and was dose-dependent.

We believe that one possible explanation for the variable nature of pathology development after radioactive iodine incorporation in a group of pregnant women could be the effect of I-131 on the genetic machinery of thyrocytes [10]. It has been convincingly demonstrated that thyroid cells contain 27 genes that exhibit varying expression activity depending on the activity of the incorporated radioactive iodine [11]. This effect can alter the synthesis of thyroid hormones (T4, T3), which are known to affect the body's basic metabolism and its various functions, leading to the development of pathology.

In this regard, in this publication, we analyzed the levels of key thyroid hormones in irradiated women and compared them with subsequent morbidity.

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MATERIALS AND METHODS

A data base on women exposed to radiation as a result of the Chernobyl accident (April–May 1986) who were at various stages of pregnancy during this period was formed using data from local authorities in the Stolin District of the Brest Region, obtained through direct measurements of the thyroid exposure dose rate (April–June 1986). Those individuals were searched and identified using the databases of the State Registry of Persons Affected by the Chernobyl Accident, for whom medical records were available. We designated this group as the main group, and it included 221 women.

Calculated absorbed doses by the thyroid gland due to radioactive iodine (I-131) were provided by S.M. Shinkarev, Doctor of Engineering, Head of the Laboratory for Reconstruction of Population Exposures at the A.I. Burnazyan Federal Medical Biophysical Center of the Federal Medical and Biological Agency of Russia. Doses were calculated using a semi-empirical model iterated in 2004.

Women from the same Stolin district of the Brest region who became pregnant later, in 1987, were included in the study as a comparison group. Due to the short half-life of I-131 (8 days), after a year, i.e., in 1987, there was almost no iodine in the environment and pregnant women were not exposed to it. However, their similar living conditions in the Stolin district, identical radiation exposure from the contaminated area, their social status, and their age served as favorable conditions for selection as a control group. The comparison group included 40 women. Both groups of women lived in areas with Cs-137 contamination density of 4-340 kBq/m2, with a median of 58 kBq/m2.

Incidence data were obtained from the State Registry of Persons Affected by the Chernobyl Accident. Only primary incidence, according to the ICD-10 classification, was considered in the study.

Thyroid function was assessed by measuring serum thyroid hormone levels using a radioimmunoassay: thyroxine (T4), triiodothyronine (T3); and an enzyme immunoassay: free T4 (fT4), and thyroid-stimulating hormone (TSH).

Thyroid function is known to depend on environmental factors: exogenous iodine deficiency, the presence of trace elements, and iatrogenic factors in food and drinking water. Therefore, it is advisable to clarify normal hormone concentrations for different regions. Normal values for the conditions of southern Belarus and the methods used, taking into account percentile correction, were: T4 - 62-141 nM/L; T3 - 1.17-2.70 nM/L; TSH - 0.32-5.0 μIU/mL; Free T4: 0.71–1.85 ng/dL.

Statistical data processing was performed using the software applications Statistika 10.0 (StatSoft.Inc., USA) and SigmaPlot 12.5 (Systat Software Inc., Germany).

RESULTS AND DISCUSSION

First of all, hormone levels (T4, T3, TSH, and free T4) were determined for various types of pathology based on the ICD-10 classification (**Fig. 1a-d**).

Figure 1a. Concentrations of hormones in the blood plasma of women: a – T4, b – T3, c – TSH, d – free T4.

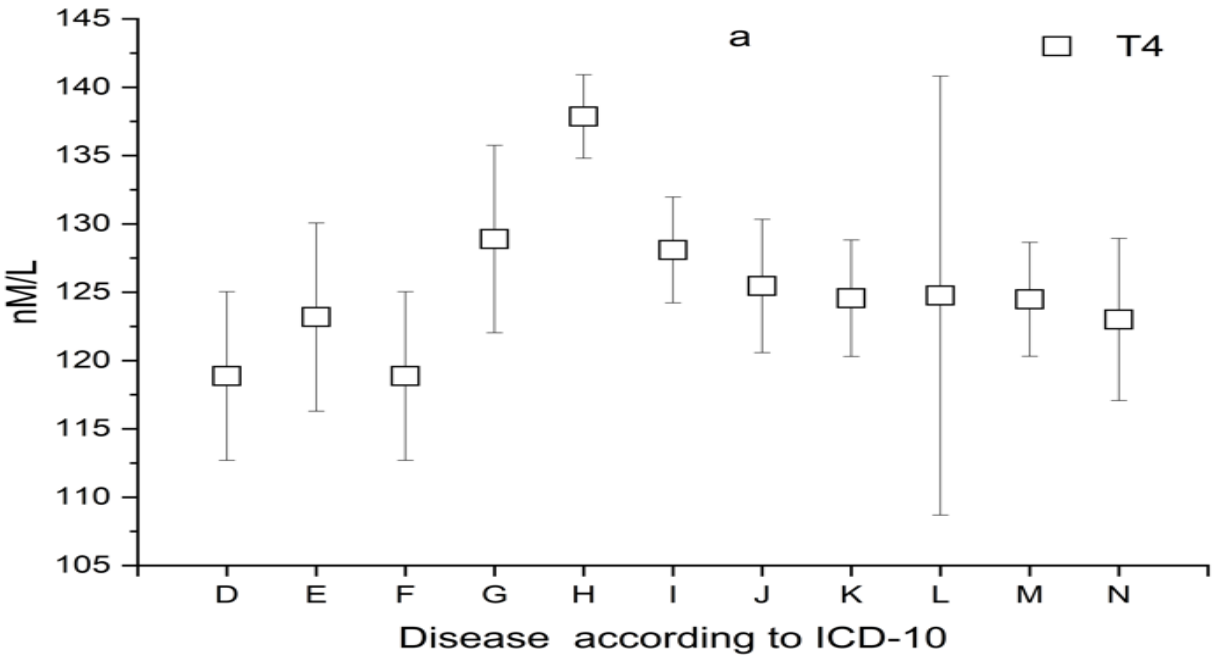


Figure 1b.

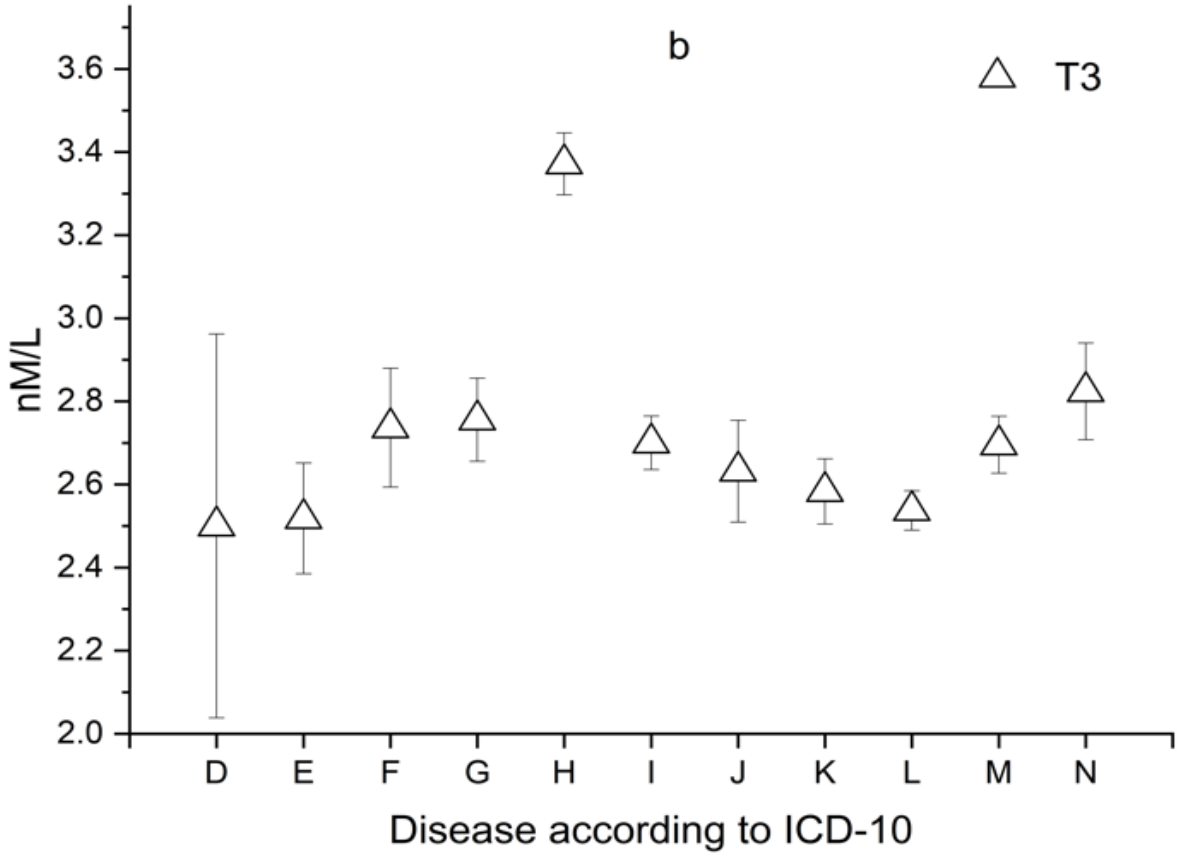


Figure 1c.

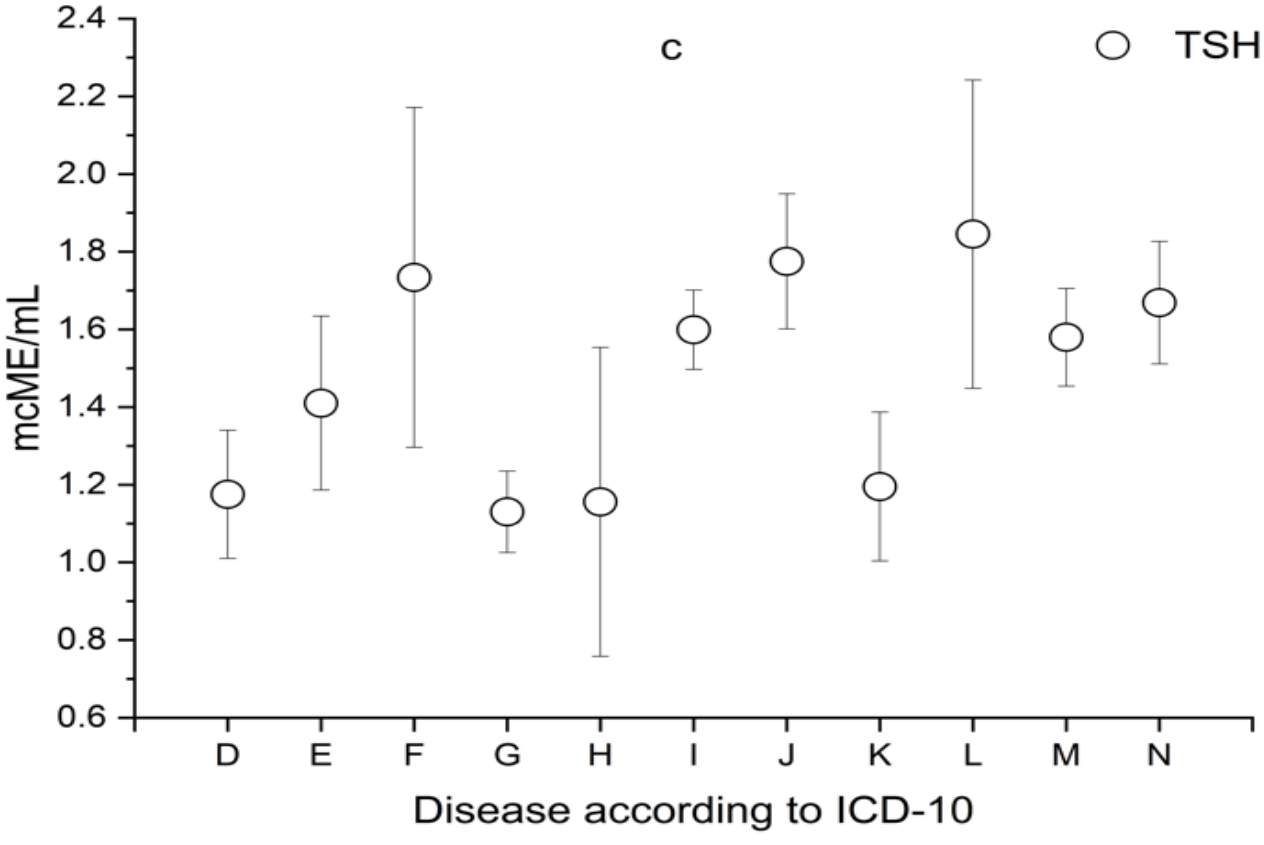
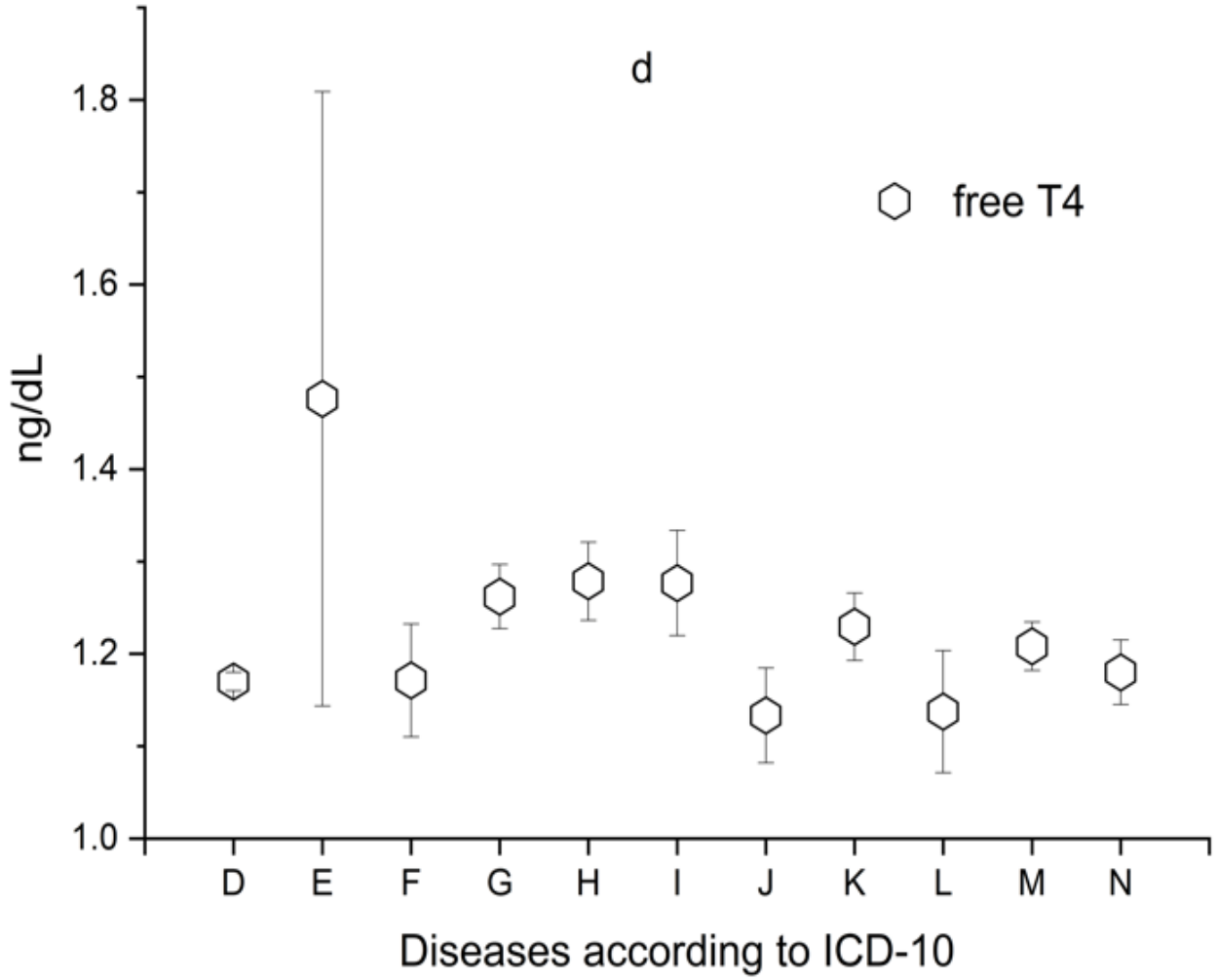


Figure 1d.



As we previously hypothesized, different primary morbidity in women is associated with variable thyroid hormone levels. Thus, T4 and T3 levels are highest in women with diseases of the eye and its adnexa (H00-H59) and lowest in those with diseases of the blood, hematopoietic organs, and certain disorders involving the immune mechanism, as well as endocrine diseases (Chapter IV). T3 levels are more labile than T4. The same can be noted for TSH. Plasma free T4 concentrations are sharply elevated in women with diseases of the endocrine system, nutritional disorders, and metabolic disorders (Chapter IV). These data may serve as indirect confirmation of our previously formulated hypothesis regarding different levels of synthesized thyroid hormones in response to the effect of I-131 on the thyroid gland's genetic apparatus and, as a result, altered morbidity in women. However, it should be recognized that the observed fluctuations in hormone levels may be characteristic of the pathological process alone and not dependent on radiation exposure.

As noted in the introduction, a distinctive characteristic of radiation-sensitive thyroid genes is their variable expression activity in response to a given radioactive iodine dose. In this regard, it will be of great interest to analyze the relationship between hormone concentrations in women's blood plasma and the corresponding predominant morbidity. **Figures 2** and **3** show these data for T4 and T3. Two concentration ranges were used in the calculations based on the laboratory data obtained: the lower range, up to half the recorded levels of each hormone, and the higher range, i.e., more than half this value. In our view, this should mimic the hormone levels observed during the accumulation of various I-131 activities during

It should be noted that when constructing the figures, the "Other" category included pathologies with a frequency of less than 3%. It can be seen that the dominant pathologies at different T4 levels included both common diseases, such as cardiovascular pathologies (I10, I25), and groups that were recorded only for those with high T4 concentration level (**Fig. 2**). Thus, in women with higher T4 concentrations (141-220 nM/L), the dominant pathologies included diseases of the nervous system (G98) and diseases of the genitourinary system (N39), which were absent in those with low T4 levels. Conversely, in women with low thyroxine levels, the dominant pathologies included mental disorders and behavioral disorders (F45).

Figure 2a. Structure of morbidity at T4 levels of 60-140 nM/L (a) and 141-220 nM/L (b).

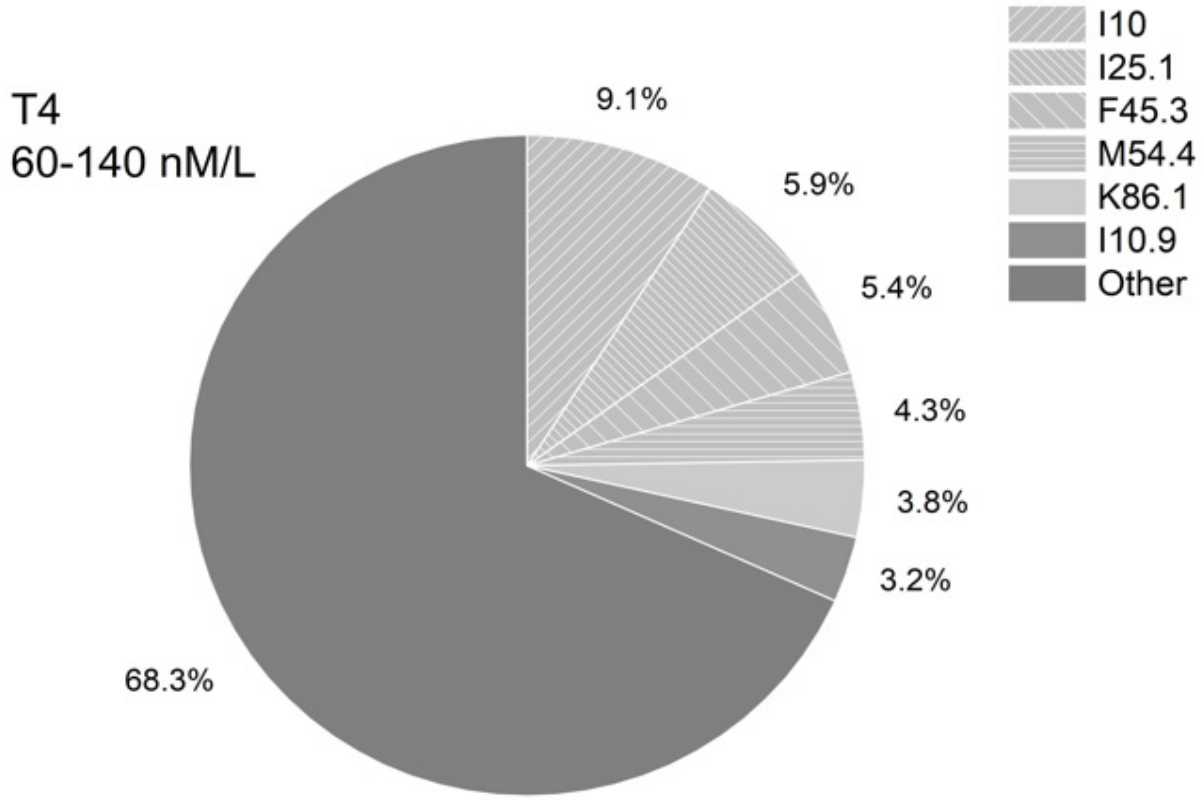
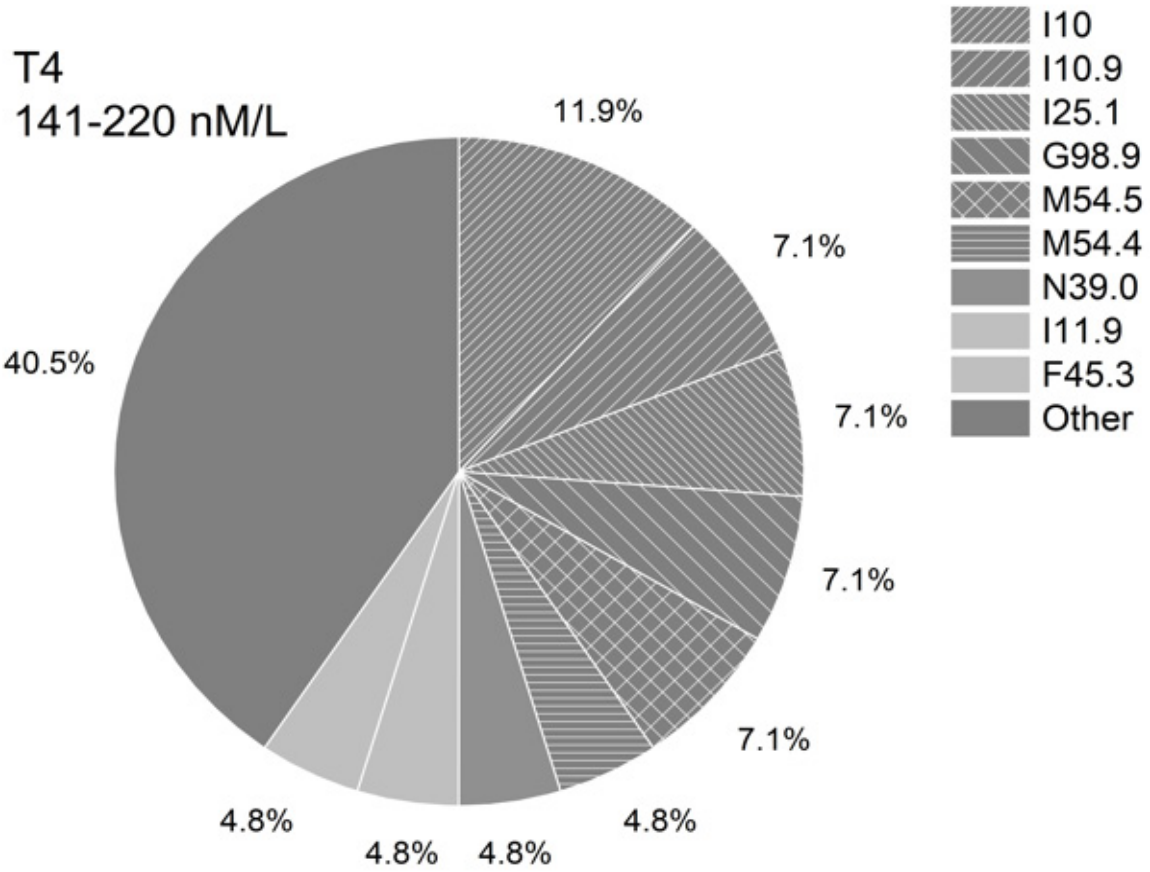


Figure 2b.



A roughly similar pattern was observed after the analysis of the dependence between the distribution of disease incidence and T3 hormone levels (**Fig. 3**). Identical disease classes were encountered (I10, I25, M54, F45), but there were also differences in the prevalence of genitourinary pathologies (N39), musculoskeletal diseases (Chapter XIII), and gastrointestinal diseases (Chapter XI).

Figure 3a. Structure of morbidity at T3 levels of 1.4–2.7 nM/L (a) and 2.8–3.9 nM/L (b).

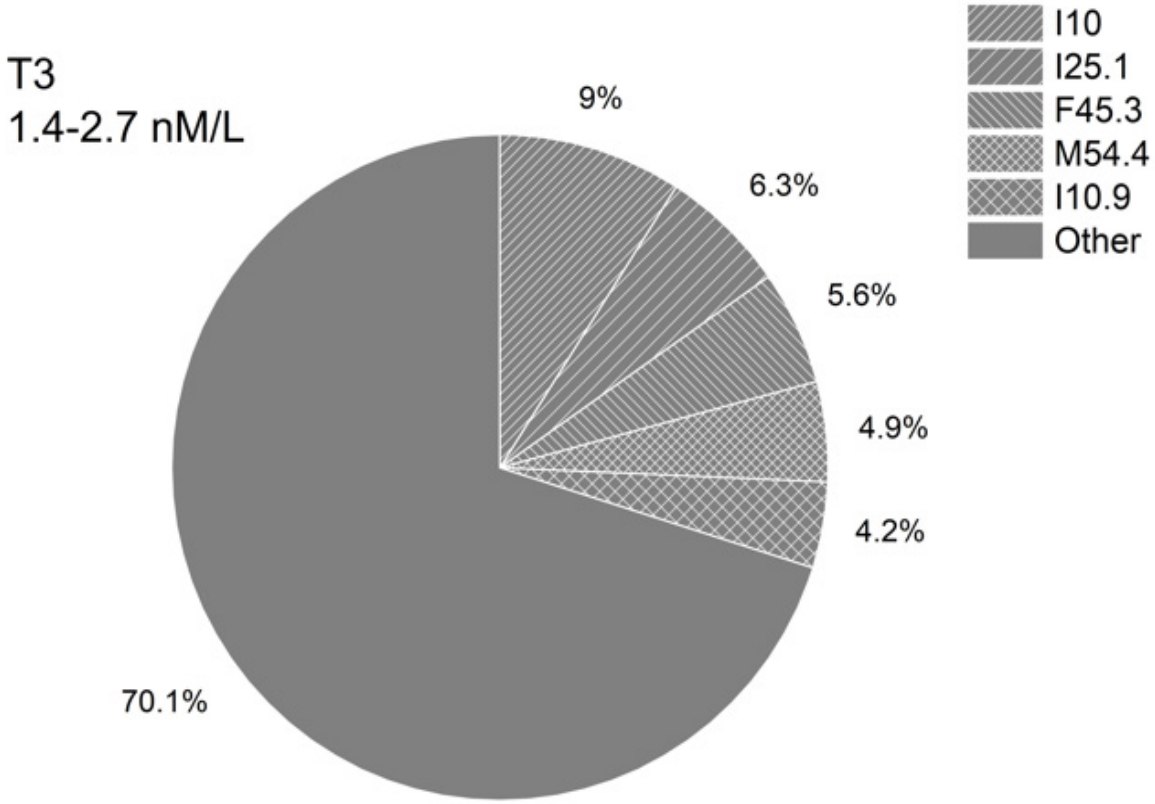
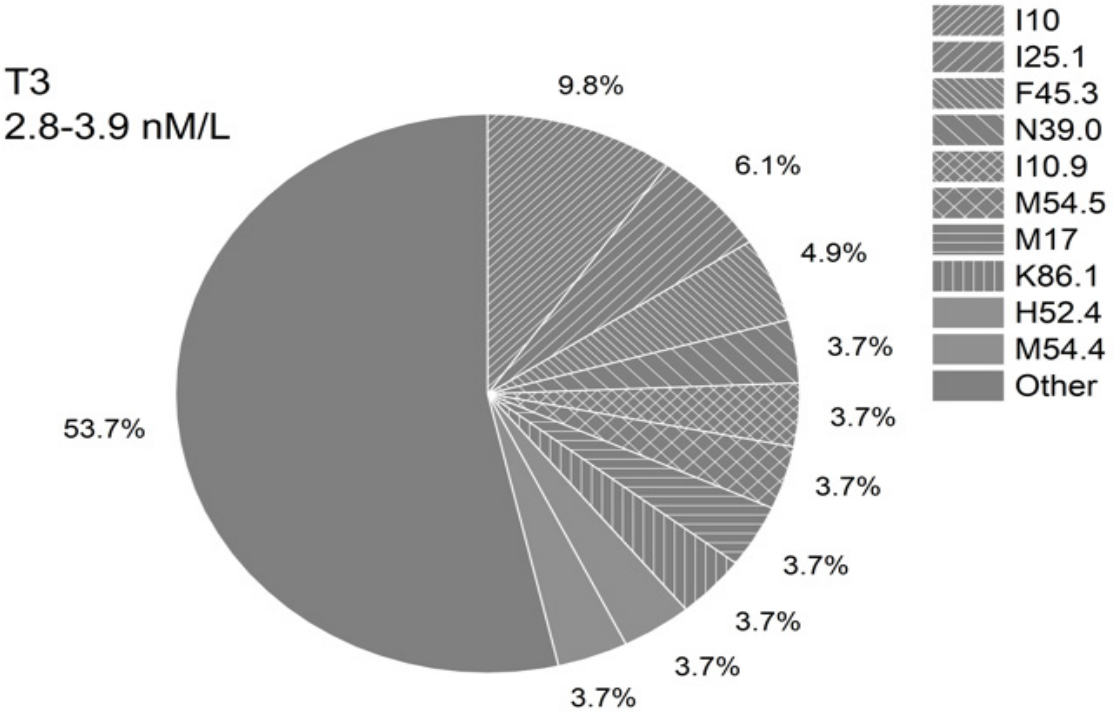


Figure 3b.



Interestingly, essential hypertension (I10) was the most common in all cases. In all likelihood, the hormone balance in this type of pathology is stimulated by thyrocyte genes, which express a wide range of activities of incorporated I-131.

Calculation of absorbed radiation doses by the thyroid gland due to radioactive iodine incorporation at the recorded hormone concentration levels revealed interesting data (**Table 1**). Low T4 levels were associated with higher absorbed doses to the thyroid gland. For triiodothyronine, the dose ratio was inverse and not very pronounced.

Table 1. Values of absorbed radiation doses by the thyroid gland (mGy) at different levels of thyroxine and triiodothyronine in the blood plasma of women.

Hormone	Serum Level, nM/L	Absorbed Dose (M±m) to the Thyroid Gland, mGy
Thyroxine (T4)	60-140	259±5.8
	141-220	80±4.3
Triiodothyronine (T3)	1.4-2.7	76±2.5
	2.8-3.9	83±4.9

These data may serve as further indirect evidence of a link between thyroid radiation levels and its hormonal functions, such as levels of excreted hormones and the incidence of certain pathologies.

For example, the Mfsd2 gene, which is much stronger inhibited at a dose of 0.85 Gy (due to the incorporation of radioactive iodine) than at a dose of 8.5 Gy, may be a candidate for such radiosensitive structures in the thyroid gland's genetic apparatus. This gene is expressed in the thyroid gland and encodes a protein that transports lysophosphatidylcholine across membranes, influencing membrane permeability and influencing brain development. Furthermore, pancreatic pathology (K86), which occurs at higher T3 levels, may also be associated with expression of this gene.

The Scara3 gene is another example of dose-dependent regulation of thyroid gene activity. At an absorbed dose of 0.85 Gy, it is more active and more readily expressed than at higher doses absorbed by thyroid. The gene encodes a protein involved in the scavenging of reactive oxygen species, i.e., oxidative stress reactions. Since thyroid hormone synthesis depends on iodine oxidation, free radicals may not be inactivated at high doses, which will affect T4 and T3 levels and lead to cardiovascular and gastrointestinal dysfunction, and consequently, to the development of related pathologies.

The S100a9 gene has a similar antioxidant effect. Its activity at a dose of 0.85 Gy is less pronounced than at a dose of 8.5 Gy. However, its expression capacity is not limited to its involvement in oxidative stress reactions.

The Per1 gene, located on chromosome 17 of thyrocytes, has the opposite effect. Its functions are quite broad, encoding components of circadian rhythms that influence numerous functions of human body, including metabolism, sleep, body temperature, blood pressure, endocrine, immune, cardiovascular, and renal functions. Disruptions in circadian rhythms can contribute to cardiovascular diseases, cancer, metabolic syndromes, aging, and other pathologies. The activity of this gene is suppressed to a greater extent with increasing activity of incorporated iodine. Other examples of the relationship between radiation levels and overall morbidity could be cited.

Thus, the formation of varying absorbed doses on the thyroid gland can affect its ability to synthesize thyroid-stimulating hormones, resulting in an imbalance in their levels, which may cause subsequent systemic pathology.

CONCLUSION

The incidence of various diseases in women who were pregnant during the Chernobyl disaster and whose thyroid glands were exposed to radioactive iodine is accompanied by changes in thyroid hormone levels (T4 and T3). Elevated or decreased levels of thyroxine and triiodothyronine are associated with the prevalence of a particular disease group, including cardiovascular disease (I-10). Fluctuations in T4 levels in various pathologies are associated with specific absorbed doses by the thyroid gland. Therefore, it can be hypothesized that the subsequent development of diseases affecting certain organs and systems in women may be related to the effects of radioactive iodine (I-131) on the genetic machinery of thyrocytes.

Conflicts of interest

The research did not receive any specific support from public, private, or not-for-profit funding bodies, and the authors state that they have no conflicts of interest.

Abbreviations

Tg – Thyroid Gland, Cnpp – Chernobyl Nuclear Power Plant, Tsh – Thyroid Stimulating Hormone, T4 – Thyroxine, T3 – Triiodothyronine, Ft4 – Free T4, Icd -10 - International Statistical Classification Of Diseases And Related Health Problems 10th Revision.

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