Applying Regression Analysis to Study the Interdependence of Thyroid, Adrenal Glands, Liver, and Body Weight in Hypothyroidism and Hyperthyroidism

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Abstract. The complexity and diversity of the structure and activity of the body cause the involvement of mathematical apparatus for its study. For the first time, be means of the regression analysis, it was investigated the possibility of using the interdependence of weight of thyroid gland, adrenal glands, liver, and body weight indicators as clinical features of hypothyroidism and hyperthyroidism. The study was conducted on white rats under model conditions of alimentary hypothyroidism and thyreoidinum-induced hyperthyroidism. Such a clinical marker of hypothyroidism has been found out to be a simultaneous increase in thyroid weight and a decrease in adrenal weight, which occur against the background of weight gain. A decrease in thyroid weight along with an increase in adrenals and liver weights is a clinical marker of hyperthyroidism. The studies have confirmed the fundamental view of body weight as an informative indicator of the general state of the organism, as well as our earlier assumptions about the affiliation of the thyroid gland, adrenal glands, and liver to a single functional module.

Keywords: regression analysis, biomedical research, body weight, thyroid gland, adrenal glands, liver, hypothyroidism, hyperthyroidism, markers.

1 Introduction

An organism is a super-system that is formed by a large number of subsystems that have less complexity [6]. The complexity and diversity of the structure and activity of the body determine the possibility of more frequent use of mathematical apparatus for his research [11,13,14]. One of the most important tasks of the study of the state of the organism is the isolation and study of certain subsystems that implement certain areas of its activity [2]. In this case, the completeness of the study can provide not only the elucidation of the properties and nature of its constituent elements, but also the establishment of relationships and interactions between these components and the organism. Such opportunities are provided by regression analysis, which is a rather informative means of finding interdependencies in establishing relationships between the quantitative parameters that characterize an organism's state [1,7,16,17].

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The use of a cause and effect approach defines the general state of the organism as a "consequence" and the state of its subsystems as a "cause". In this case, the variable that is the cause is independent (exogenous, factorial), and the variable that is the consequence is dependent (endogenous, resultant). In the study of the whole variety of stochastic dependencies between variables, there is a kind of relation between two random variables, in which a change in the mean of one of them (x) leads to a change in the mean of the other $\bar{y}_x$. Let y be some initial parameter whose value determines the state of the organism/diagnosis of the disease. The value of y depends on the vector of input parameters:

$$x = (x_1, x_2, x_3, \ldots, x_n)$$

Then the relationship between them can be represented by the regression equation y to x:

$$\bar{y}_x = f(x) \tag{1}$$

To investigate the correlation between the variables x and y, a linear regression equation (correlation-regression model) is used after establishing cause-effect relationships.

$$y = a_0 + a_1 x_1 + a_2 x_2 + \ldots a_n x_n + \varepsilon \tag{2}$$

where a_0 is a free member of the correlation-regression model; a_1, a_2, a_n are regression coefficients; ε is a random variable that includes certain observations and measurements errors; however, a_0, a_1, a_2 … a_n are unknown parameters that determine the least squares method.

Since the output parameter y depends on the experimental conditions under which the coefficients a_0, a_1, a_2 ... a_n have been determined, the regression model is strictly bound to certain defined experimental conditions; with changing conditions, such models no longer meet the new conditions.

The thyroid gland (producer of thyroid hormones that provide the flow of a large number of processes occurring in the body), adrenal glands (focus of application of adverse effects, in particular changes in functional activity of the body) - a target for thyroid hormones, a site of metabolism of thyroid and steroid hormones).

Hypothyroidism is a pathology of the thyroid gland, the main manifestation of which is a decrease in its functional capacity. In such cases, there is an expansion of the thyroid tissue, body weight increases, the liver increases, resistance to stress effects decreases, etc.

The main manifestation of hyperthyroidism is an increase in the functional activity of the thyroid gland. Dystrophy of the muscles and tissues of the internal organs, which accompanies hyperthyroidism, is manifested by weight loss, impaired liver and adrenal glands.

In clinical medicine combinations of the thyroid gland and liver diseases are known [8,9]. An informative indicator of the general state of an organism is its weight. Despite this, an in-depth study of the relationship between the state of these organs and body weight has received little attention as an integrative indicator of the overall condition of the organism [10].

2 Purpose of the study

To substantiate the use of indicators of weight of thyroid and adrenal glands and liver as clinical markers of hypothyroidism and hyperthyroidism.

3 Materials and methods

The study was conducted on 30 nonlinear white male rats of initial body weight 140-160 g. Intact rats of group 1 were on standard common animal feed under euthyroidism (ET); they served as a control to determine changes in hypo- and hyperthyroidism. Rats of groups 2 and 3 were kept under model conditions of subclinical hypothyroidism (SChT) and subclinical hyperthyroidism (SCHT), which created consumption of iodine-deficient isocaloric starch-casein diet and addition to the iodine-deficient isocaloric starch-casein diet of thyreoidinum (Belgorodvitaminy LLC, Russia). The conditions of SChT and SCHT were verified by biochemical and histological methods. The study design is presented in Table 1. After 30 days, the animals were decapitated under ether anesthesia. At all stages of the study, the requirements of the European Convention for the Protection of Animals Used for Experimental and Other Scientific Purposes were observed (Strasbourg, 1986). The body weight of rats was determined on a laboratory balance (error of ±0.5 g). The investigated internal organs were carefully separated from the connective tissue and weighed: thyroid and adrenal glands - on torsion balance (absolute error of ±0.1 mg), liver - on analytical balance (measuring range ±10 mg). The obtained digital parameters were averaged to determine the arithmetic mean (M) and its standard error (m), which made it possible to represent them as M±m. The statistical program Statistica 6.0 was used in mathematical data processing. Drawings were made using the program Microsoft Excel 2016.

Table 1. Study design of the white rats' body weight dependence on the weights of the thyroid, adrenal glands and the liver (n=30).

Group, Number of animals	Animal nutrition conditions	Duration of the study, (days)	Residual iodine content in the diet, (µg per rat a day)	Thyreoidinum, (mg per 100 g body weight)
1 n=10	SVD	30	full-fledged food	was not given
2 n=10	ISCSD	30	1.6-1.8	was not given
3 n=10	ISCSD	30	1.6-1.8	15

Note. SVD - standard vivarial diet; ISCSD - isocaloric starch-casein synthetic diet.

The problem of establishing the relationship between the body weight of rats and the weight of their internal organs was solved by regression analysis using the equation (2); in that case, it has the appearance:

$$M(y) = a_0 + a_1 x_1 + a_2 x_2 + a_3 x_3 \quad (3)$$

where *M(y)* is the mathematical expectation of rat body weight indices at some values of x_1, x_2, x_3 under the model conditions of SChT and SCHT; x_1 - the absolute weight of the thyroid gland of rats; x_2 is the absolute weight of the adrenal glands of rats; x_3 is the absolute weight of the liver of rats; a_1, a_2, a_3 are parameters that show the degree of influence of each corresponding characteristic x_1, x_2, x_3 on the average value of *M(y)* and are determined by the least squares method, by which the sum of the squares of deviations of the actual values of *y* from the equation (3) is the minimum.

4 Results and discussion

The body weight of the rats, their thyroid glands, adrenal glands, and liver in the model conditions of SChT and SCHT are presented in Table 2, and Fig. 1, Fig. 2.

Table 2. White rats' body weight and weights of their thyroid glands, adrenal glands and the liver under the conditions of different functional activity of the thyroid glands (n=30).

Group, Number of animals	Conditions of the study	Body Weight, (g)	Organ Weight		
			Thyroid, (mg)	Adrenals, (mg)	Liver, (g)
		M±m	M±m	M±m	M±m
1 n=10	ET	176.0±3.1	21.9±0.79	35.2±0.11	9.0±0.37
2 n=10	SChT	244.2±0.9 p<0.01 (1)	25.0±0.8 p<0.05 (1)	31.0±0.7 p<0.05 (1)	9.1±0.6
3 n=10	SCHT	213.3±0.51 p<0.05 (1)	13.4±0.4 p<0.01 (1)	38.0±1.37 p<0.05 (1)	9.3±0.4

Note. ET - euthyroidism; SChT - subclinical hypothyroidism; SCHT - subclinical hyperthyroidism; numbers in brackets indicate the number of the group which the comparison was made with; at p>0.05 the indices were not entered in the table.

The dependence of the body weight of rats on the indicators of weight of the thyroid, adrenals and liver in the model conditions of SChT and SCHT was determined using the linear regression equation (3). The results obtained look as follows:

group 2

$$y = 247.9559 + 113.6494\, x_1 - 143.5190\, x_2 - 0.1313\, x_3 \quad (4)$$

group 3

$$y = 220.5105 - 248.7794\, x_1 + 15.6600\, x_2 - 0.4809\, x_3 \quad (5)$$

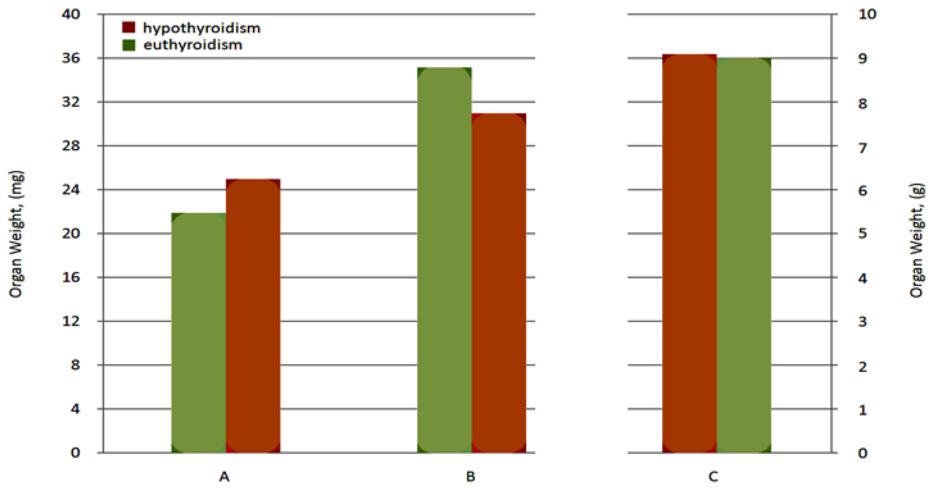

Fig. 1. The profile of the “thyroid gland – adrenal glands – liver” functional module in the conditions of subclinical hypothyroidism: A - Thyroid, B - Adrenal Glands, C - Liver.

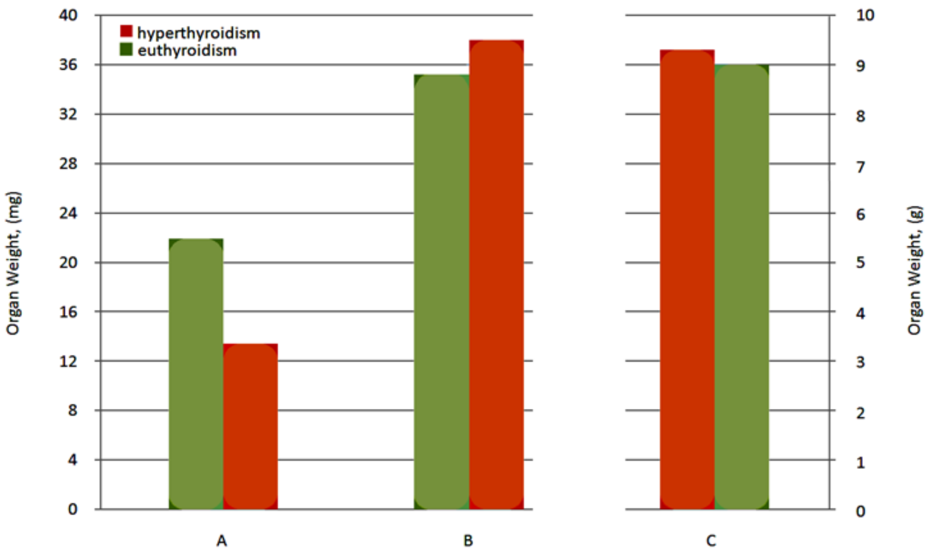

Fig. 2. The profile of the “thyroid gland – adrenal glands – liver” functional module in the conditions of subclinical hyperthyroidism: A - Thyroid, B - Adrenal Glands, C - Liver.

It is advisable to use partial regression equations to describe the result (body weight) of one of the factors under consideration, provided that the other factors assume some constant values (usually mean values). In Fig. 3, Fig. 4, and Fig. 5 presented the linear regression lines of body weight dependence on the weight of the thyroid gland, adrenal glands and liver under SChT and SCHT conditions.

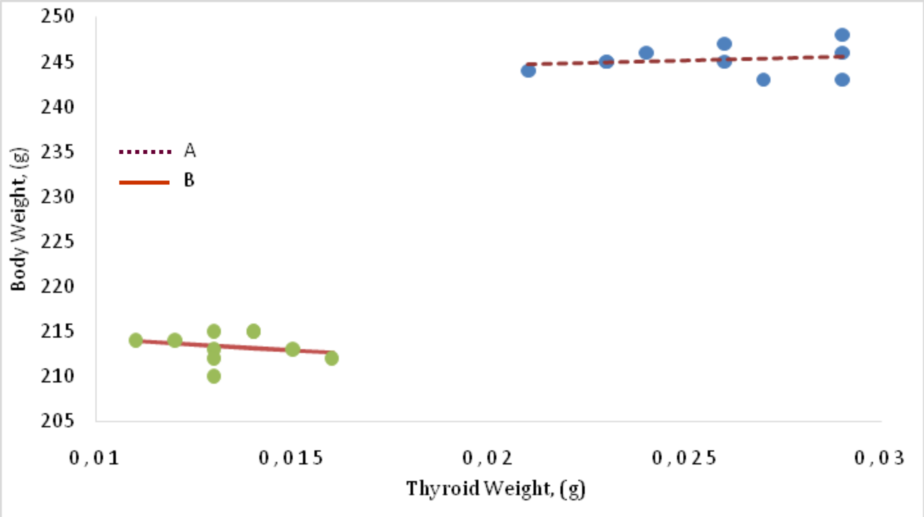

Fig. 3. The linear regression lines of body weight dependence on the thyroid gland's weight in the conditions of: A - subclinical hypothyroidism, B - subclinical hyperthyroidism.

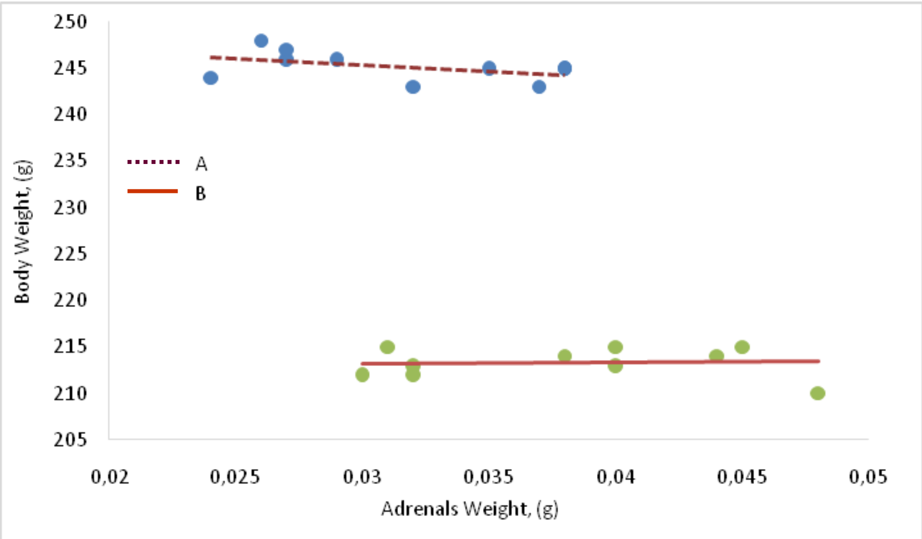

Fig. 4. The linear regression lines of body weight dependence on the adrenal glands's weight in the conditions of: A - subclinical hypothyroidism, B - subclinical hyperthyroidism.

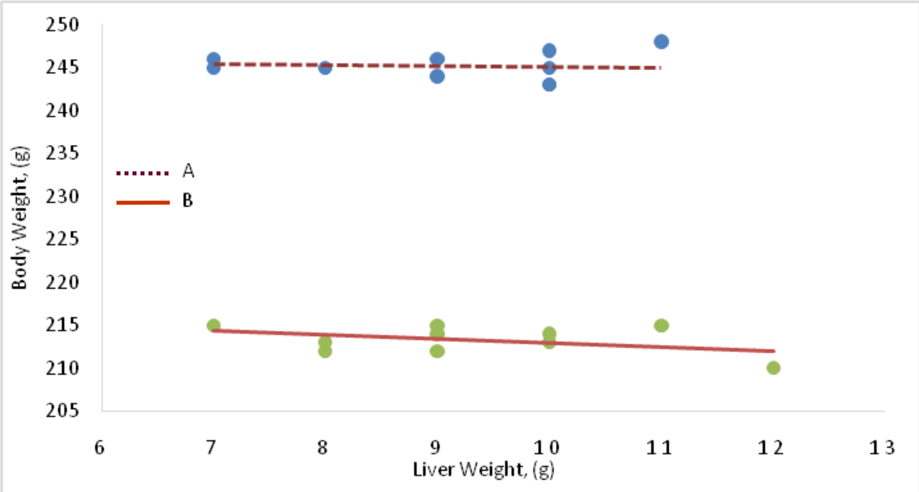

Fig. 5. The linear regression lines of body weight dependence on the liver's weight in the conditions of: A - subclinical hypothyroidism, B - subclinical hyperthyroidism.

Summary of the data obtained is presented in Table 3. The processing of the obtained digital parameters showed that the presence of rats of group 2 in the model conditions SChT was accompanied by the following changes with respect to indicators in intact rats of group 1: an increase in the weight of the thyroid glands by 13.6 % ($p<0.01$), a decrease in the weight of the adrenal glands 11.4 % ($p<0.05$), a decrease in liver weight by 1.1 % ($p>0.5$). The body weight of the animals in the study group was 38.63 % greater than in intact rats ($p<0.01$).

In our opinion, a moderate increase in body weight against the background of a moderate increase in weight of the thyroid glands and a moderate decrease in the weight of the adrenal glands in the absence of changes in the weight of the liver indicates that in conditions of SChT, despite the considerable tension in the activity of the thyroid glands, the resulting activity of the organism as a whole system is due to a sufficient level of compensatory and adaptive mechanisms.

The results of the analysis of the data obtained by equation (4) showed that when the thyroid weight increased by 0.01 mg, the body weight of rats increased by 1.136 g, which is consistent with the literature data on the growth of body weight under conditions of hypothyroidism [3]. An increase in the weight of the adrenal glands by 0.01 mg leads to a decrease in body weight by 1.435 g, which indicates a moderate stress effect, which for the body is staying on an iodine-deficient diet. In this case, the increase in liver weight by 0.1 g is accompanied by a decrease in body weight by only 0.1313 g. As a result, the tendency of increasing the body weight of rats of the second group indicates that anabolic processes prevail in the body. The findings deepen the preliminary conclusion that, under the conditions of SChT, the organism has sufficiently powerful mechanisms to adapt to adverse conditions and compensate for disorders.

Table 3. Dependence of white rats' body weight on changes in the thyroid glands, adrenal glands and the liver weights (n=20).

Group, Number of animals	Body Weight	Organ Weight					
		Thyroid		Adrenals		Liver	
	direction of change	direction of change	index	direction of change	index	direction of change	index
2 n=10	increase	↑	1.136	↓	1.435	↓↓	0.1313
3 n=10	decrease	↓	2.488	↑	0.157	↓↓	0.4809

Note. ↑ - increase of the studied internal organ's weight to 0.01 g; ↓- decrease of the studied internal organ's weight to 0.01 g; ↑↑ - increase of the studied internal organ's weight to 1.0 g; ↓↓- decrease of the studied internal organ's weight to 1.0 g .

In the model conditions of SCHT (group 3), the following changes of the investigated parameters in relation to similar parameters in intact rats of group 1 were established: a significant decrease in the weight of the thyroid glands by 55.33 % ($p<0.01$), a certain increase in the weight of the adrenal glands and liver respectively 8.5 % and 3.33 % ($p<0.05$ and $p>0.5$). Such character of changes of indicators of weights of investigated internal organs we consider as a consequence of activation of functional activity of a thyroid gland by reception of an exogenous thyroid hormone. At the same time, the nature of changes in adrenal and liver weights indicates that, despite some stress-related effect due to thyreoidinum, metabolic disorders were not significant. This is evidenced by the rat body weight index of the discussed group, which was larger than that of intact animals of group 1 ($p<0.01$).

Analyzing linear regression equation (5) data showed that a 0.01 mg increase in thyroid weight was accompanied by a decrease in body weight by 2.488 g, and an increase in liver weight by 1.0 g occurred on the background of decrease in body weight by 0.481 g. What has been found out, indicates activation of the functional activity of the thyroid gland. Nevertheless, with an increase in the adrenal weight of the rats of the group under discussion by 0.01 mg, an increase in their body weight of 0.157 is observed. We consider the results obtained as a manifestation of the body's adaptation to the conditions of hyperthyroidism.

The generalization of the data we have obtained confirms [4] the thought that the deviation of the weights of internal organs from their normal values may indicate changes in these organs. The existence of a link between the organ's weight and specific disease is also indicated [15]. These authors believe that since body weight is an indicator of the general condition of the organism, the study of the interdependence that exists between body weight and weights of internal organs is appropriate. This view of body weight coincides with our understanding of the value of researching and analyzing indicators obtained from weighing [12]. The relationship between organ weight and body weight established in the representative studies indicates changes in the body and indicates their direction (see Fig. 6).The interdependence of body weight, thyroid gland, adrenal gland and liver is related to the functional state of the thyroid gland [5]. This gives reasons to consider changes in the weights of these internal organs clinical marker of functional disorders such as hypothyroidism and hyperthyroidism, and an indicator of disturbance of the general state of the organism.

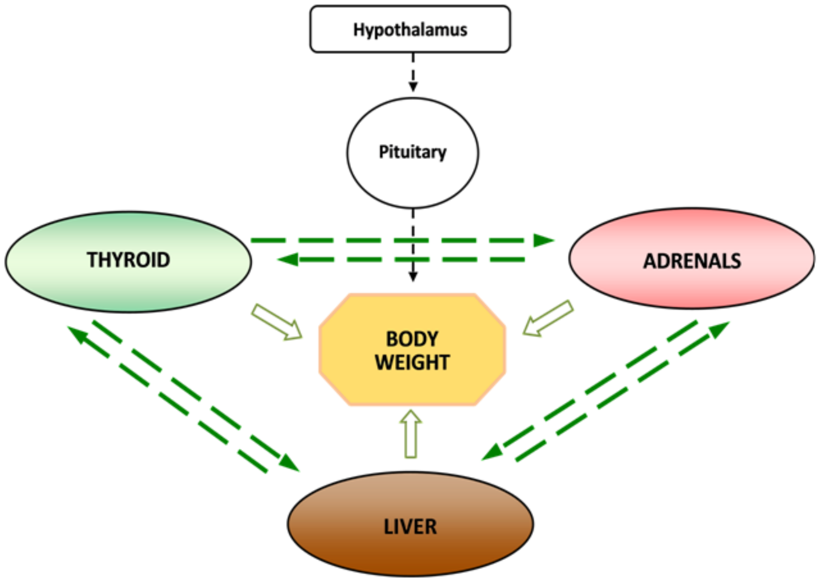

Fig. 6. The scheme of functional connections between organs of the "thyroid gland – adrenal glands – liver" functional module.

5 Conclusion

In the conditions of functional pathology of the thyroid gland, an indicator of the general state of the organism is a set of indicators, the constituent elements of which are respectively changed parameters of the weights of the thyroid gland, adrenal glands and liver. Increasing thyroid weight while decreasing adrenals weight amid weight gain is a clinical marker of subclinical hypothyroidism. A decrease in thyroid weight along with an increase in adrenals and liver weights is a clinical marker of hyperthyroidism.

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