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Relationship Between Pituitary-Thyroid Axis Hormones and

Anthropometric Parameters in Czech Adult Population

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SHORT TITLE: RELATIONSHIP PITUITARY-THYROID AXIS TO

ANTHROPOMETRIC PARAMETERS

Summary

Although the relationships between thyroid function and anthropometric parameters were studied in patients with thyroid disorders and in morbidly obese subjects, such data in normal healthy population are scarce. In our study, relationships between factors of body composition, fat distribution and age with hormones of the pituitary-thyroid axis were evaluated in a large, randomly selected sample of normal adult Czech population comprising of 1012 men and 1625 women. Our results exhibited weak, but significant relationships between body composition, body fat distribution and the parameters of pituitary-thyroid axis. Some of these associations were gender-specific. As shown by backward stepwise regression model, body fat distribution evaluated by centrality index (subscapular/triceps skinfold ratio) was negatively associated with free triiodothyronine (fT3) serum levels only in women, while a positive correlation of fT3 with BMI was specific for men. BMI was inversely related to free thyroxine (fT4) concentrations in women but not in men. The centrality index (CI) was positively related to TSH levels in both genders. The fT3/fT4 ratio, reflecting deiodinase activity, was inversely related to age and positively related to BMI in both genders, while the highly significant negative correlation between CI and fT3/fT4 ratio was specific for women.

Keywords

anthropometry - body composition - body fat distribution - thyrotropin - free thyroxine - free triiodothyronine.

Introduction

Although the relationships between thyroid function and anthropometric parameters were studied in patients with thyroid disorders and in morbidly obese subjects before and after weight reduction (Kozlowska and Rosolowska-Huszcz 2004), data on these associations in random population samples is rather scarce. Until now only a few epidemiological studies evaluating the association between levels of thyroid hormones and TSH with body composition, and/or body fat distribution were carried out. It has been shown that BMI is positively associated with serum TSH levels (Knudsen *et al.* 2005, Nyrnes *et al.* 2006), and negatively related to fT4 levels, whereas it has been revealed that there is no association between BMI and fT3 (Knudsen *et al.* 2005).

The prevalence of apparent hypothyroidism (11,8 %) and subclinical hypothyroidism (7,7 %) in morbidly obese subjects is high - 19.5% (Michalaki et al. 2006). Compared to normal weight subjects, morbidly obese have higher levels of total triiodothyronine, free triiodothyronine (fT3), total thyroxine, and thyrotropic hormone (TSH), probably due to the reset of their central thyrostat at higher level (Michalaki et al. 2006). Kozlowska and Rosolowska-Huszcz (2004) studied the effect of a 4-week weight regiment (20% decreasing energy intake) on antropometric and hormonal parameters in obese woman. In response to the negative energy balance, the T4 to TSH ratio increased, whereas the fT4, T4, and fT4 to TSH ratio did not change. Therefore TSH serum concentration and its ratio to total thyroxine and free thyroxine (fT4) before weight reduction could be a good predictor of successful weight loss (Kozlowska and Rosolowska-Huszcz 2004). On the other hand, Manji et al. (2006) found no difference in serum TSH and free T4 between euthyroid lean and obese subjects. Another study revealed significant association of weight change with fT3, but not with fT4 in euthyroid adult subjects; weight gain over a 4-year period was associated with low serum T3 concentrations (Ortega et al. 2007). As suggested by Chomard et al. (1985), a decrease in serum total and fT3 concentrations is dependent on nutrient intake. It was obvious that thyroid dysfunction affects body weight; however, possible association of minor perturbations in thyroid function with changes in anthropometric measures needed be elucidated. Therefore, we attempted to evaluate the relationships between anthropometric characteristics and serum concentrations of the pituitary-thyroid axis hormones in a randomly selected sample of the Czech population.

Methods

Subjects

A sample of 1012 men and 1625 women (18–65 years of age), randomly selected from the Central registry of Czech Republic, was investigated in 15 areas. Levels of TSH, fT4 and fT3 in fasting serum samples were determined. Anthropometric characteristics including age, body weight, body height, body mass index (BMI), suprailiac skinfold (SIL), abdominal skinfold (ABD), subscapular skinfold (SSC), triceps skinfold (TRI), percent of body fat (Fat%), lean body mass (LBM), waist circumference (Waist), hip circumference (Hip), neck circumference (Neck), waist to hip ratio (WHR), subscapular skinfold/triceps skinfold ratio (centrality index, CI) were measured according to the WHO recommendations (WHO Expert Committee 1995). BMI was calculated as the ratio of body weight (kg) to body height (m²). Centrality index was expressed as the subscapular skinfold to triceps skinfold ratio. Body composition was calculated from 4 skinfolds as reported elsewhere (Bláha *et al.* 2007, Pařízková 1977, Saller 1957).

Analytical methods

TSH was measured using commercially available noncompetitive immunoassay (normal range 0.17-4.2 mIU/l). The intra- and inter-assay coefficient of variation (CV) of the method was 2.1% and 3.3%. Both fT3 and fT4 were measured using competitive immunoassay. Normal range was 2.5 - 9.3 pmol/l (fT3) or 11.8 - 24.6 pmol/l (fT4), intra-

assay coefficient of variation were 2.5 % (fT3) and 2.9% (fT4), inter-assay coefficients of variation were 4.7% (fT3), and 6.6 % (fT4).

Statistical data analysis

At first, the relationships between anthropometric characteristics and thyroid hormones were evaluated by age-adjusted Spearman's correlations. To check the homogeneity of the multivariate data set, the F-distributed Mahalanobis distance was computed. The experimental points for which the Mahalanobis distance reached significance (p<0.001) were excluded from the correlation analysis as multivariate outliers.

Secondly, regression models were built which included one of the thyroid parameters as the dependent variable and four explanatory variables. As a general rule for constructing regression models the explanatory variables should be independent of each other to avoid problems with multicollinearity and to allow for simple interpretation of the results. Our main effort centered around the goal of finding a minimum number of explanatory variables describing all key features of the system under investigation. Thus the model consisted of the parameters of age, body composition, body fat distribution and body growth. In addition to age and height (as the parameters of body growth), the model included BMI as a bodycomposition indicator and CI as an indicator of body fat distribution. It is more common to express the indicator of body fat distribution by waist circumference. However, in contrast to CI, which exhibits low correlations with markers of body composition, waist circumference shared more than 50% of variability with the latter indices as was clearly demonstrated by the respective Spearman's correlation coefficients exceeding the value 0.7 (Table 3). It has been clearly demonstrated that skinfold indices measure a different dimension of fat distribution than circumference indices (Selby et al. 1990). There is also evidence of a genetic influence on subcutaneous fat distribution, but less evidence for such an influence on the WHR (Selby

et al. 1990). WHR and centrality index do not measure the same dimension of fat patterning (Cardon *et al.* 1994).

Due to non-Gaussian data distribution in most of the variables, the original data was treated by a power transformation as described elsewhere (Meloun *et al.* 2000). The maximum conformity of the variables used in regression with Gaussian distribution was chosen in order to find the optimum transformation parameters. For this purpose, the two-parameter linear regression between fractiles of Gaussian distribution and fractiles of transformed variable was used. The optimum transformation parameter was reached at the maximum correlation coefficient of the linear regression and at the minimum of the mean standard error of prediction. The homogeneity of the data and further assumptions for correct regression analysis were checked using the regression diagnostics as described elsewhere (Meloun *et al.* 2004, Meloun *et al.* 2002).

Statgraphics Plus v. 5.1 from Manugistics (Rockville, MD, USA) and NCSS 2002 from Number Cruncher Statistical Systems (Kaysville, UT, USA) were used for data analysis.

Results

Table 1 shows the summary statistics of the anthropometric parameters and indices of thyroid function in the sample of randomly selected adults of both genders. The age-adjusted Spearman's correlations showed weak but significant relations between several anthropometric characteristics and thyroid parameters (Table 2). Due to the large complexity of the anthropometric parameters, multiple regression analysis (see data analysis) was more informative than correlation analysis. The regression model elucidated relationships between thyroid parameters and the four independent variables, which characterized the key features of age, body composition, fat distribution and growth, provided that the three remaining explanatory variables are constant. Table 3 shows age- and height-adjusted Spearman's correlations among anthropometric parameters, which were considered as independent

indicators of body composition and body fat distribution in regression models. As shown on Table 3, Fat%, waist circumference and BMI are strongly inter-correlated while the CI is relatively independent of the aforementioned parameters indicating the different character of this parameter.

As demonstrated in Table 4, fT3 in men is inversely correlated with age but positively with BMI. Alternatively, fT3 in women exhibits independence of all anthropometric parameters except for a negative correlation with CI (Table 5). fT4 negatively correlates with BMI in women only. TSH negatively correlates with age in men (Table 4) but not in women (Table 5). In both genders, positive correlation between TSH and CI was observed. Positive correlation of BMI with TSH was shown in women only (Tables 4 and 5). The fT3/fT4 ratio, which may reflect deiodinase activity, negatively correlates with age but positively with BMI in both genders (Tables 4 and 5). In addition, women exhibit negative correlations of the fT3/fT4 ratio with CI (Table 5).

Discussion

The aim of our study was to evaluate relationships between pituitary-thyroid axis hormones and anthropometric characteristics in a representative sample of the population of Czech adults. Because of low correlations with the remaining explanatory variables, the selection of age, height, BMI (as parameter of body composition) and CI (as parameter of body fat distribution) appeared to be an optimum combination of independent variables for building a regression model (see Table 3). Except for the aforementioned correlations, the remaining explanatory variables used in the model are relatively independent of each other, which mean that they are suitable for building the regression model.

In contradiction to the report of Manji *et al.* (2006) and coworkers, our data concerning a normal adult population showed a number of relatively weak but highly significant relationships between anthropometric characteristics and pituitary-thyroid gland

function. Iodine supplementation in this sample was not examined. However, Knudsen *et al.* (2005) failed to find any significant association of iodine supplementation with BMI. It is apparent that currently BMI is much more influenced by total energy and nutrient intake and physical activity level and resulting energy balance than by iodine intake per se, but only under normal conditions.

Some of the relations between anthropometric indices and thyroid parameters were gender specific. In men all thyroid indices (fT3, fT4, TSH, and fT3/fT4 ratio) negatively correlated with age (Table 4). In women only the fT3/fT4 ratio exhibited a negative relationship with age (Table 5). In men, fT3 positively correlated with BMI but not with CI or body height (Table 4), although in women fT3negatively correlated with CI but not with other parameters (Table 5). In both genders, TSH positively correlated with CI. TSH was independent of BMI in men but correlated positively with BMI in women (Tables 4 and 5). Knudsen et al. (2005) revealed positive correlation between TSH and BMI in both genders. This positive association is caused by signals from adipose tissue, which produces leptin, playing an important role in the central regulation of thyroid function via stimulation of TRH (Knudsen et al. 2005). Zimmerman-Belsing et al. (2003) et al. found positive correlation between serum leptin and serum TSH. The increase in TSH levels may reflect a higher need for production of thyroid hormones with increasing BMI. Some authors demonstrated that the leptin-induced increase in TSH secretion via hypothalamic effects lead to an increase in serum free T4 (Chan et al. 2003, Welt et al. 2004). On the contrary, women examined in our study exhibited a decrease in serum fT4 with increasing BMI. This is in agreement with the findings of Knudsen et al. (2005), who demonstrated decreased fT4 with the increase of BMI in both genders. This situation gives support to the hypothesis that alterations in thyroid function with normal pituitary feedback regulation (high TSH and low fT4) is the primary event, while alterations BMI via alterations in energy expenditure the secondary event. The increase in BMI and fat mass may then lead to an increase in leptin, and a positive correlation between TSH and serum leptin would be expected. The fT3/fT4 ratio, probably reflecting deiodinase activity (Maia *et al.* 2005), negatively correlated with age but positively with BMI regardless of gender (Tables 4 and 5). The latter finding allows speculation about a compensatory mechanism counterbalancing either relative iodine deficiency or lower production of TSH via increase in deiodinase activity. In contrast to the positive correlation of fT3/fT4 ratio with BMI which was independent of gender, the negative correlation of the fT3/fT4 ratio with CI was specific to women only (Table 5).

Conclusions

Our study demonstrated significant relationships between body composition, body fat distribution and parameters of the pituitary-thyroid axis. Some of these relations were gender-specific. We observed that the fT3/fT4 ratio was inversely related to age and positively related to BMI in both genders. The fT3/fT4 ratio reflects deiodinase activity which might be largely influenced by energy and nutrient intake.

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There is no conflict of interest.

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Variable	Men			Women			
	(n=1012))	(n=			
	mean	SD	median	mean	SD	median	
Age (years)	41.8	13.7	44.0	42.2	12.4	44.0	
Body weight (kg)	82.2	13.8	81.6	69.6	14.2	67.2	
Height (cm)	176	7	176	164	6	164	
BMI (kg/m2)	26.5	4.3	26.2	26.2	5.0	25.6	
Suprailiac skinfold (mm)	13.7	7.9	12.0	16.4	8.2	15.0	
Abdominal skinfold (mm)	20.9	11.4	20.0	25.0	10.1	25.0	
Subscapular skinfold (mm)	17.6	8.3	16.0	22.3	11.3	20.0	
Triceps skinfold (mm)	17.7	7.7	18.0	21.5	8.8	20.0	
Fat (%)	16.3	4.7	15.9	18.1	5.3	18.3	
Lean body mass (%)	83.7	5.4	84.1	81.9	6.9	81.7	
Waist (cm)	98	12	98	96	15	94	
Hip (cm)	103	8	102	105	9	104	
Neck circumference (cm)	42.1	6.0	41.0	36.4	2.9	36.0	
WHR	0.96	0.09	0.96	0.93	0.09	0.92	
Subscapular skinfold/triceps skinfold	1.015	0.306	1.000	1.048	0.396	1.000	
Free triiodothyronine (pmol/l)	5.9	1.5	5.8	5.4	1.7	5.2	
Free thyroxine (pmol/l)	16.2	2.8	16.1	15.6	2.9	15.3	
TSH (mIU/l)	2.3	18.7	1.4	2.0	3.7	1.4	
fT3/fT4	0.373	0.108	0.357	0.355	0.113	0.335	

Table 1. Anthropometric characteristics and thyroid parameters in a random, representative sample of the Czech population

		Men				Women				
	fT3	fT4	HST	fT3/fT4	fT3	fT4	HST	fT3/fT4		
Weight	0.030	-0.023	0.046	0.044	-0.008	-0.073	0.072	0.027		
Height	0.340	0.469	0.146	0.163	0.761	0.004	0.004	0.280		
	-0.038	0.000	0.049	-0.044	-0.069	0.014	0.009	-0.073		
	0.239	0.997	0.124	0.165	<i>0.006</i>	0.586	0.719	0.004		
BMI	0.239 0.067 0.037	-0.016 0.614	0.124 0.011 0.725	0.105 0.073 0.022	0.000 0.021 0.399	-0.088 0.000	0.719 0.072 0.004	0.004 0.061 0.015		
SIL	0.022 0.497	-0.058 0.068	0.094 0.003	0.061 0.055	0.032 0.200	-0.146 0.000		0.103 0.000		
ABD	0.012	-0.069	0.054	0.048	0.048	-0.124	-0.009	0.104		
	0.712	0.031	<i>0.091</i>	<i>0.129</i>	0.055	0.000	0.726	0.000		
SSC	0.020	-0.071	0.048	0.060	-0.045	-0.080	0.063	0.002		
	0.536	0.026	<i>0.136</i>	0.060	0.071	0.001	0.012	0.928		
TRI	0.049 <i>0.122</i>	-0.094 0.003	0.037 0.241	0.097 0.002	0.045 0.070	-0.104 0.000		0.095 0.000		
Fat%	0.027	-0.078	0.061	0.071	0.020	-0.120	0.033	0.079		
	<i>0.400</i>	0.015	0.056	0.025	0.427	0.000	<i>0.194</i>	0.002		
LBM%	-0.012	0.063	-0.050	-0.045	-0.036	0.116	0.003	-0.088		
	0.715	0.048	0.117	0.157	0.157	0.000	<i>0.907</i>	0.000		
Waist	0.069	-0.033	0.047	0.086	0.109	-0.075	0.041	0.134		
	0.030	0.305	<i>0.144</i>	0.007	0.000	0.003	<i>0.104</i>	0.000		
Нір	0.077	-0.014	0.022	0.075	0.011	-0.085	0.080	0.049		
	0.015	0.654	<i>0.492</i>	0.018	<i>0.660</i>	0.001	0.001	<i>0.050</i>		
Neck	0.100	-0.003	0.011	0.093	0.053	-0.009	0.065	0.054		
	0.002	0.918	<i>0.732</i>	0.003	0.033	0.715	0.009	0.033		
WHR	0.014	-0.047	0.083	0.051	0.169	-0.037	-0.011	0.172		
	<i>0.670</i>	0.145	0.009	<i>0.110</i>	0.000	0.138	0.653	0.000		
CI	-0.063	0.076	0.014	-0.095	-0.137	0.089	0.055	-0.169		
	0.050	0.018	<i>0.651</i>	0.003	0.000	0.000	0.027	0.000		

Table 2. Age-adjusted Spearman's correlations between anthropometric characteristics and thyroidparameters in 986 adult men and 1586 adult women

SIL - suprailiac skinfold, ABD - abdominal skinfold, SSC - subscapular skinfold, TRI - triceps skinfold, Fat% - per cent of body fat, LBM - lean body mass, Neck - neck circumference, WHR - waist to hip ratio, CI - (Centrality index, SSC/TRI), fT3 - free triiodothyronine, fT4 - free thyroxine (Significant correlations are in bold. The upper and lower parts of the cells represent correlation coefficients and their *statistical significances*.) **Table 3.** Age- and height- adjusted Spearman's correlations among Fat%, waist circumference, body mass index and index of centralization (SSC/TRI ratio) in 1586 adult women and 985 adult men

	Women (upper right cells)						
	Fat%	0.751 <i>p</i> =0.000	0.801 <i>p</i> =0.000	0.057 p=0.024			
en e	0.703 p=0.000	Waist	0.856 <i>p</i> =0.000	0.094 <i>p=0.000</i>			
Men (lower left cells)	0.706 <i>p=0.000</i>	0.881 p=0.000	BMI	0.158 <i>p=0.000</i>			
	0.127 <i>p=0.000</i>	0.208 <i>p=0.000</i>	0.197 p=0.000	SSC/TRI			

SSC - subscapular skinfold, TRI - triceps skinfold, Fat% - per cent of body fat, BMI - body mass index (The upper and lower parts of the cells represent correlation coefficients and their statistical significances. Relationships with correlation coefficients >0.2 are in bold.)

	All variables					Backward stepwise regression				
	Parameter				Parameter					
Dependent variable	Independent variables	Mean	Standard error	T-statistic	p-value	Mean	Standard error	T-statistic	p-value	
	CONSTANT	2.78	0.26	10.9	0.0000	2.93	0.16	18.6	0.0000	
	Age	-0.00488	0.00082	-5.94	0.0000	-0.00468	0.00079	-5.94	0.0000	
0.5	-(BMI ^{-0.5})	1.78	0.71	2.53	0.0115	1.65	0.71	2.33	0.0197	
fT3 ^{0.5}	log(SSC/TRI)	-0.0202	0.0347	-0.58	0.5603					
	-(Height ^{-1.2})	-0.0896	0.1026	-0.87	0.3825					
	$R^2 = 3.56\%, p < 0.0001$					R^2 :	= 3.45%, p<	0.0001		
	CONSTANT	1.80	0.05	35.0	0.0000	1.87	0.01	304.9	0.0000	
	Age	-0.000628	0.000166	-3.78	0.0002	-0.000753	0.000139	-5.41	0.0000	
0.00	-(BMI ^{-0.5})	-0.297	0.143	-2.09	0.0370					
fT4 ^{0.22}	log(SSC/TRI)	0.00986	0.00698	1.41	0.1579					
	-(Height ^{-1.2})	-0.00247	0.02070	-0.12	0.9052					
	$R^2 = 3.41\%, p < 0.0001$					<i>R</i> ² =2.87%, <i>p</i> <0.0001				
	CONSTANT	1.11	0.05	22.5	0.0000	1.05	0.01	177.6	0.0000	
	Age	-0.000314	0.000158	-1.99	0.0466	-0.000354	0.000134	-2.64	0.0083	
0.1	-(BMI ^{-0.5})	0.0624	0.1358	0.46	0.6457					
TSH ^{0.1}	log(SSC/TRI)	0.0146	0.0067	2.19	0.0282	0.0139	0.0067	2.07	0.0382	
	-(Height ^{-1.2})	0.0245	0.0197	1.24	0.2143					
		$R^2 = 1.29\%, p=0.0127$				$R^2 = 1.03\%, p=0.0064$				
	CONSTANT	0.938	0.021	43.7	0.0000	0.950	0.013	71.7	0.0000	
	Age	-0.000246	0.000069	-3.57	0.0004	-0.000236	0.000066	-3.57	0.0004	
<i></i>	-(BMI ^{-0.5})	0.199	0.059	3.36	0.0008	0.192	0.060	3.23	0.0012	
(fT3/fT4) ^{0.1}	log(SSC/TRI)	-0.00266	0.00292	-0.91	0.3610					
	-(Height ^{-1.2})	-0.00701	0.00862	-0.81	0.4160					
		$R^2 = 1.54\%, p = 0.0004$								

Table 4. Relationships between thyroid parameters and anthropometric characteristics in 1012 men as evaluated by multiple regression (for details see Statistical data analysis)

SSC - subscapular skinfold, TRIC - triceps skinfold, fT3 - free triiodothyronine, fT4 - free thyroxine R^2 - variability of dependent variable explained by the model

	All variables					Backward stepwise regression			
	Parameter				Parameter				
Dependent variable	Independent variables	Mean	Standard error	T-statistic	p-value	Mean	Standard error	T-statistic	p-value
	CONSTANT	2.20	0.20	10.9	0.0000	2.30	0.01	304.5	0.0000
	Age	-0.00164	0.00072	-2.29	0.0220				
	-(BMI ^{-0.5})	0.720	0.451	1.60	0.1104				
fT3 ^{0.5}	log(SSC/TRI)	-0.159	0.027	-5.78	0.0000	-0.161	0.028	-5.72	0.0000
	-(Height ^{-1.2})	-0.142	0.078	-1.82	0.0683				
		$R^2 = 2.00\%, p < 0.0001$							
fT4 ^{0.22}	CONSTANT	1.76	0.04	43.5	0.0000	1.78	0.02	113.1	0.0000
	Age	0.000174	0.000144	1.21	0.2257				
	-(BMI ^{-0.5})	-0.300	0.091	-3.31	0.0009	-0.238	0.079	-3.03	0.0024
	log(SSC/TRI)	0.0101	0.0055	1.83	0.0675				
	-(Height ^{-1.2})	0.00302	0.01557	0.19	0.8463				
		$R^2 = 0.832\%, p=0.0102$				<i>R</i> ² =0.578%, <i>p</i> =0.0024			
	CONSTANT	1.14	0.04	27.2	0.0000	1.08	0.02	65.5	0.0000
	Age	-0.000066	0.000148	-0.45	0.6544				
0.1	-(BMI ^{-0.5})	0.274	0.094	2.93	0.0034	0.229	0.083	2.78	0.0055
TSH ^{0.1}	log(SSC/TRI)	0.0161	0.0057	2.82	0.0048	0.0162	0.0057	2.84	0.0046
	-(Height ^{-1.2})	0.0192	0.0160	1.20	0.2313				
		R ² =1.36%, p =0.0003			R ² =0.769 %, p =0.0006				
	CONSTANT	0.904	0.017	53.6	0.0000	0.931	0.009	104.5	0.0000
	Age	-0.000172	0.000060	-2.88	0.0039	-0.000143	0.000058	-2.48	0.0132
(fT3/fT4) ^{0.1}	-(BMI-0.5)	0.128	0.038	3.40	0.0007	0.137	0.038	3.64	0.0003
	log(SSC/TRI)	-0.0126	0.0023	-5.51	0.0000	-0.0130	0.0023	-5.65	0.0000
	-(Height ^{-1.2})	-0.0123	0.0065	-1.89	0.0588				
		$R^2 = 2.57\%, p < 0.0001$							

Table 5. Relationships between thyroid parameters and anthropometric characteristics in 1625 women as evaluated by multiple regression (for details see Statistical data analysis)

SSC - subscapular skinfold, TRIC - triceps skinfold, fT3 - free triiodothyronine, fT4 – free thyroxine R^2 - variability of dependent variable explained by the model