THYROID FUNCTION AND CHOLESTEROL LEVEL: PARADOXICAL FINDINGS IN LARGE GROUPS OF POPULATION WITH HIGH CHOLESTEROL FOOD INTAKE

[1]P. Langer, [2]A. Kocan, [3]M. Tajtakova, [2]J. Petrik, [1]J. Koska, [1]M. Hucková, [4]E. Hanzen, [1]L. Ksinantova, [1]Z. Radikova, [1]R. Imrich, [2]T. Trnovec, [5]P. Blazicek, [1]E. Sebokova, [1]I. Klimes

[1]Institute of Experimental Endocrinology, Slovak Academy of Sciences, 833 06 Bratislava, Slovakia; [2]Institute of Preventive and Clinical Medicine, Bratislava; [3]1st Clinic of Internal Medicine, Faculty of Medicine, P. J. Safarik University, Kosice, Slovakia; [4]National Institute of Endocrinology and Diabetology, Lubochna, Slovakia; [5]Department of Clinical Biochemistry, Hospital of Ministry of National Defense, Bratislava, Slovakia
e-mail: pavel.langer@savba.sk

Objective. To compare the levels of serum cholesterol with thyroid function as estimated by the level of thyrotropin and free thyroxine with possible participation of thyroperoxidase antibodies in large number of adults examined within large field surveys focused on the evaluation of thyroid status of Slovak rural population.

Subjects and Methods. Serum level of cholesterol and thyrotropin (TSH) was estimated in a total of 2786 adults. In addition, in 2038 of them also the level of free thyroxine (FT4), total triiodothyronine (TT3), cholesterol, triglycerides and phospholipids was measured. The levels of TSH, anti-TPO and FT4 were estimated by supersensitive electrochemiluminiscent immunoassay using the automatic system Elecsys (Roche, Switzerland).

Results. A total of 2786 adults was stratified into 7 groups according to the range of TSH level as related to generally recognized level of thyroid function, e.g. 1. TSH <0.10 mU/L (overt hyperthyroidism, N=41), 2. TSH 0.11-0.30 mU/L (overt or subclinical hyperthyroidism, N=149), 3. TSH 0.31-2.50 mU/L (normal level, N=1750), 4. TSH 2.51-4.50 (”high normal” level, N=607), 5 TSH 4.51-6.50 (mild or incipient subclinical hypothyroidism, N=137), 6. TSH 6.51-10.00 mU/L (mild hypothyroidism, N=50), 7. TSH 10.01-99.00 mU/L (severe hypothyroidism, N=53). The average levels of cholesterol in all groups were very similar ranging from 5.53 to 6.17 mmol/L and no interrelations with TSH level were found. In addition, no considerable differences between these groups were found when considering the levels of medians, upper quartiles and 90th percentiles of individual groups. When male and female subjects were divided into age groups according to the decades, an age dependent increase of cholesterol level was found in both sexes.

The fraction of 2038 subjects was divided into the same TSH related groups as defined above. Similarly as above, no considerable differences in cholesterol, triglycerides and phospholipids level were observed. However, the levels of FT4 and TT3 were significantly decreasing with the increase of TSH level which confirmed the continuing decrease of thyroid function. The frequency of positive anti-TPO in subjects with TSH >6.5 mU/l (71/86 = 82.5 %) was significantly higher than that in subjects with TSH <6.5 mU/l (468/1952 = 23.9 %).

Conclusions. No difference in the level of cholesterol and triglycerides was found in large groups of rural adults from Slovakia with various thyroid function as estimated by the level of TSH, FT4, TT3 and anti-TPO. It is assumed that this interrelation resulted from very high cholesterol intake due to inappropriate general nutritional status of rural population resulting from the consumption of unhealthy foods.

Key words: Thyroid function – TSH – Thyroid hormones – Autoantibodies – Serum lipids

Table 1
Interrelations between the level of TSH and cholesterol in serum of 2787 subjects

TSH level (mU/l)	Number of subjects	Serum cholesterol level (mmol/l)				
		Mean± SD	Range	Median	Upper quartile	10th decile
<0,10	41	6.10 ± 1.25	2.82 – 8.61	5.91	7.30	7.51
0,11 – 0,30	149	6.04 ± 1.18	3.39 – 9.30	5.98	6.75	7.72
0,31 – 2,50	1750	5.60 ± 1.09	2.45 – 10.23	5.52	6.25	6.91
2,51 – 4,50	607	5.53 ± 0.99	3.23 – 9.18	5.47	6.11	6.85
4,51 – 6,50	137	5.51 ± 1.06	3.58 – 9.10	5.41	6.21	6.93
6,51 – 10,00	50	5.85 ± 1.26	3.23 – 9.88	5.84	6.17	7.93
10,01 – 99,00	53	6.17 ± 1.22	3.89 – 9.61	5.83	7.06	7.93
TOTAL	2787					

It is generally well known and repeatedly published that patients with subclinical hypothyroidism as diagnosed by high thyrotropin (TSH) level show increased level of cholesterol and some other serum lipids (O'Brien et al. 1993; De Bruin et al. 1993; Wiseman et al. 1993; Engler and Riesen 1993; Kung et al. 1995; Yamamoto et al. 1995; Pazos et al. 1995; Peterson and Kjellstrom 2001; Duntas et al. 2002; Kanaya et al. 2002) which is beleived to result from impaired metabolism due to a decreased thyroid function. Vice versa, several authors showed a significant reduction of such lipid levels after restoration of euthyroid state with thyroxine substitution treatment. Some authors also suggested that, in overt hypothyroidism, a greatly elevated serum cholesterol is almost a part of clinical diagnosis (Kinlaw 1991) or, perhaps more precisely, that high serum cholesterol level in subjects with "high normal" TSH levels should extend the definition of subclinical hypothyroidism (Michalopoulou et al. 1998). However, some controversy exists in this respect, since some reports showed that the high lipid levels are most likely to be restored in patients with the highest pretreatment levels of TSH (Efstathiadou et al. 2001; Glueck and Streicher 2003). Steinmetz et al (2002) established that probability of beneficial thyroid hormone effect on serum lipids increased 5.4 fold in patients with pretreatment TSH level of >6.0 mU/l and 7.0 fold with that level >64 mU/l. Also Caraccio et al. (2002) concluded that total and LDL-cholesterol decreased in their patients with pretreatment TSH level of 3.7-15.0 mU/l.

In our previous report (Langer et al. 1997) we found very high levels of cholesterol (e.g. 110/278 or 39.5 % of cases in a range of 6.6-9.5 mmol/l and 25/278 or 8.9 % cases in a range of 8.1-9.5 % mmol/l) and triglycerides (e.g. 85/278 or 30.6 % of cases in a range of 2.6-6.7 mmol/l and 20/278 or 7.2 % values in a range of 3.6-6.7 mmol/l) in Slovak rural population. It was surprising to us that there was no any correlation between those levels and thyrotropin level. Thus, the aim of this study was to compare the levels of serum cholesterol with the thyroid function as estimated by the level of thyrotropin and free thyroxine with possible participation of thyroperoxidase antibodies in large number of adults examined within large field surveys focused on the evaluation of thyroid status of Slovak rural population.

Subjects and Methods

Subjects. Within three field surveys conducted during last few years serum cholesterol, thyrotropin (TSH) and thyroperoxidase antibody (anti-TPO) serum level was estimated in a total of 2786 adults. In addition, in 2038 of them (which were examined within the last survey) also the level of free thyroxine (FT4), total triiodothyronine (TT3) and phospholipids (PL) was measured. Details on age and sex distributrion of the examined population are shown in Table 2.

Laboratory methods. Blood samples were obtained from cubital vein after overnight fasting.

After centrifugation of blood in refrigerated centrifuge, the plasma aliquots were transported to the laboratory in a portable freezer and kept at 20 °C until assayed. The levels of cholesterol, triglycerides and phospholipids were estimated with the aid of com-

Table 2
Cholesterol levels in serum of 1075 males as related to age decades

Age	Males (number)	Serum cholesterol level (mmol/l)				
		Mean± SD	Range	Median	Upper quartile	10th decile
21-30	203	4.72 ± 0.89	2.54 – 7.95	4.67	5.31	6.03
31-40	124	5.46 ± 1.05	3.19 – 8.81	5.26	6.11	6.92
41-50	338	5.71 ± 1.04	2.91 – 10.22	5.61	6.31	6.95
51-60	327	5.64 ± 0.99	3.23 – 10.01	5.55	6.21	6.87
61-70	62	5.83 ± 1.13	3.39 – 9.04	5.78	6.47	7.23
71-80	21	5.81 ± 1.28	2.82 – 8.77	5.67	6.46	7.58
TOTAL	1075					

mercial enzymatic metods. The levels of TSH, anti-TPO and FT4 were estimated by supersensitive electrochemiluminiscent assay using the automatic assay system Elecsys (Roche, Switzerland).

Statistical evaluation. Standard statistical methods were used such as ANOVA followed by multiple range Tukey test and Yates chi-square test.

Results

Since the level of TSH is generally considered the first step marker of thyroid function, all subjects were retrospectively divided into 7 groups according to their level of TSH (Table 1). The first group consisted of 41 subjects with TSH <0.10 mU/L which should be very likely considered as suffering from overt hyperthyroidism. Similarly, the second group of 13 subjects with TSH level of 0.11-0.30 mU/L should be considered at least as subclinically hyperthyroid (Koutras 1999; Toft 2001). The most abundant group of 1233 subjects with TSH level was apparently euthyroid. This view is based namely on the data obtained by NHANES III study (Hollowell et al. 2002) in which about 95 % subjects a total of 13,344 examined showed the mean level of TSH of of about 1.50 mU/L (range about from 0.5 to 2.5 mU/L). Next group of 607 subjects has been defined according to the TSH level in the range of 2.51 – 4.50 mU/L which is also called "high normal level" (Michalopoulou et al. 1998; Staub 1998). Considering a current general opinion that subjects with TSH level higher than about 4.00 or 4.50 mU/L should be considered as hypothyroid (Caraccio et al. 2002), the subjects with such levels were divided into three groups, e.g. 4.51-6.50 mU/l (subclinical hypothyroidism), 6.51-10.00 mU/l (mild overt hypothyroidism) and 10.01-99.00 mU/l (severe hypothyroidism).

Table 1 shows that, although there was some fluctuation of the average values, no considerable differences in cholesterol level could be observed between the individual groups, especially between that of hyperthyroid (e.g. 6.10 ± 1.25 mmol/l) and severely hypothyroid subjects (e.g. 6.02 ± 1.25 mmol/l). Similarly, no considerable differences appeared in the values of medians, upper quartiles and 90th percentile. From this it was concluded that no considerable interrelations between the thyroid function and cholesterol level could be found.

When the same subjects were divided into males (Table 2) and females (Table 3) and subsequently each sex group stratified according to the age irrespectively of TSH level, a continuous increase of cholesterol level ($P<0.01$) was found especially in females after 50th year of age. This was supported also by high levels of medians, upper quartiles and 90th percentiles in the appropriate age groups. In contrast, the lowest cholesterol levels were found in both sexes aged 21-30 years, while the groups between 31 and 60 years did not show any remarkable differences. Since the average levels of TSH showed irregular fluctuation according the frequency of extremely high values in some age groups, the values of upper quartiles are shown in Tables 2 and 3 which support the view that no remarkable differences in the thyroid function could be detected in 75 percent of subjects as related to age.

Table 3
Cholesterol levels in serum of 1712 females as related to age decades

Age	Females (number)	Serum cholesterol level (mmol/l)				
		Mean ± SD	Range	Median	Upper quartile	10th decile
21-30	218	4.81 ± 0.89	2.45 – 7.71	4.74	5.41	6.01
31-40	173	5.34 ± 0.90	2.68 – 8.08	5.28	5.88	6.51
41-50	690	5.72 ± 0.98	2.90 – 13.53	5.65	6.33	6.98
51-60	460	6.07 ± 1.04	3. 43 – 9.88	6.05	6.75	7.40
61-70	131	6.33 ± 1.07	3.70 – 9.10	6.12	7.10	7.81
71-80	40	6.49 ± 1.31	3.52 – 9.20	6.59	7.30	8.10
TOTAL	1712					

In general, Table 4 supported the data concerning the cholesterol levels as shown in Table 1. In addition, it showed similar small fluctuations of average values of triglycerides and phospholipids in the groups with different thyroid function. However, the levels of FT4 showed a regular decrease ($P<0.01$) from 24.54 ± 6.05 pmol/l in hyperthyroid group to 11.14 ± 3.64 pmol/l in hypothyroid group which strongly supported the views on different thyroid function in TSH related groups as defined above. This was further supported by a parallel decrease ($P<0.01$) of TT3 levels from 2.48 ± 0.93 nmol/l in hyperthyroid to 1.72 ±0 .48 nmol/l in hypothyroid group.

Discussion

In this study no considerable differences in the level of cholesterol and triglycerides were found between large groups of hyperthyroid, euthyroid and hypothyroid subjects. Although the average and median levels were either in normal range or only slightly elevated, the values of upper quartile and 10th decile and also these of upper range limit were definitely highly elevated in all groups. Such finding certainly is not surprising for hypothyroid groups as supported by several observations (see above the Introduction), but it would be hardly expected for hyperthyroid group with very low TSH level and high levels of FT4 and TT3. Such high FT4 level apparently represents also the increased level of total thyroxine and may be compared to that occurring during the thyroxine substitution treatment of hypothyroidism. However, it has been repeatedly shown that such treatment results in a decrease of cholesterol level namely in patients with highly increased TSH level (Duntas 2002; Kanaya et al. 2002), but also in those with "high normal" level (Michalopoulou et al. 1998), while in hyperthyroid groups examined in this study high cholesterol and triglyceride levels were a common finding.

Thus, the question appears where the high levels of cholesterol in hyperthzroid subjects come from. It was repeatedly demonstrated that in hypothyroid subjects the lipid metabolism is severely impaired which results, among others, in increased plasma level of lipoprotein (a), apolipoprotein B, LDL lipoprotein and others which tend to decrease after thyroxine replacement therapy (Pazos et al. 1995; Kung et al. 1995; Tanis et al. 1996; Staub 1998; Caraccio et al. 2002)

Since very high cholesterol levels were found in a number of hyporthyroid subjects examined in this study and since traditionally very high consumption of animal fat (lard, butter, cream, high fat milk and milk products), high fat red meat (mainly pork), eggs etc. by the rural population in this country. is well known and repeatedly reported, it is hypothesized that this might be the cause of the observed paradoxical findings as described above. Similar circumstances apparently exist in rural population of surrounding countries (Poland, Czech Republic, Hungary etc.) as recently supported by the description of dietary habits in a previous German Democratic Republic (Eastern Germany) and their changes after German reunification and their relations to dietary lipids resulting mainly in decreased consumption of butter (from 26.8 to 10.2 %) which resulted in an increased consumption of mono- (from 7.3 to 22.1 %) and polyun-

Table 4
Interrelations between the level of TSH and levels of lipid fractions, thyroid hormones and frequency of positive anti-thyroperoxidase levels

TSH	Number of Subjects	Cholesterol	Triglycerides	Phospholipids	Free T4	Total T3	anti-TPO >35,0 U/ml
mU/l		mmol/l	mmol/l	g/l	pmol/l	nmol/l	cases (%)
< 0,10	17	5.88 ± 1.04	2.51 ± 1.60	2.50 ± 0.45	24.54 ± 6.05	2.48 ± 0.93	6 (33.3 %)
0,11 – 0,30	13	5.64 ± 1.11	2.05 ± 1.08	2.54 ± 0.49	20.49 ± 5.51	2.15 ± 0.45	5 (38.5 %)
0,31 – 2,50	1233	5.41 ± 0.97	1.73 ± 1.15	2.37 ± 0.43	16.85 ± 2.64	1.98 ± 0.38	249 (20.2 %)
2,51 – 4,50	564	5.48 ± 0.98	1.95 ± 1.75	2.38 ± 0.44	16.13 ± 2.30	1.94 ± 0.33	160 (28.3 %)
4,51 – 6,50	125	5.41 ± 0.97	1.99 ± 1.34	2.41 ± 0.38	16.03 ± 2.75	1.94 ± 0.36	48 (38.5 %)
6,51 – 10,00	44	5.81 ± 1.34	2.46 ± 0.51	2.46 ± 0.50	14.10 ± 2.39	1.96 ± 0.36	31 (70.4 %)
10,01 – 99,00	42	6.20 ± 1.29	2.67 ± 0.48	2.65 ± 0.48	11.14 ± 3.64	1.72 ± 0.46	40 (95.2 %)
TOTAL	2038						

saturated fatty acids from 19.5 to 39.5 % of total intake of fatty acids (Wahrburg et al. 1995). From this it may be also suggested that close interrelations between thyroid function and lipid levels exist perhaps mainly in developed industrialized countries in which most of inappropriate dietetic factors may be excluded (at least in middle and upper class). The same may be true even for the countries (e.g Japan) with traditionaly low intake of those unhealthy foods.

Acknowledgements

A majority of presented data has been obtained within the 5th Framework Programme of European Commision (project PCBRISK QLK4-2000-00488) which is sincerely acknowledged by the authors. Other parts of the study were kindly spported by Ministry of Environment Slovak Republic (Contract 105/98-2.4.), Slovak Grant Agency VEGA (reg. No. 2-309923) and Merck Slovakia, Ltd.

References

Caraccio N, Ferrannini E, Monzani F: Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab **87,** 1533-1538, 2002

De Bruin TWA, Van Barlingen H, Van Linde-Sibenius Trip, Van Vuurst de Vries AR, Akveld MJ, Erkelens DW: Lipoprotein (a) and apoliporpotein B plasma concentrations in hypothyroid, euthyroid, and hyperthyroid subjects. J Clin Endocrinol Metab **76,** 121-126, 1993

Duntas LH: Thyroid disease and lipids. Thyroid **12,** 287-293, 2002

Engler H, Riesen W: Effect of thyroid function on concentrations of lipoprotein (a). Clin Chem **39,** 2466-2469, 1993

Hollowell JG, Staehling NW, Hannon WH, Flanders WD, Gunter EW, Spencer CA, Braverman LE: Serum thyrotropin, thyroxine, and thyroid antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrin Metab **87**, 489-499, 2002

Kanaya AM, Harris F, Volpato S, Perez-Stable EJ, Bauer DC: Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study. Arch Intern Med **162,** 773-779, 2002

Kinlaw WB: Atherosclerosis and the thyroid. Thyroid Today **14,** 1-8, 1991

Koutras DA: Subclinical hyperthyroidism. Thyroid **9,** 311-315, 1999

Kung AWC, Pang RWC, Janus ED: Elevated serum lipoprotein (a) in subclinical hypothyroidism. Clin Endocrinol **43,** 445-449,1995

Langer P, Hanzen E, Tajtakova M, Putz Z, Kreze A, Sebokova E, Bohov P, Gasperikova D, Huckova M, Klimes I: High lipid levels in Slovak rural population: Consequence of thyroid dysfunction or nutritional status? Ann NY Acad Sci **827,** 568-574, 1997

Michalopoulou G, Alevizaki M, Piperingos G, Mitsobounas D, Mantzos E, Adamopoulos P, Koutras DA: High serum cholesterol levels in persons with "high normal" TSH levels: Should one extend the definition of subclinical hypothyroidism? Eur J Endocrinol **138,** 141-145, 1998

O'Brien T, Dinneen SF, O'Brien PC, Palumbo PJ: Hyperlipidenmia in patients with primary and secondary hypothyroidism. Mayo Clin Proc **68,** 860-866, 1993

Pazos F, Alvarez JJ, Rubies/Prat J, Varela C, Lasuncion MA: Long term thyroid replacement therapy and levels of lipoprotein (a) and other lipoproteins. J Clin Endocrinol Metab **80,** 562-566, 1995

Staub JJ: Minimal thyroid failure: effects on lipid metabolism and peripheral target tissues. Eur J Endocrinol **138,** 137-138, 1998

Steinmetz J, Spyckerelle Y, Fournier B, De Talance N, Giordanella JP: Three-year follow-up of intraclinical hypothyroidism: Course in a cohort of 97 women aged 45 to 70 years attending health care screening conters. Ann Endocrinol **63**, 505-510, 2002

Tanis BC, Westendorp RGJ, Smelt AHM: Effect of thyroid substitution on hypercholesterolemi in patients with subclinical hypothyroidim: a reanalysis of intervention studies. Clin Endocrinol **44,** 643-649, 1996

Toft AD: Subclinical hyperthyroidism. New Eng J Med **345,** 512-516, 2001

Wahrburg U, Martin H, Bergmann S, Schuilte H, Jaross W, Assmann G and DRECAM team: Dietary habits in Eastern Germany. Changes due to German reunification and their relations to serum lipids: results of the DRECAN study. Nutr Metab Cardiovascv Dis **5,** 201-210, 1995

Wiseman SA, Powell JT, Humphries SE, Press M: The magnitude of the hypercholesterolemia of hypothyroidism is associated with variation in the low density lipoprotein receptor gene. J Clin Endocrinol Metab **77,** 108-112, 1993

Yamamoto K, Ozaki I, Fukushima N, Setoguchi Y, Kajihara S, Mizuta T, Yanagita T, Sakai T: Serum lipoprotein (a) levels before and after subtotal thyroidectomy in subjects with hypothyroidism. Metabolism **44,** 4-7, 1995

Corresponding author: Pavel Langer, M.D., DrSc.
Institute of Experimental Endocrinology
Slovak Academy of Sciences
Vlárska 3, 833 06 Bratislava
Slovakia
e-mail: pavel.langer@savba.sk