ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN—POLONIA
VOL. XXXIX, 18 SECTIO D 1984

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Research on the Chemical Composition of the Vascular Wall. XXI. The Influence of Atherogenic Diet and Hypothyroidism on the Content of Collagen, Elastin, Supporting Proteins and Glycosaminoglycans in the Aorta Wall of Rabbits *

Badania nad składem chemicznym ściany naczyniowej.
XXI. Wpływ diety miażdżycorodnej i hipotyreozy na zawartość kolagenu, elastyny, białek podporowych i glikozoaminoglikanów w ścianie aorty królików

Исследование химического состава сосудистой стенки. XXI. Влияние артероматозной диеты и гипотиреоза на содержание коллагена, эластина, интерстициального белка и гликозамингликогена в стенке аорты кроликов

Previous research works have shown that the experimental hyperthyreoidism in rabbits caused by the administration of *Thyreoideum* (Polfa) does not essentially influence the development of atherosclerosis in animals on a rich cholesterol diet (7, 19). In the examined experimental groups no major differences in the content of collagen, elastin, supporting proteins and glycosaminoglycans in the intima-media layer of aorta were found. On the other hand, the noticed directions of changes in the chemical composition of aorta wall in the course of experimental atherosclerosis and atherosclerosis combined with hyperthyroidism seem

* This work was supported by Institute of Cardiology, Warsaw, Poland, problem No 10-RMZ-I/1.47.

to suggest that thyroid hormones neutralize the soluble collagen content decrease and the increase of sulfuric glycosaminoglycans content. This might confirm the suggestions of other authors (10) concerning protective properties of thyroid hormones in the development of atherosclerosis.

A very common symptom of hypothyroidism is the increase of total lipids in the blood serum and mainly hypercholesterolemia. The increase of cholesterol concentration may be treated as a major risk factor of atherosclerosis. In the present study an attempt was made at deciding the degree to which the experimental hypothyroidism in rabbits influences the formation of aorta atherosclerosis and the degree to which it influences the chemical composition of connective tissue ground substance in aorta wall.

MATERIAL AND METHODS

Investigations were carried out on 25 New Zealand rabbits, aged 8 months, weight 2.8—4 kg, divided into four groups:

I — control group — 6 rabbits;
II — group with experimental atherosclerosis — 6 rabbits;
III — group with experimental hypothyroidism — 6 rabbits;
IV — group with atherosclerosis and hypothyroidism — 7 rabbits.

All the rabbits were kept in identical conditions, fed with standard laboratory fodder, fresh vegetables and water. At the beginning of the experiment the rabbits from group III and IV went through thyroidectomy under ether anesthesia. After the postsurgery wounds had been healed up, the rabbits from group IV, and II received cholesterol dosed 0.5 g/kg for 90 days. In order to maintain hypothyroidism, independently of thyroidectomy, the rabbits from group III and IV received Methizole dosed 0.1 mg/kg of a rabbit's weight. The hypothyroidism was estimated on the basis of the decrease of thyroid hormones concentration in the serum.

After the experiment had ended, the rabbits were killed by an air embolism and immediately after that their heart blood was collected. The aortas were prepared from the ascending part to the place of division into femoral arteries. The following components were determined in the blood serum: a) total protein with biuret method; b) total and protein-bound hydroxyproline with a modified Prockop and Undenfriend method (16); c) total cholesterol with a method based on Lieberman-Burchard reaction (2); d) triglyceride according to Giegel and Soloni (5); e) phospholipides with Baginski and Zak method (1); free fatty acids with Laurell and Tibbling method (11); g) thyroxine and triiodothyronine with radioimmunologic methods using the Thyro-Con reagent kit, VEB Feinchemie, GDR and the Tri-Set from IBJ, Świerk.

The prepared aortas were cut lengthwise, the intensification of atherosclerotic changes was estimated through a macroscopic way, then the intima-media layer was separated. The isolation and fractionation of protein, collagen and elastin were carried out according to the procedure described in detail in our earlier paper (18). The content of each component was expressed in mg/g of fresh wet tissue.

In order to estimate the content and composition of glycosaminoglycans, the intima-media layer of aorta were homogenized in water delipidated with acetone

and ether, and then purified and separated according to a modified Svejcar and Robertson procedure (6). The glycosaminoglycans content was expressed in μg of uronic acid for 100 mg of dry deffeted tissue. The obtained results went through statistical analysis according to Student t test for unpaired means, assuming that statistically significant are the differences for which $p<0.05$.

RESULTS OF INVESTIGATIONS

The average results of the determinations carried out in the blood serum of the examined rabbits are presented in Table 1. In the blood serum of rabbits from group III and IV a significant decrease of thyroid hormones and particularly thyroxine concentration could be noticed. In the experimental conditions no differences in total protein were found, but like in earlier investigations (17), in the groups which were on an atherogenic diet there was an increase of protein-bound hydroxyproline. Also a significant increase of free and peptide-bound hydroxyproline concentration was observed in the serum of rabbits with hypothyroidism.

Table 1. Thyroid hormones, protein, hydroxyproline and lipid concentrations in the serum of rabbits with experimental atherosclerosis and hypothyreosis

	Unit	Control group	Group with experimental atherosclerosis	Group with experimental hypothyroidism	Group with atherosclerosis and hypothyroidism
		$\bar{X}$ ±SD	$\bar{X}$ ±SD	$\bar{X}$ ±SD	$\bar{X}$ ±SD
Thyroxine	μg/dl	2.28 ±1.20	3.26 ±1.45	0.57 ±0.35*	0.39 ±0.30*
Triiodothyronine	μg/dl	121 ± 27	176 ± 32	93 ± 30	59 ± 12*
Total protein	g/dl	6.76 ±0.84	7.20 ±0.40	6.69 ±0.49	7.69 ±0.59
Total OH-Pro	μg/ml	12.6 ±1.1	13.4 ±1.7	11.9 ±1.2	15.5 ±1.8
Protein OH-Pro	μg/ml	10.4 ±1.6	12.2 ±0.6	7.8 ±0.9	11.6 ±2.1
Free OH-Pro	μg/ml	2.2 ±0.8	1.2 ±0.6	4.1 ±1.2*	3.9 ±1.0*
OH-Pro/Total protein	μg/mg	0.154	0.169	0.116	0.151
Total lipids	mg/dl	303 ±53	1390 ±182*	386 ±86*	1388 ±279*
Cholesterol	mg/dl	70.2 ±18.0	727.7 ±64.6*	96.8 ±34.3*	772.8 ±103.8*
Triglicerides	mg/dl	95.3 ±18.5	153.1 ±69.3*	150.8 ±37.0*	192.3 ±81.9*
Phospholipids	mg/dl	120.8 ±27.0	558.0 ±64.6*	131.6 ±27.5*	414.8 ±90.5*
Free fatty acids	mmol/l	0.210 ±0.060	0.473 ±0.100*	0.270 ±0.110	0.360 ±0.170*

* Statistically significant differences $p<0.05$.

The influence of the hypothyroidism on the lipids concentration found expression in an essential increase of cholesterol and triglyceride in group III as compared to the control group. The applied atherogenic diet, just like in our earlier experiments, caused a major increase of all

the lipid components of plasma, particularly cholesterol, phospholipids and free fatty acids. On the other hand, no big differences were found between group II with experimental atherosclerosis and group IV with atherosclerosis and hypothyreoidism. Admittedly, the cholesterol and triglyceride concentration were higher in group IV, but the difference was of no statistical importance.

MORPHOLOGICAL FINDINGS

In the control group and group III with hypothyroidism no macroscopic atherosclerotic plaques in aorta were found. The changes were observed in all rabbits from group II and IV which were on a cholesterol-rich diet for 90 days. Attempts at finding the acceleration of the changes by coexisting hypothyroidism were not successful. On the contrary, if in group II the changes included from 30 to 50% of aorta's surface, in group IV the situation was not so clear. In 2 cases from the 7 examined aortas slight atherosclerotic plaques located mainly in the ascending part and the arch of aorta were noticed. They did not exceed 15% of the surface. In the next 2 cases the intensification degree of atherosclerotic changes could be classified as medium. In the remaining 3, the changes were comparable to the ones observed in group II.

COLLAGEN AND SOLUBLE PROTEINS OF AORTA

The average soluble protein and collagen fractions content in the intima-media layer of rabbit's aorta in the examined experimental groups is presented in Table 2. No significant differences in the total content

Table 2. Proteins and collagen fractions in intima-media layer

Group	Fraction soluble in 0.4 M NaCl			Fraction soluble in 0.5 M CH_3COOH		
	Protein mg/gwt	Collagen mg/gwt	%	Protein mg/gwt	Collagen mg/gwt	%
Control	17.85 ±2.23	1.02 ±0.17	5.7	3.90 ±0.62	0.38 ±0.07	9.7
With experimental atherosclerosis	15.28 ±1.34*	0.63 ±0.12*	4.1	5.62 ±0.71*	0.25 ± 0.07*	4.4
With experimental hypothyroidism	14.71 ±0.96*	1.08 ±0.09	7.3	5.13 ±1.00*	0.36 ±0.08	7.0
With atherosclerosis and hypothyroidism	18.50 ±2.05	1.13 ±0.20	6.1	5.44 ±0.90*	0.41 ±0.08	7.2

* Statistically significant differences as compared to the control group, $p<0.05$.

of soluble proteins and collagen of aorta subject to the conditions of the experiment were noticed. Only in group II with experimental atherosclerosis a slightly lower total collagen content could be observed. There was also a major decrease of soluble collagen fractions in 0.45 mol NaCl and in 0.5 mol acetic acid. The composition of protein fractions in group III and IV did not differ much from that of the control group. The content of collagen soluble in the solutions of neutral salts and weak organic acid constituted about 6% of its total quantity.

COLLAGEN, ELASTIN AND SUPPORTING PROTEINS OF AORTA WALL

The total content of supporting proteins, collagen and elastin in the intima-media of aorta in the examined animal groups is presented in Table 3. In the aorta wall of rabbits the total protein content constitutes 13% of fresh wet tissue mass and does not vary much in groups with atherosclerosis and experimental hypothyroidism. Elastin constituted about 50% of the aorta wall proteins. Elastin's highest content was observed in group II with experimental atherosclerosis. Unlike group II, in group III and group IV with atherosclerosis associated with hypothyroidism a higher content of supporting proteins and collagen was observed. The collagen: elastin ratio was also higher.

TOTAL CONTENT OF AORTA GLYCOSAMINOGLYCANS

Average results of glycosaminoglycans determination in aorta wall of the examined experimental groups are shown in Table 4. No essential differences were found in the content of whole glycosaminoglycans ex-

of aorta of rabbits with experimental atherosclerosis and hypothyroidism

Gelatynizing fraction /insoluble fraction/			Fraction soluble in 0.1 M NaOH			Total collagen fraction	
Protein mg/gwt	Collagen mg/gwt	%	Protein mg/gwt	Collagen mg/gwt	%	Protein mg/gwt	Collagen mg/gwt
36.97 ±2.72	22.27 ±2.01	57.1	7.98 ±1.26	0.37 ±0.04	4.6	63.70 ±6.63	24.04 ±2.12
35.20 ±3.80	20.26 ±2.32	57.5	8.40 ±0.81	0.35 ±0.06	4.2	64.50 ±6.56	21.49 ±2.46
40.78 ±2.85	21.82 ±1.57	53.5	8.23 ±1.47	0.50 ±0.15	6.1	68.85 ±5.98	23.76 ±1.78
39.43 ±3.38	22.69 ±3.00	57.5	7.30 ±0.98	0.44 ±0.12	6.0	70.67 ±9.81	24.67 ±3.25

gwt — 1 g of wet tissue.

Table 3. Content and composition of protein fractions in the intima-media layer of rabbits aorta

Group	Total protein fraction	Protein fraction						Collagen / Elastin
		Structural protein		Collagen		Elastin		
	mg/gwt	mg/gwt	%	mg/gwt	%	mg/gwt	%	
Control	135.60	44.66	32.9	24.04	17.7	66.90	49.4	0.359
With experimental atherosclerosis	139.40	43.10	30.9	21.49	15.4	71.90	53.7	0.299
With experimental hypothyroidism	132.35	45.09	34.1	23.76	17.9	63.50	48.1	0.374
With atherosclerosis and experimental hypothyroidism	130.47	46.00	39.1	24.67	19.5	59.80	41.4	0.412

gwt — 1 g of wet tissue.

Table 4. Glycosaminoglycans content in the intima-media layer of aorta of the rabbits with experimental atherosclerosis and hypothyroidism

Group	Uronic acid content		Percentage recovery %
	in dry defatted tissue µg/100 mg dt	in purified GAG fraction µg/100 mg dt	
Control	261.3 ±40.4	182.1 ±26.8	69.7
With experimental atherosclerosis	247.4 ±36.0	170.0 ±29.4	68.7
With experimental hypothyroidism	277.4 ±38.5	195.5 ±37.3	70.5
With atherosclerosis and experimental hypothyroidism	286.0 ±47.5	207.9 ±43.6	72.7

mg dt — mg of dry defatted tissue.

pressed as uronic acids in dry, defatted tissue. The content of glycosaminoglycans purified by means of precipitation with potassium acetate in ethanol and by complexing with N-cetylpyridinium chloride did not show major differences dependent on the conditions of the experiment.

THE COMPOSITION OF GLYCOSAMINOGLYCANS OF AORTA WALL

The percentage of each kind of glycosaminoglycans after chromatography on a cellulose column, in the examined experimental groups, is presented in Table 5. Though the attempts to find out statistically significant differences were not successful, it is worthwhile underlying

that in both groups with experimental atherosclerosis one could notice a slightly higher content of sulfuric glycosaminoglycans: heparin sulfate, chondroitin-sulfates and dermatan sulfate. They constituted in those groups 64% of total glycosaminoglycans, while in group I and III the sulfuric glycosaminoglycans fraction was not higher than 60%. Group III with hypothyroidism seems to be characterized also by a higher percentage noncomplexing fraction which contains keratan sulfate and some glycoproteins.

Table 5. Percentage content of the glycosaminoglycans fractions in the intima-media layer of aorta wall of rabbits with experimental atherosclerosis and hypothyreoidism

Group	Glycosaminoglycans fractions						
	Non complexing fractions	Hyaluronic acid	Heparan sulphate	Chondroitin-4-sulphate	Chondroitin-6-sulphate	Dermatan sulphate	Heparin
Control	22.5 ±6.0	13.8 ±4.5	17.3 ±2.5	19.8 ±3.1	15.7 ±3.4	7.6 ±1.3	3.3 ±2.1
With experimental atherosclerosis	20.7 ±2.8	12.8 ±7.0	20.4 ±4.0	26.9 ±3.4	13.1 ±2.6	4.0 ±3.7	2.1 ±3.4
With experimental hypothyroidism	27.2 ±7.4	12.3 ±3.8	19.0 ±2.8	20.0 ±2.7	11.9 ±4.1	8.1 ±3.2	1.6 ±0.9
With atherosclerosis and hypothyroidism	20.5 ±2.6	[illegible] ±1.4	18.5 ±3.7	20.5 ±5.2	17.8 ±6.6	8.1 ±1.6	2.1 ±1.1

DISCUSSION

A possible participation of thyroid hormones in the creation and development of atherosclerosis may be considered in at least two aspects: their influence upon lipid metabolism and a direct influence on the metabolism of smooth muscle cells. In the first case, as it is well known, thyroid hormones reduce lipid concentration in blood serum, mainly cholesterol. Its content is moderately reduced in hyperthyroidism, and as a rule, distinctly increased with the hypofunction of thyroid gland. The same tendency of changes could be observed in rabbits with hyperthyroidism (17) and with experimental hypothyroidism which is examined in this paper. The attempts to show a direct correlation between lipid level and formation of atherosclerotic plaques were not successful. Such changes did not appear in aortas of rabbits with experimental hypothyroidism in spite of increased cholesterol and tryglycerides concentration in serum. In the group of animals on a cholesterol-rich diet, after thyroidectomy, there was a similar or even smaller atherosclerosis de-

velopment than in the group being on an atherogenic diet only.

The fact that the observed lipid changes of plasma due to hypothyroidism do not correlate with the intensification of atherosclerosis may be accounted for in many ways. In the first place, one should remember that a strong aterogenic stimulus used in our experiments may exclude the appearance of subtle changes which are due to an impaired hormonic homeostasis. In the second place, as it is known, the participation of hyperlipemia in formation and development of atherosclerosis is complex and may have many interpretations. For example, it is thought that the main risk factor is cholesterol of LDL fraction whereas the high HDL-cholesterol might even be of protective importance (13). While testing lipoproteins extracted from the normal and atherosclerotic wall of aorta and from LDL of plasma it was proved that except certain significant similarities, there are also differences characteristic of pathologic changes (8). It is possible that certain lipoprotein particles are characterized not only by a different way of penetration into the aortic wall but also by a different way of initiating the pathologic processes in smooth muscle cells which may lead to atherosclerosis. In the light of the above hypothesis, the results of the carried out experiments allow an assumption that the experimental hypothyroidism in rabbits is the cause of increase of those lipoprotein fractions of plasma which are not pathognomic for aterosclerotic process.

The influence of thyroid hormones upon smooth muscle cells metabolism and extracellular components of connective tissue has not been explained so far. According to some authors (3), thyroid hormones stimulate protein synthesis and intensify the incorporation of amino acids when testing *in vivo*. According to other (20) they do not influence the incorporation of C^{14}-proline, and in some cases even acts as inhibitor. Lorenzen (12) did not find any differences in the content of hydroxyproline in rabbit's aortas after the thyroidectomy. The decrease of total proteins and hydroxyproline content in the aortas of rats after thyroidectomy was observed by Bydlowski et al. (4). Kivirikko and Risteli (9) are of opinion that thyroxine does not influence collagen synthesis in fibroblast and that thyroid hormones defficiency may handicap collagen tissue catabolism.

In our study no major differences were found in the content of collagen and other proteins of aorta wall as a result of the experimental atherosclerosis and hypothyroidism. However, it is worthwhile underlying that the protein composition of aorta wall in rabbits with both atherosclerosis and hypothyroidism shows a greater similarity to the control group than to the atherosclerotic one. Not settling a question of thyroid hormones influence on the metabolism of aorta scleroproteins,

it seems to be the result of the diminished intensity of atherosclerotic changes in group IV. Differences in free hydroxyproline concentration in the blood serum speak for the participation of thyroid hormones in collagen metabolism. The hydroxyproline concentration was higher indeed in blood of the animals after the thyroidectomy which may be indicative of both an intensified catabolism and in intensified biosynthesis of this protein.

The role of thyroid hormones in glycosoaminoglycans metabolism has not been explained, either. The above mentioned hormones control the wearing out process of respective precursors of carbohydrate metabolism (15) and probably condition the activity of some enzymes taking part in the biosynthesis of polysaccharide chains (14). After the thyroidectomy no decrease of sulfate incorporation was observed which might have found expression in sulfuric glycosamioglycans content decrease. In our study we did not find essential differences in the total content of glycosaminoglycans of aorta wall in groups with hypothyroidism and atherosclerosis. Nonetheless, a little lower sulfuric glycosaminoglycans percentage in animals after thyroidectomy may be the result of reduced activity of corresponding sulfotransferases. This low glycosaminoglycans percentage may be also a reducing factor in the formation of atherosclerotic changes in spite of hypercholesterolemia.

In the light of the obtained results, it seems that a more detailed explanation of this very interesting fact — hypothyroidism as a restraining factor in the development of atherosclerosis in the examined experimental model, requires further study with a particular attention paid to lipoproteins metabolism and their participation in pathogenesis of atherosclerosis.

CONCLUSION

1. The hypothyroidism bred in rabbits as a result of thyroidectomy reduces macroscopic changes of the intima aorta layer characteristic of atherosclerosis caused by a rich cholesterol diet.

2. The hypothyroidism caused a moderate increase of concentration of cholesterol and triglycerides in the blood serum. Also in the group on a rich cholesterol diet the concentration of lipids was higher in rabbits which had the thyroidectomy.

3. In the blood serum of rabbits with experimental hypothyroidism an essentially higher concentration of free and peptide-bound hydroxyproline could be observed.

4. In rabbits with experimental hypothyroidism as compared to the control group no significant differences were observed in the content and composition of collagen fractions, elastin, supporting proteins and glycosaminoglycans of the intima-media layer of aorta.

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Otrzymano 22 VI 1983.

STRESZCZENIE

Badano wpływ hipotyreozy na rozwój miażdżycy doświadczalnej u królików. Wyróżniono 4 grupy zwierząt, z których grupa I stanowiła kontrolę, grupa II pozostawała na diecie miażdżycorodnej, w grupie III wywołano hipotyreozę doświadczalną, a w grupie IV — jednocześnie hipotyreozę i miażdżycę doświadczalną. Stopień hipotyreozy oceniano oznaczając trójjodotyroninę w surowicy krwi. Po 90 dniach oznaczano stężenie frakcji lipidowych w surowicy oraz rozwój zmian miażdżycowych na podstawie badań makroskopowych i histochemicznych. Jednocześnie w warstwie środkowej i wewnętrznej aorty oznaczano zawartość kolagenu, elastyny, białek podporowych i glikozoaminoglikanów. Stwierdzono, iż wywołana w następstwie tyreoidektomii hipotyreoza ogranicza makroskopowe zmiany warstwy wewnętrznej, charakterystyczne dla miażdżycy doświadczalnej, mimo umiarkowanego wzrostu stężenia cholesterolu i trójglicerydów w surowicy krwi. Obserwowano również znaczący wzrost stężenia hydroksyproliny wolnej i peptydowej w surowicy krwi zwierząt po tyreoidektomii. W porównaniu z grupą kontrolną nie stwierdzono natomiast istotnych zmian w zawartości frakcji kolagenowych, elastyny i glikozoaminoglikanów w aortach królików z hipotyreozą oraz u zwierząt z hipotyreozą i miażdżycą doświadczalną.

РЕЗЮМЕ

В данной работе авторы исследовали влияние гипотиреоза на развитие экспериментального атеросклероза у кроликов. Исследования проводились в 4-х группах. Первая группа животных была контрольной, вторая — находилась на атеросклеротической диете, у животных третьей группы вызывался экспериментальный гипотиреоз, а в четвертой группе одновременно вызывался гипотиреоз и экспериментальный атеросклероз. Степень гипотиреоза оценивалось при помощи обозначения трийодтиронина в сыворотке крови животных. По истечении 90 дней обозначено степень насыщенности липидной фракции в сыворотке, а также определялось развитие изменений атеросклероза на основании макроскопических и гистохимических исследований. Одновременно обозначалось содержание коллагена, эластина, интерстициального белка и гликозамингликанов во внутреннем и среднем слое аорты. Констатировано, что гипотиреоз, вызванный тиреоидектомией, ограничивает макроскопические изменения, характерные для экспериментального атеросклероза внутреннего слоя аорты, несмотря

на умеренное повышение насыщенности холестерина и триглицеридов в сыворотке крови. Наблюдалось также значительное повышение насыщенности свободного и пептидного гидроксипролина в сыворотке крови животных после тиреоидектомии. По сравнению с контрольной группой не обнаружено существенных изменений в содержании коллагеновых фракций, эластина и гликозаминогликанов в аортах кроликов с гипотиреозом, а также у животных с гипотиреозом и экспериментальным атероматозом.