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THE ROLE OF XANTHINE DEHYDROGENASE/XANTHINE OXIDASE IN ATHEROGENESIS IN PATIENTS WITH HYPERLIPIDAEMIA

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Summary: The activity of xanthine dehydrogenase/xanthine oxidase has been a target of considerable interest. In the metabolic pathway of purines, XO catalyzes the oxidation of xanthine and hypoxanthine to uric acid and thereby produces reactive oxygen metabolites. It is proposed that endothelial cells are major stores of XD and its converting XO form that, during ischaemia/reperfusion injury, generates free radicals and causes direct damage to vascular endothelium, whilst the circulating XO may lead to subsequent damage to other remote organs. As hyperlipidaemia ultimately leads to endothelium damage in the blood vessel, the activity of XO was examined in patients with hyperlipidaemia, diabetes, and hypertension. Given the parameter values of cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol, the patients were divided into groups on the basis of hyperlipoproteinaemia types according to Fredrickson. The most frequent types of HLP were IIa, IIb and IV. The activity of XO revealed a significant increase in the serum of all three patients groups, as well as in all types of HLP as compared to healthy subjects. A significant positive correlation was noticed between the activity of XO and atherogenic lipids and a negative correlation with protective HDL cholesterol. A significant decrease in XD activity was identified in patients of all three groups and in all HLP types. The activity of XD correlated inversely with atherogenic lipids and positively with HDL cholesterol. The end product of purine metabolism, uric acid, showed a significant increase in the serum of all three patients groups, as well as a positive correlation with XO activity and a negative correlation with XD activity. Given the results of the study, it may be concluded that the activity of XO is a significant biochemical parameter and a marker of the extent of endothelium damage in atheromatose blood vessels, the fact that may be a novel diagnostic approach to atherogenesis and modification of hyperlipidaemia treatment in clinical practice.

Key words: xanthine oxidase, xanthine dehydrogenase, uric acid, hyperlipidaemia, atherogenesis

Introduction

Xanthine oxidase (XO, EC 1.2.3.2) catalyzes the oxidation of xanthine and hypoxanthine to uric acid in the catabolic pathway of purines. Xanthine dehydrogenase and xanthine oxidase are metalloflavoproteins denoting alternate forms of the same gene product (1). In normal *in vivo* settings, the enzyme exists in its dehydrogenase form. XD is composed of two identical and independent subunits of which contains three redox centres, where the Mo centre appears as a link between xanthine substrate and enzyme, and the FAD prosthetic group is declared as the site of oxygen free radical formation (2). The conversion of XD to XO may occur reversibly via the activity of molecular oxygen (3) by enzymatic and chemical modification of thiol groups (4) due to deficiency of reduced glutathion in elevated concentrations of the substrates (xanthine and hypoxanthine). The irreversible conversion of dehydrogenase to oxidase is promoted via limited proteolysis through the activity of trypsin and chymotrypsin proteases, as well as lysosomal and Ca-dependent proteases (5). XO is the first registered biological source of oxygen free radicals and plays the leading

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Abbrevations:
XD/XO, xanthine dehydrogenase/xanthine oxidase
HLP, hyperlipidaemia; HOL, cholesterol; TG, triglycerides; LDL-c, LDL-cholesterol; HDLc, HDL-cholesterol.

Skraćenice: XD/XO, ksantin dehidrogenaza/ksantin oksidaza; HLP, hiperlipidemija; HOL, holesterol; TG, trigliceridi; LDL-c, LDL-holesterol; HDLc, HDL-holesterol.

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role in the pathogenesis of tissue damage by production of superoxide anion, hydrogen peroxide, and hydroxyl radical (6).

It is proposed that endothelial cells are major stores of XD and its converting XO form that, during ischaemia/reperfusion injury, generates free radicals and causes damage to vascular endothelium. Damaged endothelial cells release a circulating XO that causes direct damage to endothelium, activates inflammatory cells, and produces reactive metabolites in the antioxidant-deficient plasma (7).

In hypoxic conditions, developed as a consequence of atherosclerotically altered blood vessels, both *in vitro* and *in vivo*, XD converts to XO. Hyperlipidaemia (HLP) may be primary, that is, of genetic origin (8), if caused by increased concentrations of specific lipoprotein classes in the serum, such as LDL, VLDL, chylomicrons, and Lp(a), and secondary if resulting from metabolic and endocrine disorders, infectious and malignant diseases, as well as the lifestyle and nutrition. Disturbances in the synthesis, transport and catabolism of lipoprotein particles are manifest through a total six HLP types, whilst common diseases that cause disruption in lipid metabolism are diabetes mellitus and hypertension (9). The oxidative modification of atherogenic LDL particles either in the blood vessel lumen or subendothelial space, as well as a decelerated delipidation cascade of VLDL triglyceride-rich particles, followed by formation of a remarkably atherogenic LDL III subfraction, increases the risk of atheromatose plaque formation, damage to the blood vessel wall, and lesion to endothelial cells (10). Hypoxia in hyperlipidaemia and energy depletion caused by degradation and decrease of ATP, in addition to increased production of substrates, lead to an increased conversion of XD to XO.

Considering the existing close link between oxidative stress and disturbed lipid metabolism, the aim of this study was to examine the effects of interrelated action between XO activity and hyperlipidaemia, as well as the role of XD/XO in atherogenesis.

Material and Methods

The study included 71 patients with HLP, 52 patients with diabetes mellitus, and 52 patients with hypertension – a total of 175 subjects. The control group comprised 55 healthy volunteers. All patients were taken the body mass index (BMI) and blood pressure. The blood pressure values were within the highest normal range in 90% of HLP patients, whilst hypertension occurred in 30% of diabetic patients and 100% of hypertensive patients. On the basis of their lipid status, all the subjects were grouped into HLP types according to Fredrickson, types IIa, IIb and IV being the most frequent.

After a 12-hour fast, venous blood was taken for the purpose of determining the lipid status and other biochemical parameters. Of routine biochemical parameters in the serum of patients, total cholesterol (HOL), triglycerides (TG), HDL-cholesterol (HDL-c), LDL cholesterol (LDL-c), glucose, uric acid, and total proteins were determined by commercial tests. Of specific enzymes, XO and XD were monitored.

The activity of XO was determined spectrophotometrically, using the UV test, according to the method of Kizaki and Sakurada (11), by measuring the concentration of uric acid released from the xanthine substrate at 292 nm.

Concomitant with the examination of XO that makes use of molecular oxygen to accept electrons, the activity of XO+XD was determined employing the method of Kizaki and Sakurada (11). Given the fact that XD makes use of NAD to accept electrons, 0.5 mmol/L of NAD was added to xanthine substrate solution (12). A difference between XO+XD and XO activity was adequate to XD activity.

The obtained results were processed with standard statistic tests (mean value, standard deviation, Student's t test, Wilcoxon-Mann-Whitney test, and the coefficient of correlation) by a statistic computer programme.

Results

On the basis of BMI, all the examined patients were obese. The monitoring of blood pressure revealed that 90% of patients in the HLP group had the values within the highest normal range. Hypertension was registered in 30% of diabetic patients and in all hypertensive patients.

The examination of lipid status parameters in HLP patients showed that cholesterol in the whole HLP group was significantly increased compared to controls (7.12 ± 1.50 mmol/L vs. 4.9 ± 0.4 mmol/L) ($p<0.001$) at the expense of the increased level of cholesterol in Type IIa ($p<0.001$) and Type IIb ($p<0.001$). A statistically significant increase in cholesterol was also registered in patients with diabetes (6.92 ± 1.60 mmol/L) and hypertension (6.49 ± 1.30 mmol/L) ($p<0.001$) as a consequence of its increase in types IIa and IIb *(Figure 1)*.

Triglycerides show a significant difference in the whole HLP group (2.90 ± 0.90 mmol/L vs. 1.34 ± 0.40 mmol/L) ($p<0.001$), as well as in types IIb and IV of HLP ($p<0.001$ for both) compared to healthy subjects. A significant increase in triglycerides in diabetics (2.84 ± 0.90 mmol/L) and hypertensive patients (2.48 ± 0.95 mmol/L) is a consequence of the increase in triglycerides in types IIb and IV of HLP.

Protective HDL cholesterol markedly decreases in the group with hyperlipoproteinaemia compared to the control (1.06 ± 0.30 mmol/L vs. 1.30 ± 0.20 mmol/L) ($p<0.001$) and is also significantly decreased in types IIa, IIb and IV ($p<0.05$, $p<0.05$ and

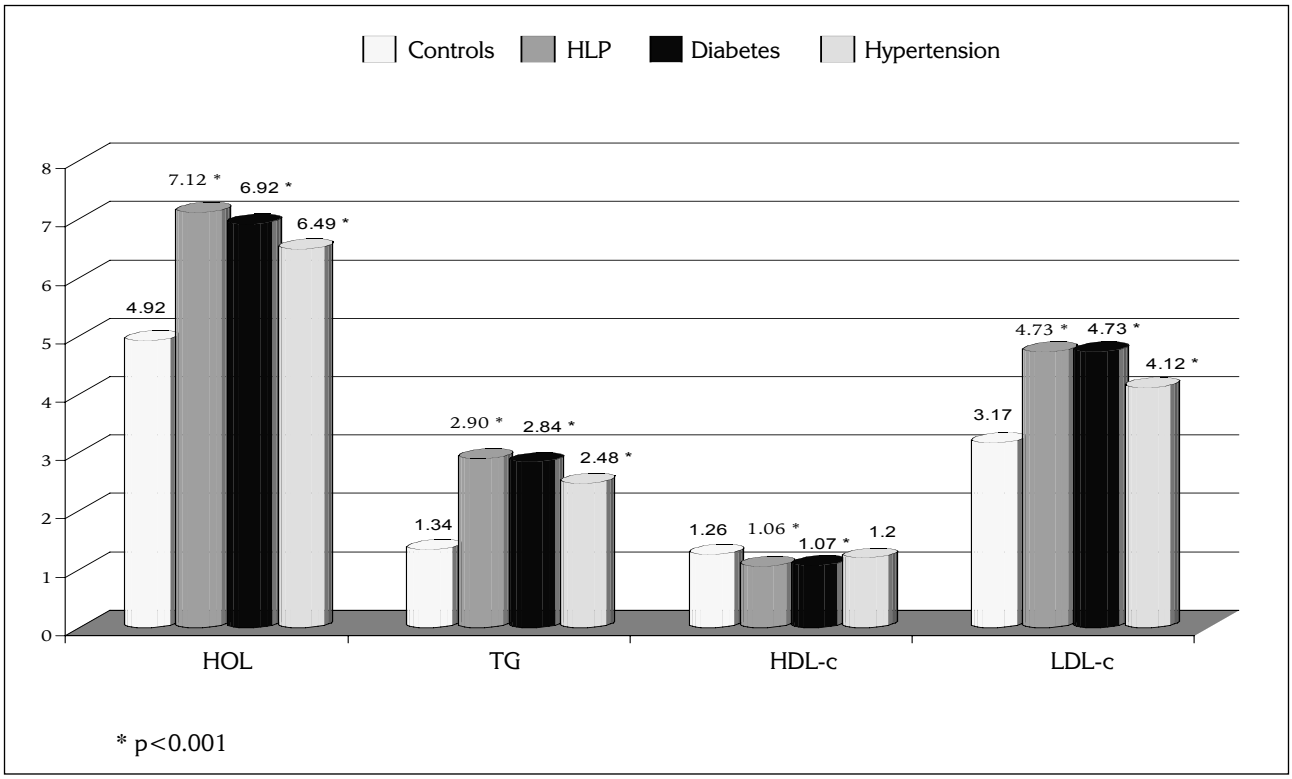

Figure 1. Lipid status in the serum of patients with HLP, diabetes, and hypertension

p<0.001), whilst a significantly decreased HDL in diabetic and hypertensive patients is a result of its decrease in types IIb and IV (*Figure 1*).

Atherogenic LDL cholesterol records a significant increase in the whole hyperlipoproteinaemia group compared to control values (4.73 ± 1.30 mmol /L vs. 3.20 ± 0.30 mmol/L) (p<0.001), being the result of this parameter increase in types IIa and IIb (p<0.001 for both). This parameter behaves in the same manner in patients with diabetes and hypertension.

The activity of XO is markedly increased in the group of hyperlipoproteinaemic patients (9.56 U/L; 6.89–12.33 U/L) compared to healthy subjects (6.0 U/L; 2.35–7.88 U/L) (p<0.001). XO activity marks a significant increase in types IIa (p<0.05), IIb (p<0.001) and IV (p<0.01) (*Table I*).

The activity of XD shows a significant decrease in hyperlipoproteinaemic patients (10.16 U/L; 6.65–14.25 U/L) compared to controls (13.66 U/L; 11.54–17.42 U/L) (p<0.001). A significant reduction in XD activity occurs in Type IIb (p<0.001) and Type IV (p<0.05) (*Table I*). The analysis of *Table I* demonstrates a significant increase in the activity of XO in patients with diabetes (11.36 U/L; 9.04–14.91 U/L) compared to healthy population (p<0.001) at the expense of Type IIa (p<0.05), Type IIb (p<0.001) and Type IV (p<0.01), and a significant decrease in XD activity (6.83 U/L; 4.04–9.04 U/L) (p<0.001) due to the activity decrease in types IIa (p<0.001), IIb (p<0.001) and IV (p<0.05). In patients with hypertension, XO activity is also increased at the expense of types IIa (p<0.01), IIb (p<0.001) and IV (p<0.001), whilst XD markedly decreases at the expense of the groups with an increasing XO.

The activity of XO in all groups has a significant positive correlation with HOL, TG, and LDL, and a negative correlation with HDL. The activity of XD shows a significant negative correlation with atherogenic lipids and a positive correlation with HDL.

The values of uric acid in patients of all three groups of diseases demonstrate a statistically significant increase when compared to control subjects (p<0.01). The concentration of uric acid in HLP types shows a significant increase in Type IIa with diabetes (p<0.05) and hypertension (p<0.001); in Type IIb, the increase is significant in all three disease groups: hyperlipoproteinaemia (p<0.001), diabetes (p<0.01) and hypertension (p<0.001); in Type IV the concentrations are markedly increased in hyperlipoproteinaemia (p<0.001), diabetes (p<0.05) and hypertension (p<0.001) (*Table II*). A significant positive correlation should be underscored between XO activity and uric acid (r = 0.48) (p<0.001) and a significant negative correlation between XD activity and uric acid (r = –0.28) (p<0.05).

Table I The activity of xanthine oxidase and xanthine dehydrogenase in sera of patients with hyperlipoproteinaemia, diabetes and hypertension

Groups	n	XO (U/L) median (interquartile range)	XD (U/L) median (interquartile range)
Hyperlipoproteinaemia			
type II a	32	6.95 (4.31–10.54)*	12.52 (7.69–16.32)
type II b	36	10.62 (8.41–12.72)***	9.59 (5.82–11.47)***
type IV	3	17.63 (13.46–17.79)**	4.15 (3.57–7.42)*
Total	71	9.56 (6.89–12.33)***	10.16 (6.65–14.25)**
Diabetes			
HLP type II a	23	9.24 (8.15–11.05)***	9.82 (7.01–11.99)***
HLP type II b	24	13.85 (10.88–17.76)***	4.63 (3.48–6.81)***
HLP type IV	5	15.78 (8.84–20.55)**	8.21 (3.52–7.24)*
Total	52	11.36 (9.04–14.91)***	6.83 (4.04–9.04)***
Hypertension			
HLP type II a	26	7.05 (6.17–9.90)**	9.74 (7.78–12.65)**
HLP type II b	18	14.09 (7.58–15.50)***	8.11 (4.79–9.70)***
HLP type IV	8	10.21 (9.58–11.01)***	7.49 (5.11–10.71)**
Total	52	9.54 (7.04–13.65)***	9.84 (6.17–12.69)***
Control group	55	6.00 (2.35–7.88)	13.66 (11.54–17.42)

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Table II Concentration of uric acid in sera of patients of all three groups of diseases. Results are presented as $\bar{x} \pm SD$ in μmol/L.

Groups	HLP	Diabetes	Hypertension
HLP type II a	219 ± 90	253 ± 45*	271 ± 60***
HLP type II b	289 ± 80***	265 ± 45**	264 ± 50**
HLP type IV	377 ± 54***	324 ± 48*	298 ± 48***
Total	261 ± 70**	255 ± 49**	272 ± 5**
Control group	228 ± 43		

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Discussion

The increase in concentrations of cholesterol and triglycerides, that is, lipoprotein LDL and VLDL complexes, is directly proportional to the development of atheromatose lesions. High-density lipoproteins (HDL), whose preventive role in atherosclerosis has been documented by extensive undisputable evidence, show an inverse correlation (13).

The most frequent and by far the most important consequence of lipid metabolic disorders is the one that occurs in blood vessels – atherosclerosis. Although relations between the metabolism of endogenous and exogenous lipids cannot be always anticipated, the effect of nutrition upon hyperlipidaemia occurrence is considerable, as shown by experiments on animals and epidemiologic studies on humans.

The alterations in concentrations of lipid parameters in sera of our patients correlate with literature results obtained by large studies.

On the basis of a many epidemiologic parameters and clinical parameters in the studies of primary and secondary prevention, conclusions are drawn that a higher risk of fatal and nonfatal cardiovascular disease is in direct correlation with concentrations of total cholesterol and LDL cholesterol in both sexes and in subjects up to 65 years of age and older. There is no cutoff value of cholesterol below which the risk does not appear (14).

In »the study of 7 countries«, which includes our country as well, a strong correlation has been documented between the level of cholesterol and coronary disease incidence. On the other hand, this study confirms that coronary disease incidence is sevenfold in the countries with high values of cholesterolaemia relative to those with lower values (15).

In the MRFIT study, the mortality of myocardium infarction is fourfold in patients with cholesterol values of 7.3 mmol/L compared to subjects with values of 4.1 mmol/L. It has been therefore determined that patients with the highest values of cholesterol and LDL cholesterol (LDL is 6–10 times as higher than normal values) often die within the second decade of their life (16).

Unlike cholesterol, the role of triglycerides as independent risk factors for the development of atherosclerosis remains controversial. In a majority of prospective and retrospective studies, a certain correlation has been established between the level of serum

triglycerides, the incidence of hypertriglyceridaemia, and the risk of atherosclerosis development. Large epidemiologic studies, primarily the Framingham study (17), demonstrate that triglycerides are an independent risk factor of the development of heart diseases. The Helsinki study (18) also shows that the standardized rates of coronary disease are higher in patients with Type IIb of HLP compared to those with Type IIa and Type IV of HLP. It appears that a combination of higher LDL, VLDL and triglycerides is associated with a lower level of HDL and followed by a higher incidence of coronary diseases (18).

The risk of cardiovascular diseases in patients with high values of LDL cholesterol is twice as much as that in patients with lower values, whilst in patients with low HDL cholesterol this effect is significantly increased (13). According to literature data, these two lipoprotein particles are considered independent risk factors of the development of the disease – the risk significantly increases parallel with LDL increase and HDL decrease (18).

All these changes in blood vessels lead to the formation of atherosclerotic plaques that are prominent in the blood vessel lumen and that, partly or totally, block the blood circulation that results in an inadequate exchange of gases between blood and cells, leading to hypoxia. In hypoxic conditions, both *in vivo* and *in vitro*, NAD-dependent dehydrogenase is converted to the oxygen-dependent oxidase form.

After a follow-up of patients with hyperlipidaemia, our study shows that there is a highly remarkable increase (almost twofold) in xanthine oxidase activity in the group of patients with HLP ($p>0.001$) and hypertension ($p>0.001$), and more than a twofold increased activity is identified in patients with diabetes ($p>0.001$).

The results of monitoring XD activity in hyperlipidaemic patients reveal a statistically significant reduction in the activity of the enzyme in all examined groups ($p>0.001$) compared to the healthy population. The greatest fall of XD activity ($p>0.001$) is detected in Type IIb of HLP. Reduction in enzyme activity, whether of inferior or even identical significance, also occurs in other groups of HLP types. When the examined groups are observed and analyzed, regularity can be noticed in their behaviour: where the activity of XO increases, the activity of XD decreases. On the basis of the obtained results, xanthine dehydrogenase is presumed to convert to xanthine oxidase.

Endothelial cells are supposed to be major stores of xanthine dehydrogenase and its converting form xanthine oxidase. As atherosclerosis is a lasting process, the circulating xanthine oxidase will cause direct damage to vascular endothelium in the period of prolonged ischaemia by oxygen free radical formation. Through the activation of inflammatory cells, which produce toxic radicals, xanthine oxidase may cause subsequent oxidative damage in the plasma (7). This has been confirmed by experimental research on animals put on cholesterol-rich foods. It has been shown that hypercholesterolaemia produces thrice as much superoxide anion compared to cholesterol normal values. The oxygen radicals, formed by the activity of xanthine oxidase, block nitric oxide (NO) in endothelium, which is an additional factor for the development of atherosclerosis (19).

By experimental studies on animals, researchers have also examined the effect of diet upon hypercholesterolaemia and reduced production of superoxide anion. The results show that the endothelium blood vessel in animals fed by cholesterol-containing foods creates 4.5 times as many oxygen free radicals compared to normal blood vessels. In the blood vessel of endothelium of animals put on diet, a reduced production of superoxide anion occurs, primarily due to endothelium capable of deleting oxygen radicals. Cholesterol decrease in these animals is markedly enhanced by blood vessel vasodilatory response to the effect of acetylcholine compared to animals with high cholesterol. Diet also contributes to the increased production of EDRF-relaxing factor and decreases the formation of oxygen free radicals, by means of which vascular integrity is preserved and development of atherosclerosis is prevented (20).

A group of scientists researching the complications in diabetes mellitus examined the alterations occurring on endothelial and smooth muscle cells of blood vessels in 20 patients with diabetes. The obtained results showed that the production of superoxide anion in endothelium of arteries in diabetics increased up to 150%, whilst the EDRF factor of relaxation reduced down to 64% (21).

The importance of the polyol pathway in endothelium was also stressed in conditions of permanent hyperglycaemia, the issue that has been already discussed. The oxidation of lipids in membranes will lead to autocatalytic chain reactions likely to disturb cell permeability, whereas the increase in intracellular Ca^{2+} will activate Ca-dependent proteases and thereby a conversion of xanthine dehydrogenase to xanthine oxidase (22).

Clinical and experimental studies have shown that an association exists between a high concentration of consumed sodium and arterial hypertension. As xanthine oxidoreductase occurs in hypoxia, researchers experimentally examined a relation between the activity of this enzyme and hypertension caused by a higher intake of salt. It was recorded that restriction in intake of sodium decreases the activity of xanthine dehydrogenase and xanthine oxidase to 40%, whilst treatment with allopurinol, which inhibits the activity of these enzymes, does not lead to changes in blood pressure of the examined animals, which served as the basis for the conclusion that the increase in xanthine

oxidoreductase occurs as a result of hypertension or as a consequence of increased intake of salt (23).

According to numerous reports, xanthine oxidase exists not only in the cytoplasm of cells but also on the surface of endothelial membranes. However, its localization outside cells needs to be clarified. Such examinations were done by Adachi et al. (24), who revealed that the human XO exerts a high affinity to heparin. By intravenous injection of heparin to healthy individuals, the authors demonstrated that the human XO in plasma showed a rapid increase. This led them to the conclusion that the human xanthine oxidase is bound to the membrane of endothelial cells by a polysaccharide chain of sulfated glycosaminoglycan (heparin). It is most likely that an extracellular superoxide anion, formed by XO activity, will head for the source cell first and cause damage to it. In this way, conditions will be created for the activation of susceptible neutrophils and their adhesion to endothelium, which will further lead to the progression of oxidative damage. The resulting destruction of cells and disturbed endothelial barrier will increase 1.5 times as much the membrane permeability for albumin in developed hypoxia (25). Hydrogen peroxide, comparatively harmless under normal conditions, enters the cell, where it interacts with a non-ferritin iron, producing a cytotoxic hydroxyl radical (OH) (26).

Hypoxia activates the adhesive system in endothelial cells (ICAM), thereby rendering an interaction with adhesive molecules of cells, such as neutrophils, which results in their accumulation in blood vessels. Neutrophils release the converting factor elastase, which converts xanthine dehydrogenase to xanthine oxidase, resulting in oxygen free radical production (27).

The conversion of xanthine dehydrogenase to xanthine oxidase also occurs in the contact of endothelial cells with existing pro-inflammatory cytokines, TNF-α and IL-β the result of which is the increased sensitivity of endothelium to toxic effect of neutrophils (29). The interaction between H_2O_2 and endothelium rapidly decreases ATP, leading to the occurrence of extracellular xanthine and hypoxanthine, whilst a decrease in ATP cannot be prevented, not even by hydrogen peroxide scavengers. The occurring synergism between proteases and H_2O_2 is most likely to lead to cell death (30).

Other experimental studies have also demonstrated that blood vessels in hypercholesterolaemia form and release a considerable amount of oxygen superoxide anion, and have thus supported the concept that blood vessels are susceptible to »oxidative stress« in hypercholesterolaemia and atherosclerosis (30).

Uric acid, as a catabolic product resulting from the activity of xanthine dehydrogenase and xanthine oxidase and as one of the non-enzymatic antioxidants, also shows significant differences between the hyperlipidaemia groups and healthy controls (from $p<0.01$ to $p<0.001$). By examination of xanthine oxidase-uric acid relations, we came to the data revealing a highly dependent correlation between xanthine oxidase and uric acid, both in the group of patients with HLP and the group of patients with diabetes and hypertension.

Kooij et al. (31) hold that xanthine oxidoreductase produces uric acid that is a major scavenger of oxygen radicals. As xanthine dehydrogenase and xanthine oxidase are both present in epithelial and endothelial cells susceptible to substantial oxidative stress, the conclusion was drawn that the activity of xanthine oxidoreductase results in uric acid production in these cells, where uric acid acts as a non-enzymatic antioxidant, i.e. has a role in the organism defence system.

By the analysis of the results obtained in this study, it can be established that XO activity increases and XD activity decreases in damaged endothelium of atherosclerotic blood vessels in hypoxia, which is a likely result of the conversion of XD to XO. It can be also concluded that elevated concentration of uric acid, as a non-enzymatic antioxidative product, plays a role in protecting endothelium against further damage. It is most likely that in large and severe damages of blood vessels this mechanism becomes insufficient, requiring an additional anti-hyperlipidaemic and antioxidative therapy in blocking advancing atherosclerosis and its fatal consequences.

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ULOGA KSANTIN DEHIDROGENAZE/KSANTIN OKSIDAZE U ATEROGENEZI KOD BOLESNIKA SA HIPERLIPIDEMIJAMA

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Kratak sadržaj: Aktivnost ksantin dehidrogenaze/ksantin oksidaze je u novije vreme od posebnog interesa s obzirom da u metaboličkom putu purina XO oksiduje ksantin i hipoksantin u mokraćnu kiselinu uz produkciju reaktivnih kiseoničnih metabolita. Smatra se da su endotelne ćelije glavni depoi XD i njene konvertne forme XO koja u periodu ishemije/reperfuzije produkuje slobodne radikale i izaziva direktna oštećenja vaskularnog endotela, a cirkulišuća XO dovodi do naknadnih oštećenja i u drugim organima. S obzirom da hiperlipidemija neminovno dovodi do oštećenja endotela krvnih sudova, aktivnost XO je ispitivana kod pacijenata s hiperlipidemijom, dijabetesom i hipertenzijom. Prema vrednostima parametara holesterola, triglicerida, LDL-holesterola i HDL-holesterola, bolesnici su svrstani u tipove hiperlipoproteinemija po Fredriksonu. Najčešći tipovi HLP-a bili su IIa, IIb i IV. Nađeno je statistički značajno povećanje aktivnosti XO u serumu sve tri grupe bolesnika, kao i u svim tipovima HLP-a u odnosu na zdrave ispitanike. Zabeležena je značajna pozitivna korelacija između aktivnosti XO i aterogenih lipida, a negativna korelacija sa protektivnim HDL holesterolom. Statistički značajno sniženje aktivnosti XD registrovano je kod bolesnika sve tri ispitivane grupe, kao i u svim tipovima HLP-a. Aktivnost XD je u značajnoj negativnoj korelaciji sa aterogenim lipidima, a u pozitivnoj sa HDL holesterolom. Krajnji produkt metabolizma purina, mokraćna kiselina, statistički je bila značajno povećana u serumu bolesnika sve tri ispitivane grupe, a takođe i u pozitivnoj korelaciji sa aktivnošću XO, a negativnoj sa aktivnošću XD. Na osnovu ovog istraživanja može se zaključiti da je aktivnost XO važan biohemijski parametar i marker obima oštećenja endotela u ateromatoznim krvnim sudovima, što može predstavljati nov dijagnostički pristup u aterogenezi i u modifikaciji terapije hiperlipidemija u praktičnom radu.

Ključne reči: ksantin oksidaza, ksantin dehidrogenaza, mokraćna kiselina, hiperlipidemije, aterogeneza

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