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Total plasma sialic acid concentrations in patients with coronary heart disease

Sialic acid (N-acyl-neuraminic acid, SA) is a major component at the non-reducing end of carbohydrate chains of glycoproteins and glycolipids. SA derivatives are usually located on the outer side of cell membranes. Sialic acid has been recognized as the most important monosaccharide with the respect to biologic function when present on cell membranes. The suggested biological functions of SA include: 1) stabilizing the conformation of cellular membranes, 2) affecting the cell to cell recognition and interaction, 3) contributing to membrane transport, 4) influencing the function, stability and survival of blood glycoproteins, 5) affecting the function of membrane receptors and 6) regulating the permeability of the basement membrane of glomeruli (11).

The majority of patients with various malignant tumors and patients with some inflammatory disorders have elevated concentration of SA in blood (2, 12). It is quite well confirmed that inflammatory process in the coronary arteries is involved in the development of atherosclerosis (5) and it is associated with acute coronary syndromes (4). Recently, association of increased levels of total SA concentration with higher cardiovascular mortality has been proved (8). For this reason total SA concentration has been considered as a new cardiovascular risk factor, among others well established risk factors of coronary heart disease such as sex, age, hypercholesterolemia, hypertension, diabetes and smoking (9). However, there are only a few publications supporting the idea that SA concentration in blood is related to severity of coronary heart disease in patients with stable angina pectoris and results are contradictory (6, 10). The aim of this study was to investigate the possible association between total plasma sialic acid concentration and the severity of coronary arteriosclerosis.

MATERIAL AND METHODS

Twenty-four patients aged 48–68 with coronary heart disease and symptoms of stable angina pectoris undergoing elective coronary artery by-pass grafting were included in the study. Other risk factors of coronary heart disease such as hypercholesterolemia, hypertriglicerydemia, hypertension, diabetes, smoking and family history of cardiovascular disorders were discussed. We regarded a level of total cholesterol/ triglycerides greater than 200 mg/dl as hypercholesterolemia/hypertriglyceridemia. Obesity was defined when BMI (body mass index calculated as weight in kg divided by height in meters squared) was above 30 kg/m^2. Hypertension was defined as diastolic blood pressure greater or equal to 90 mmHg and/or on treatment. Regular smoking was regarded as smoking at least one cigarette per day, every day. Positive family history was defined as occurrence of coronary heart disease among first-degree relatives prior to age 60 years.

Patients are divided into two subgroups (comparable with number, gender and age): 1) patients with double vessel disease, 2) patients with triple/multiple vessel disease. Fifteen healthy subject – blood donors (14 men and 1 woman) aged 24–54 served as control group. Concentration of total SA was assayed by the modified thiobarbituric acid method of Warren (14), protein by the biuret method. Data were statistically analyzed using the Software STATISTICA for Windows (Copyright Statsoft, Inc. 1993 release 5.1). The non-parametric Mann-Whitney test was used to compare mean values. Correlation was calculated with using Pearsons test. P values less than 0.05 were considered significant.

RESULTS

Mean total sialic acid values equal to 2.17±0.73 mmol/L in a group of patients with double vessel disease, 2.53±0.86 mmol/L in a group of patients with triple/multiple vessel disease and 1.52± 0.20 mmol/L in the control group, see Figure 1. The comparison of mean values of total SA in the control group with those in patients in particular subgroups indicates that total SA values were significantly increased in both subgroups (patients with double vessel disease and patients with triple/ multiple vessel disease) and in the whole group of patients as well. The mean plasma total SA concentration in patients with triple/multiple vessel disease was higher than this in patients with double vessel disease, however the difference was not significant (p=0.26). The index of total SA/ protein equal to 26.11±7.77 μmol/g in the group of patients with double vessel disease, 35.01±10.52 μmol/g in the group of patients with triple/multiple vessel disease and 21.53±4.39 μmol/g in the control group, see Figure 2. The index of total SA/ protein was found to be significantly higher in patients with triple/multiple vessel disease than in patients with double vessel disease (p=0.01).

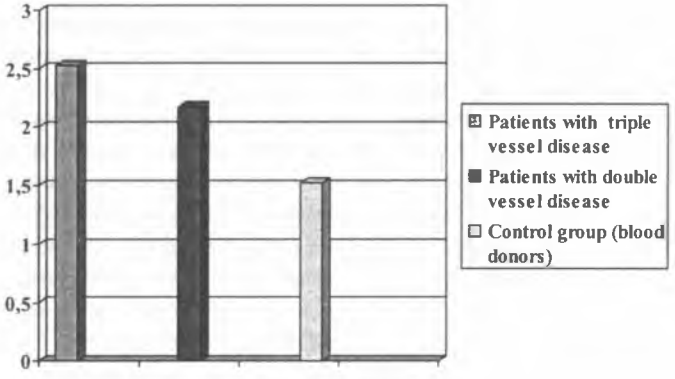

Fig.1. The levels of total SA in patients with triple/multiple vessel disease, double vessel disease and in healthy blood donors

The results of the statistical analysis of the total plasma cholesterol and the total plasma triglycerides in the group of patients with triple/multiple vessel disease and in patients with double vessel disease are summarized in Table 1. Total cholesterol level in patients with triple/multiple vessel disease was higher than in patients with double vessel disease (p=0.05). The level of triglycerides was found to be significantly higher in patients with triple/multiple vessel disease when compared with patients with double vessel disease (p=0.02).

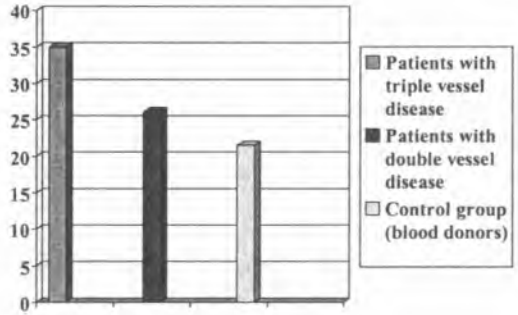

Fig. 2. The levels of TSA/ protein index in patients with triple/ multiple vessel disease, double vessel disease and in healthy blood donors

Table 1. Comparison of total cholesterol and triglycerides in patients with triple/multiple vessel disease and in patients with double vessel disease

	n	Total cholesterol (mg/dL)	Triglycerides (mg/dL)
Patients with triple/multiple vessel disease	12	228.92±48.78	208.58±139.46
Patients with double vessel disease	12	189.66±19.17	106.50±34.53*

*p<0.05

We investigated correlations between total SA level and SA/protein index and other risk factors of coronary heart disease such as age, level of total cholesterol and level of triglycerides. We found significant correlation in the group of patients with triple/multiple vessel disease (r=0.6; p=0.03), see Figure 3. We observed in the whole group of patients significant correlation between level of total SA and level of triglycerides (=0.53; p=0.006), between protein index and level of triglycerides (r=0.5; p=0.01), see Figure 4, and between total SA/ protein index and number of performed by-pass grafts (r=0.45; p=0.02).

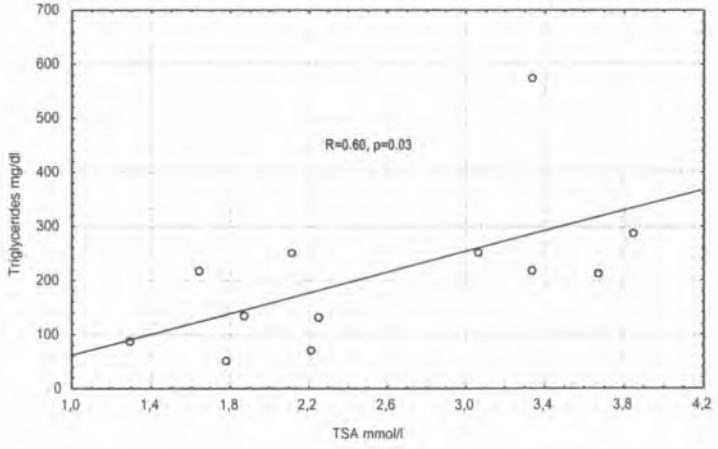

Fig. 3. Correlation between plasma level of TSA (mmol/l) and triglycerides (mg/dl) in the group of patients with triple/multiple vessel disease

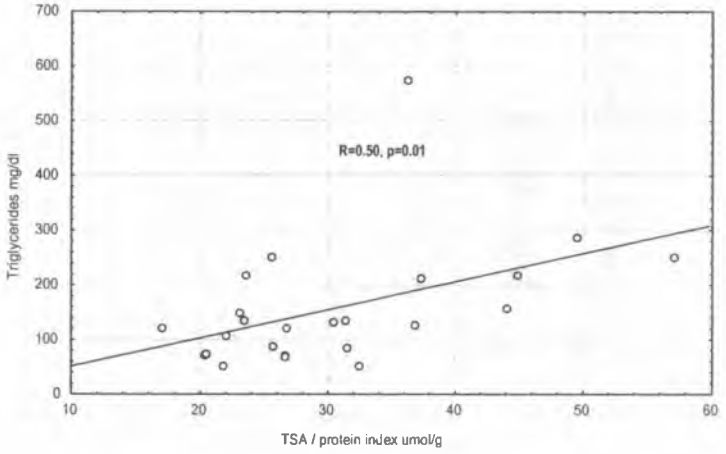

Fig. 4. Correlation between TSA /protein index (μmol/g) and triglycerides (mg/dl) in total group of patients

DISCUSSION

Recently there has been considerable interest in the assay of sialic acid concentration in blood since it was found to correlate with coronary heart disease. It was previously shown that sialic acid concentration is associated positively with mortality from coronary disease and stroke (8). Increased SA concentration in blood has been observed in myocardial infarction (3). Possible relationship between sialic acid level and severity of coronary heart disease was determined but results are contradictory. Allain et al. (1) who investigated the level of total SA alone in patients with coronary heart disease reported that total SA level correlates with the number of involved vessels. This finding was confirmed by Gokmen et al. (6) who found a significant difference between the level of total SA and lipid bound SA in patients with single vessel didease and in patients with double/triple vessel disease. On the other hand, Wu et al. (15) demonstrated that there is no significant difference between the SA serum level and the number of diseased coronary arteries. In our study we have found that the mean serum total sialic acid concentration in patients with double vessel disease and patients with triple/multiple vessel disease were significantly increased in comparison with healthy controls. In this study we have not found significant differences in total sialic acid concentration in patients with different stage of severity of coronary heart disease. Our data suggest that although the increased level of plasma total sialic acid is associated with the occurrence of coronary heart disease, however, it does not appear to be associated with the extent or severity of coronary arteriosclerosis in patients with stable angina pectoris.

The possible source of elevated SA concentration in blood is a release of intracellular SA as a result of myocardial ischaemia. Another source well established in a lot of cases is the process of the shedding and secreting SA from the cell membrane surface (11). Activity of sialidase, an enzyme that is responsible for the removal of SA moieties from the glycoproteins is increased in patients with coronary heart disease or myocardial infarction (13). It may contribute to SA secretion into bloodstream. As described before, coronary heart disease is a chronic inflammatory process that is associated with a release of different inflammatory markers. A great majority of acute phase proteins are glycoproteins with SA residues at their oligosaccharide moieties. Another possible source of increased SA level is output from the liver during acute phase reaction.

In the present study we have investigated a correlation between total SA and other risk factors of coronary heart disease. Elevated levels of total cholesterol and low density lipoprotein (LDL) and low levels of high density cholesterol (HDL) are important risk factors for coronary arteriosclerosis. It was proven that although concentration of total cholesterol over 240 mg/dl is obviously related to high risk of myocardial infarct but almost 20% of acute coronary events occur when value of total cholesterol is below 200 mg/dl. A particular attention in evaluating the risk of coronary heart disease is paid to concentration of low density lipoproteins, the most atherogenic fraction of lipoproteins. In patients with concentration of LDL cholesterol between 130 and 160 mg/dl often occur coronary incidents. High level of small, dense LDL particles, hipertriglycerydemia and low concentration of protective fraction of HDL cholesterol creates triplet very often observed in diabetes and metabolic syndrome X, especially contributing to vascular atherosclerosis development (7). In the previous studies (6) a positive relationship between plasma LDL cholesterol and an inverse correlation between HDL cholesterol and coronary atheromatous load was proved. In our study significant differences in total cholesterol in subgroups of patients and association with total SA or SA/protein index was not observed. There was found a significant correlation between total SA concentration and level of triglycerides. These findings confirm reported earlier association of increased total SA concentration with hypertriglycerydemia (3). Other well established risk factors for coronary artery disease associated with an elevated level of total SA concentration are smoking, hypertension, obesity and diabetes (9). In our study higher percentage of obese individuals in the group of patients with triple/multiple vessel disease and higher frequency of hypertension and family history in the group of patients with single vessel disease was observed. However, no correlation between these risk factors and SA concentration was found.

In conclusion, our data may partly explain the influence of sialic acid metabolism on the development of coronary heart disease and support the view that increased sialic acid may be considered as a coronary risk factor. However, because of no specificity of serum SA its clinical usefulness as an indicator of severity of coronary arteriosclerosis is limited. Nevertheless, when combined with other markers, SA concentration is helpful in assessing the risk of coronary heart disease.

REFERENCES

1. Allain P. et al.: Increase of sialic acid concentration in the plasma of patients with coronary disease. Presse Med., 25, 96, 1996.
2. Berbeć H. et al.: Total serum sialic acid concentration as a supporting marker of malignancy in ovarian neoplasia. Eur. J. Gyneac. Oncol., 20, 389, 1999.
3. Crook M., Tutt P.: Serum sialic acid concentration in patients with hypertriglycerydaemia showing the Fredrickson's IIB phenotype. Clin. Sci., 83, 593, 1992.
4. Crook M. et al.: Plasma sialic acid and acute phase proteins in patients with myocardial infarction. Angiology, 45, 709, 1994.
5. Fong I. W.: Emerging relations between infectious diseases and coronary artery disease and atherosclerosis. CMAJ, 163, 49, 2000.
6. Gokmen S. et al.: Association between total and lipid-bound sialic acid concentration and the severity of coronary atherosclerosis. J. Lab. Clin. Med., 140, 110, 2002.
7. Grundy S. M.: Small LDL, atherogenic dyslipidaemia and metabolic syndrome. Circulation, 95, 1, 1997.

8. Lindenberg G. et al.: Serum sialic acid concentration and cardiovascular mortality. BMJ, 302, 143, 1991.
9. Ponnio M. et al.: Serum sialic acid in a random sample of general population. Clin. Chem., 45, 1842, 1999.
10. Salomone O. A. et al.: Serum total sialic acid concentration is not associated with the extent or severity of coronary artery disease in patients with stable angina pectoris. Am. Heart J., 136, 620, 1998.
11. Schauer R.: Chemistry, metabolism, and biological functions of sialic acids. Adv. Carbohydr. Chem. Biochem., 40, 131, 1982.
12. Silanaukee P. et al.: Occurrence of sialic acids in healthy humans and different disorders. Eur. J. Clin. Investig., 29, 413, 1999.
13. Sonmez H. et al.: Carbohydrate-deficient transferrin and sialidase levels in coronary heart disease. Thromb. Res., 99, 311, 2000.
14. Warren L. J.: The thiobarbituric acid assay of sialic acids. Biol. Chem., 234, 1971, 1959.
15. Wu E. B. et al.: Plasma sialic acid and coronary atheromatous load in patients with stable chest pain. Atherosclerosis, 145, 261, 1999.

SUMMARY

There is an association between increased levels of total sialic acid concentration and higher cardiovascular mortality, so total sialic acid has recently been considered as a cardiovascular risk factor. However, there are only a few studies assessing the relationship between sialic acid concentration and severity of coronary heart disease in patients with stable angina pectoris, and conclusions are contradictory. The aim of this study was to investigate the possible association between total plasma sialic acid concentration and the severity of coronary arteriosclerosis. In a group of 24 patients with coronary heart disease undergoing elective coronary artery by-pass grafting, concentration of total sialic acid was assayed. Well established risk factors of coronary heart disease such as hypercholesterolaemia, hypertriglicerydemia, hypertension, diabetes, smoking and family history of cardiovascular disorders are determined. Fifteen healthy subjects – blood donors served as control group. Total sialic acid values were significantly increased in the group of patients with double vessel disease (2.17±0.73 mmol/L), patients triple/multiple vessel disease (2.53±0.86 mmol/L) and in the whole group of patients (2.35±0.80 mmol/L) in comparison with the control group (1.52±0.20 mmol/L). Our results confirm that total sialic acid concentration is associated with occurrence of coronary atherosclerosis.

Poziom całkowitego kwasu sialowego w osoczu krwi pacjentów z chorobą wieńcową

Ponieważ udowodniono, że podwyższone stężenie kwasu sialowego wiąże się ze zwiększoną śmiertelnością z przyczyn sercowo-naczyniowych, toteż wysoki poziom kwasu sialowego zalicza się do czynników ryzyka choroby wieńcowej. W nielicznych pracach poszukiwano związku pomiędzy stężeniem kwasu sialowego a zaawansowaniem procesu miażdżycowego u pacjentów z chorobą wieńcową w postaci stabilnej dusznicy bolesnej. Wyniki badań były jednak sprzeczne. Celem pracy była ocena związku pomiędzy poziomem całkowitego kwasu sialowego w osoczu a zaawansowaniem miażdżycy naczyń wieńcowych. Wśród 24 pacjentów, którzy zostali poddani chirurgicznej rewaskularyzacji mięśnia sercowego, oznaczono stężenie całkowitego kwasu sialowego we krwi.

Oceniono również występowanie innych czynników ryzyka choroby wieńcowej, takich jak: hipercholesterolemia, hipertriglicerydemia, nadciśnienie, cukrzyca, palenie tytoniu i obciążenia rodzinne. Stężenie całkowitego kwasu sialowego było istotnie wyższe w podgrupach pacjentów z chorobą dwunaczyniową (2,17±0,73 mmol/L), trójnaczyniową/ lub wielonaczyniową (2,53± 0,86 mmol/L), jak i w całej grupie badanej (2,35±0,80 mmol/L) w porównaniu z grupą kontrolną (1,52±0,20 mmol/L). Wyniki naszych badań potwierdzają fakt, że u pacjentów z chorobą wieńcową występuje podwyższone stężenie kwasu sialowego w osoczu.