

ULTRASONIC DETERMINATION OF PLAQUE VULNERABILITY IN CAROTID ARTERIES AND CORRELATION WITH VISCERAL FAT THICKNESS IN PATIENTS WITH DIABETES MELLITUS TYPE 2

Muamer Suljić and Aleksandar Jovanović

The basic pathohistological substrate of vascular complications is atherosclerotic plaque and, therefore, the adequate treatment of patients with vascular disease is conditioned by timely and precise diagnosis. The introduction of ultrasound technology in clinical practice was enabled by Edler and Hertz in 1954, when they presented the myocardial motions, then by Yoshida in 1956, Sotomura in 1959, and Franklin in 1961, who used ultrasound to display the blood flow in the human blood vessels.

The aim of our study was to determine the incidence and vulnerability of plaques in the carotid arteries and to examine the association between plaque vulnerability and visceral fat thickness in patients with diabetes mellitus type 2.

The investigation involved 82 subjects divided into two groups. The first group included 51 subjects suffering from diabetes mellitus type 2, while the second group involved 31 healthy controls.

Among the examinees, a significantly higher incidence of plaque vulnerability was reported in the patients suffering from diabetes mellitus type 2. Average thickness of intraabdominal fatty tissue was significantly higher in the patients with diabetes mellitus type 2 compared to controls. The incidence of vulnerable plaques significantly correlated with diabetes mellitus incidence and thickness of intraabdominal fatty tissue.

Visceral obesity and diabetes mellitus type 2 showed significant association with atherosclerosis. Ultrasound determination of carotid stenosis and intraabdominal fatty tissue thickness are the most important criteria for classification of patients with high risk of ischemic stroke. *Acta Medica Medianae* 2009;48(4):40-44.

Key words: plaque, carotid artery, visceral fat, diabetes mellitus

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Introduction

Diabetes, especially type 2, is a global problem of modern man due to a marked increase in the prevalence to pandemic proportions, but also due to vascular complications. It is believed that over 60% of diabetic patients die due to cardiovascular complications, that mortality from myocardial infarction and stroke is 2 to 4 times higher.

Even 1000 years BC the famous Persian physician Avicenna for the first time described gangrene as a complication (vascular) of diabetes.

Basic pathohistological substrate of the vascular complications in patients with diabetes mellitus is atherosclerotic plaque, and therefore, an adequate treatment of patients with a vascular disease is conditioned by timely and precise diagnosis.

It would be unjustified to write about the Doppler sonography and not mention Cristian Doppler, an Austrian physicist born in Salzburg in 1803, who described in 1842 the principle of the change in the frequency between the two moving bodies.

The introduction of ultrasound technology in clinical practice was enabled by Edler and Hertz when they showed the myocardial movements in 1954, and then Yoshida (1956) and Sotomura (1959), Franklin (1961), who demonstrated blood flow in the blood vessels of humans using ultrasound.

Clinical criteria for the diagnosis of both morphology and haemodynamics related to normal and pathological conditions in the blood vessels were developed along with development of technology.

Chronic complications of diabetes mellitus

The chronic complications of DM affect many organic systems and are responsible for a large number of cases of morbidity and mortality associated with diabetes. The chronic complications are divided into vascular and non-vascular complications, while vascular ones are further subdivided into macrovascular and microvascular complications (1).

Microvascular complications: eye disease, neuropathy, nephropathy.

Macrovascular complications: coronary artery disease, peripheral vascular disease, cerebrovascular disease.

Non-vascular complications: gastrointestinal, genitourinary, skin and other complications.

The risk of chronic complications increases with the duration of disease, they usually become visible in the second decade of hyperglycaemia. Since type 2 DM may have a long asymptomatic

period of hyperglycaemia, many people with type 2 DM have complications at the time of diagnosis. Relevant clinical studies (UKPDS, Framingham Study) showed a significant increase in the risk for microvascular (37% -50%) and macrovascular complications (2-3 times higher risk for cardiovascular diseases, 3-6 times higher risk for myocardial infarction) (1).

Ultrasonic features of atherosclerotic plaque

The most common disease of large arteries is atherosclerosis. Ultrasonic diagnosis is a sovereign among angiographic methods for the assessment of carotid atherosclerotic plaque. It enables not only quantitative analysis of plaque (length, width, thickness, degree of lumen stenosis), but also qualitative analysis, or the composition of plaque, the surface of plaque area, and the presence of appositional thrombus. Based on this analysis, it can be estimated how much the plaque is "dangerous" for the occurrence of cerebrovascular disease, and whether there is an indication for surgical removal (endarterectomy) (2).

Plaques may be homogeneous (uniform homogeneous structure), but they are often heterogeneous (uneven, heterogeneous echo structure).

The division of plaques that have clinical implications is the division into:

- complicated (vulnerable, unstable) and
- uncomplicated (nonvulnerable, stable)

plaques.

Complicated plaques are those whose surface is exulcerated (ulceration in places where there has been a separation of lipid plaque or a thrombosis (hypoechoic structure of appositional thrombus) or haemorrhage in the plaque) (2).

These complicated plaques are unstable and tend to detach pieces with the possibility of embolisation of the distal arteries.

Anatomical features of atherosclerotic plaque

They are classified into early, late and complicated atherosclerotic lesions of the tunica intima. In addition to this classification, there is a growing acceptance of the American Heart Association classification and its Committee for vascular lesions from 1994. It is a pathohistological classification with six main types of lesions, marked by Roman numerals. Type I and type II are the early lesions. Type III is a transitional form between the early and late lesions. Type IV and Type V are delayed, and type VI lesions are the complicated atherosclerotic lesions of the tunica intima.

The lesions were clearly defined and described pathohistologically, histochemically and ultrastructurally. This classification is suitable for standard diagnostics, it provides insight into the development phase of the disease, and allows the correlation with clinical manifestations of disease and modern diagnostic techniques (3).

Fissures (cracks), ulcerations (defects) and the rupture (split) of plaque (lesion type VIA) appear on the surface of already created atherosclerotic plaques. Since there is no protective layer above the atheromatous core, it

has a direct contact with blood. Atheroma can be emptied through a defect directly into the circulation and be the source of atheromatous embolism. If the emboli, originating from atheromatous material, mainly consist of cholesterol crystals, cholesterol embolism occurs (3).

Obesity

Different distribution of fat in the body is not just an aesthetic feature, but there is a high correlation with certain diseases and pathological conditions, so that the distribution of fat is even a better indicator of health risk than BMI. For such estimates, it is very useful to calculate WHR index (Waist / Hip Ratio). It should be less than 1 in men, and less than 0.85 in women. Based on this index, obesity is divided into android - male (apple) obesity and gynoid - female (pear) obesity. In the gynoid type of obesity the excess of fatty tissue builds up subcutaneously in the lower parts of the body around the pelvis and thighs, and it generally contains alpha 2 adrenergic receptors through which catecholamines exhibit their lipogenic effect. In these people, greater affinity for the appearance of mechanical complications in the form of difficult movement, peripheral venous insufficiency and respiratory insufficiency has been perceived. It is important to emphasize that this type of obesity may be present in both sexes. In the android type of obesity (the central or visceral type) fat tissue builds up in the area of shoulders, chest and abdomen. It contains mainly beta adrenergic receptors through which catecholamines exhibit their effects and directly lead to an increase in endogenous triglyceridemia. The amount of intraabdominal fatty tissue and the ratio between intraabdominal and subcutaneous fatty tissue are very important (1,4). The android type of obesity is characterized by the fact that the intra-abdominal fat increases insulin resistance and is associated with a group of risk factors (i.e. components of the metabolic syndrome - glucose intolerance, decreased HDL cholesterol, increased triglyceride concentration, hypertension and obesity), called Syndrome X by Reaven (4,5).

Aims

1. To determine the incidence of atherosclerotic plaque in the carotid arteries in examinees with the type 2 diabetes mellitus compared to healthy examinees.

2. To examine the difference in the specific variability of plaques by ultrasound between examinees with diabetes mellitus type 2 and healthy examinees.

3. To examine the dependence of vulnerability of atherosclerotic plaque and the quantity of intraabdominal fat.

Material and methods

The examinees were divided into two examination groups: the group of examinees with manifest diabetes mellitus type 2 (51 examinees) and the control group of healthy subjects (31 examinees). Diabetes mellitus was diagnosed based on fasting glucose higher than 7 mmol/l, verified on at least two occasions, i.e. on the

basis of clinical documentation and OGTT test. Glycemia was determined photometrically, by GOD-PAP method where the reference values were 3.6-6.1 mmol/l.

The testing of vulnerability of atherosclerotic plaque in the carotid arteries was done using the ultrasound method on the apparatus Toshiba Cori Vision Pro and Madison, on the basis of plaque translucency, its global appearance, homogeneity, sizes, the regularity of edge and the clarity of fibrous caps.

The thickness of intraabdominal fat is determined by ultrasound as the distance between the abdominal aorta and abdominal muscular layer, 5 cm above the umbilicus using the frequency of 3.5MHz with quiet breathing at the end of expiration.

Results

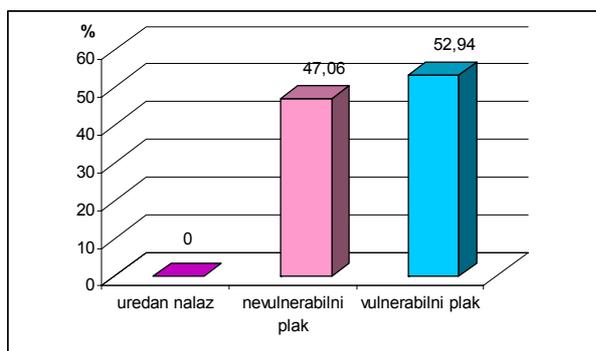


Diagram 1. Distribution of patients according to the presence and type of plaque in group with diabetes mellitus type 2

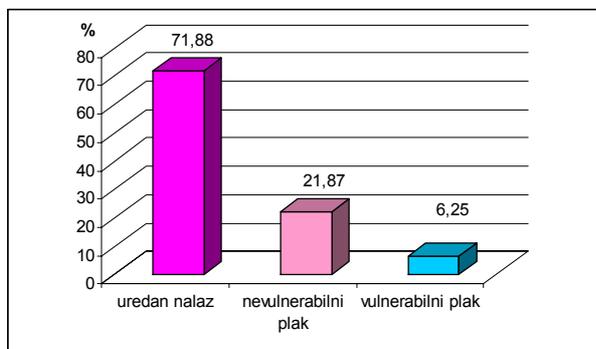


Diagram 2. Distribution of patients according to the presence and type of plaque in control group

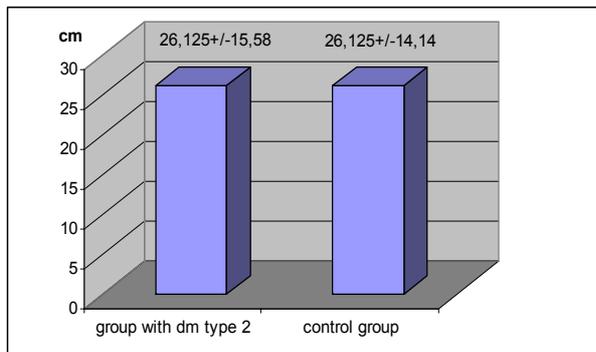


Diagram 3: Average thickness of intraabdominal fat tissue among patients with diabetes and control group

Table 1: Statistically significant correlation of atherosclerotic plaque vulnerability with relevant research parameters

	Spearman's correlation coefficient(P):	Statistical significance (P)
Presence of diabetes	0.709	p<0.0001
Age	0.738	p<0.0001
Length of diabetes	0.659	p<0.0001
Glycemia	0.692	p<0.0001
Waist circumference	0.334	p=0.001
Waist/hip ratio	0.54	p<0.0001
Intraabdominal fatty tissue thickness	0.267	p=0.007

Diagrams 1 and 2 show the distribution of patients according to the presence and type of atherosclerotic plaque in the carotid arteries in the study and control group examinees. Plaque was found in 100% of diabetic patients versus 28.12% of patients in the control group.

The vulnerability of atherosclerotic plaque correlates significantly with the age of the examinees, presence of diabetes, its length, and amount of glucose.

Diagram 3 shows that there is a noticeable and statistically highly significant difference (p<0.01) between the average thickness of intraabdominal fatty tissue among patients with diabetes and healthy subjects. Actually, the thickness of intraabdominal fatty tissue in the group of patients with type 2 diabetes mellitus was 35.11 ±15.58 cm, while it was 26.12 ±14.14 cm in the group of healthy subjects.

The vulnerability of atherosclerotic plaque correlates significantly with the age of the examinees, the presence of diabetes, its length, level of glucose, waist circumference, waist / hip ratio, the amount of intraabdominal fatty tissue, the ratio of intraabdominal fatty tissue / subcutaneous fat tissue, weight, the presence of hyperlipoproteinemia and the presence of hypertension (Table 1).

Discussion

Nowadays, there are 200 million people worldwide suffering from diabetes, and over 500,000 in our country. Over 90% of all patients are suffering from diabetes type 2. The number of patients increases, the length of life is extended and therefore there is an increase in the incidence of late complications of diabetes.

Atherosclerosis is a complex chronic diffuse inflammatory process, activated by a number of complex genetic and other environmental factors. Inflammation of blood vessels is one of the main factors leading to atherosclerosis, and diabetes worsens the degree of inflammation (6).

All these and other similar studies have shown that diabetes leads to deterioration of atherosclerosis, but it could be said that the true connection between diabetes and atherosclerotic inflammatory process is not known. It has been shown in several studies that type 2 diabetes is a significant risk for CVD. Twenty-year-survival

was followed in the most famous study (Framingham) and showed that the risk of atherosclerosis in diabetes is higher from 2 to 3 times, while there is no significant difference between males and females for cardiovascular mortality (7).

At the end of the 70's of the last century, there was a worrying rise, almost of epidemic proportions, in the clinical sequelae of atherosclerosis in developed countries. In the United States, about 640.000 people used to die yearly from coronary insufficiency. There was also a large and growing number of people who died from cerebral insult, and almost 56% of them had cerebral atherosclerosis (8). In our country, it was Yugoslavia at that time, the development of knowledge about this epidemic was closely monitored and the development of complications of atherosclerosis were carefully registered (9,10). The mentioned studies found that risk factors (older age, smoking, obesity, increased skin folds on the upper arm and under the scapula, hypercholesterolemia, hypertriglyceridemia, longer duration of hypertension, family burden of risk factors) are more frequent in patients with hypertension (1.027 examinees) than in the entire population (5.210 examinees). According to epidemiological analyses made in Yugoslavia, it may be concluded that this heart disease shows the growth prevalence from younger to older age groups, with the tendency of "rejuvenation" and greater representation in urban areas, with a mortality rate of 15.4 compared to all cardiovascular diseases.

The increase of atherosclerosis in developed countries was associated with certain metabolic disorders and life styles. These factors (the causes of atherosclerosis) which were common (or the most common) were called the risk factors. For the first time the concept (perception, conception) of risk factors has appeared in the publications of the results of Framingham's study (11). The idea of introducing the term "risk factor" has been started with the publications from Framingham's study (Framingham Study).

However, the same author Kannel WB et al. stated that the access to any risk factor in order to prevent is neither fully (maximally) logical nor efficient. For example, as for height of blood pressure or cholesterol levels in the blood, the risk of cardiovascular disease depends on other risk factors as well. (Kannel WB et al. add that "risk factor" is attributed to proven weight, or causal relationship with coronary heart disease, especially if it is supported by the demographic, psychological, pathoanatomical and physiological changes as well. Further studies associate the gained data (or the features of risk factor) with sex, race and socioeconomic conditions (12).

Based on numerous results, it may be concluded that atherosclerosis is a multifactorial disease (13).

The term "vulnerable plaque" refers to the subgroup of atherosclerotic lesions, usually of moderate size, which are prone to rupture or erosion, leading directly to a vascular incident. The term vulnerable plaque does not define best the structure of atherosclerotic plaque though it is used most. A better term would be "fibro-atheroma with a thin cap" (14).

The studies based on autopsy have shown that the plaques prone to rupture have the following characteristics: a thin fibrous cap (<65 μ m), large core with a high lipid content and the increased activity of macrophages in the core (15).

It is believed that the following cellular mechanisms predispose the development of vulnerable plaque: the reduced synthesis of collagen, locally (in the blood vessel wall) increased the activity of collagen and apoptosis of arterial smooth muscle cells. These molecular changes are most prominent on the top of the plaque where mechanical forces exert the strongest effect.

It is believed that during the rupture of cap, procoagulation factors are released into the circulation, tissue factor in particular. Thereby, it creates a nidus for the thrombus formation, and then this may be followed by an acute coronary incident.

Although the vulnerable plaques rupture occur constantly throughout the organism, only some of them form occlusive thrombus and have clinical significance. The factors leading to the formation of occlusive thrombus are not known (16).

Ultrasonic determined degree of carotid stenosis is one of the most common quoted criteria for the classification of patients with a high risk of ischemic stroke. Today, it is more and more said about the morphology of plaques (i.e. stability, vulnerability) as a risk for brain ischemia. The people with less organized plaques (soft or dense) carry a higher risk of transient ischemic attack (TIA) and stroke even if stenosis is less than 75% i.e. less than haemodynamically significant stenosis (17,18)

Some studies say that about 95.5% of symptomatic patients have fresh or old haemorrhage in plaque as opposed to 27% of asymptomatic patients who had intramural bleeding (19). Some studies indicate the association between heterogeneous carotid plaques and the development of new neurological deficit. On the basis of all of these studies, a clear relationship between the plaque and ipsilateral stroke can be established (20).

Conclusions

1. The frequency of plaque in the carotid arteries was significantly higher among patients with diabetes mellitus.

2. The average intraabdominal thickness of fat tissue was significantly higher in patients with diabetes mellitus type 2 compared to the control group.

3. The frequency of vulnerable plaques is also higher and significantly correlates with diabetes mellitus and the thickness of intraabdominal fat tissue.

4. Abdominal obesity and diabetes mellitus type 2 are significantly related to atherosclerotic changes in the blood vessels. Ultrasonic determination of the degree of carotid stenosis is one of the important criteria for classifying patients with a high risk of ischemic stroke based on the thickness of intraabdominal fat.

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ULTRAZVUČNO ODREĐIVANA VULNERABILNOST PLAKOVA NA KAROTIDNIM ARTERIJAMA I KORELACIJA SA DEBLJINOM INTRAABDOMINALNOG MASNOG TKIVA KOD OSOBA OBOLELIH OD DIJABETES MELITUSA TIPA 2

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Osnovni patohistološki supstrat vaskularnih komplikacija kod bolesnika sa dijabetes melitusom je upravo aterosklerotski plak, te je zbog toga adekvatan tretman bolesnika sa vaskularnim oboljenjem uslovljen pravovremenom i preciznom dijagnostikom. Uvođenje ultrazvučne tehnike u kliničku praksu omogućuje prikaz strujanja krvi u sudovima čoveka.

Cilj istraživanja bio je da se odredi učestalost pojave i vulnerabilnosti plaka na karotidnim arterijama i da se ispita veza između vulnerabilnosti plakova i debljine intraabdominalnog masnog tkiva kod osoba obolelih od dijabetes melitusa tip 2.

U ispitivanju su učestvovala ukupno 82 osobe podeljene u dve grupe. U prvoj grupi je bio 51 bolesnik oboleo od dijabetes melitusa tip 2, a u drugoj, kontrolnoj, 31 zdrav ispitanik.

Među ispitanicima je značajno veća učestalost pojave i vulnerabilnosti plaka bila u grupi ispitanika obolelih od dijabetes melitusa tip 2. Srednja debljina intraabdominalnog masnog tkiva je značajno veća kod obolelih od dijabetes melitusa tip 2 u odnosu na kontrolnu grupu. Učestalost vulnerabilnih plakova je takođe viša i značajno korelira sa dijabetes melitusom i debljinom intraabdominalnog masnog tkiva.

Abdominalna gojaznost i dijabetes melitus tip 2 su značajno povezani sa aterosklerotskim promenama na krvnim sudovima. Ultrazvučno određivanje stepena karotidne stenoze jedan je od značajnih kriterijuma za klasifikaciju bolesnika sa visokim rizikom ishemijskog moždanog udara na osnovu debljine intraabdominalnog masnog tkiva. *Acta Medica Medianae* 2009;48(4):40-44.

Ključne reči: plak, karotidne arterije, intraabdominalno masno tkivo, dijabetes melitus