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Review article

DIABETIC CARDIOMYOPATHY: INTERSECTION OF MACROVASCULAR AND MICROVASCULAR DISEASE, OR MUCH MORE?

ДИЈАБЕТСКА КАРДИОМИОПАТИЈА: ВКРСТУВАЊЕ НА МАКРОВАСКУЛАРНАТА И МИКРОВАСКУЛАРНАТА БОЛЕСТ, ИЛИ МНОГУ ПОВЕЌЕ?

Irena Mitevska and Marijan Bosevski

University Cardiology Clinic, "Ss Cyril and Methodius" University, Medical Faculty, Skopje, Republic of Macedonia

Апстракт

Кардиоваскуларните болести се одговорни за повеќе од 75 проценти од смртноста кај пациенти со дијабетес, која главно е предизвикана од коронарна артериска болест и срцева слабост. Кардиоваскуларниот морбидитет и морталитет кај пациенти со дијабетес можат да бидат независно поврзани и со други патофизиолошки механизми освен коронарната артериска болест, епикардијалната и микроваскуларната болест. Постои зголемување на идејата дека пациентите со дијабетес страдаат и од дополнителни срцеви состојби наречена "дијабетична кардиомиопатија". Постојат неколку клинички, експериментални, патолошки и епидемиолошки истражувања, кои го поддржуваат постоењето на еден специфичен ентитет "дијабетска кардиомиопатија". Ова се пре́тпоставува дека е под влијание на комплексно взаемно дејство на неколку метаболни промени што води кон двете функционални и структурни промени на дијабетскиот миокард. Во овој ревијален труд се презентирани епидемиолошките аспекти и клиничките импликации на оваа состојба.

Клучни зборови: дијабетска кардиомиопатија, дијагноза, третман

Abstract

Cardiovascular disease is responsible for over 75% of deaths in diabetic patients, the majority caused by coronary artery disease (CAD) and heart failure. Cardiovascular morbidity and mortality in diabetic patients might be independently associated with other pathophysiologic mechanisms than coronary artery disease, epicardial and microvascular disease. There is an increasing notion that diabetic patients suffer from an additional cardiac condition named "diabetic cardiomyopathy". There are several clinical, experimental, pathological and epidemiological researches that support the existence of a specific "diabetic cardiomyopathy". This is assumed to be influenced by complex interaction of several metabolic changes that leads to both functional and structural alterations of the diabetic myocardium. In this review epidemiological aspects and clinical implications of this condition are presented.

Keywords: diabetic cardiomyopathy, diagnosis, treatment

Correspondence to: Irena Mitevska, University Cardiology Clinic, "Vodnjanska" 17, 1000 Skopje, R. Macedonia; E-mail: peovskai@yahoo.com

Diabetes and cardiovascular risk

Diabetes is a well-known risk factor for the development of coronary artery disease (CAD) and also for sudden cardiac death [1,2] It has been considered as CAD equivalent, placing the diabetic patients in the high-risk population for cardiovascular events. The most common cause of death in diabetes is cardiovascular disease, including heart failure, and amongst those with heart failure diabetes is an adverse prognostic marker. The prevalence of HF is around 22% in patients with DM type 2. Diabetic men have more than twice increased risk of heart failure than non-diabetic, while diabetic women have a fivefold increased risk of developing heart failure [1]. This excessive risk of heart failure persists despite correcting for age, hypertension, obesity, hypercholesterolemia, and coronary artery disease. Asymptomatic patients with diabetes type 2 initially are in the stage A of heart failure (absence of symptoms and structural heart abnormalities), which could potentially progress to stage B and stage C as clinically manifested heart failure, depending on early diagnosis and diabetes control [3-5].

Diabetic patients have 2-4 fold increased risk for fatal and non-fatal CAD [6-10]. Furthermore, despite a comparable infarct size, diabetic patients have a far greater risk of developing HF post-MI compared with nondiabetic patients [11-13]. Patients with diabetes mellitus type 2 have diffuse CAD, more often multivessel disease, in-

creased incidence of silent myocardial ischemia and larger myocardial infarction with poor collateral vessels development. Heart failure due to coronary artery disease in these patients is caused by myocardial ischemia, hibernation and myocardial necrosis. Microangiopathic changes in the small vessels of the heart of diabetic patients may contribute to diabetic cardiomyopathy as well. Less appreciated is the fact that an increase in left ventricular mass is observed in diabetic patients. This is seemingly unrelated to the extent of coronary artery disease. Many patients with diabetes have associated hypertension (28-68%), so that some of the left ventricular hypertrophy common in diabetics is likely related to high blood pressure.

When hypertension is superimposed on the diabetic state, significant myocardial morphologic damage is intensified, producing a powerful substrate for the development of heart failure. Diabetic women tend to have much greater left ventricular mass, and increased left ventricular wall thickness and chamber size. Other abnormalities noted in human diabetic hearts include microvascular constriction, interstitial fibrosis, and edema. In clinical practice, it is difficult to separate out the mutual role of hypertension and ischemia in the development of diabetic cardiomyopathy. Studies have shown that diabetics with hypertension have greater interstitial connective tissue deposition comparing to patients with either diabetes or hypertension as isolated entities, and concomitant hypertension further increases the development of necrotic cell death in myocytes and endothelial cells but does not increase apoptosis [14,15]. These differences are attributed to increased angiotensin II receptor and to oxidative stress in diabetic hearts.

It is proved and clinically known that the major cardiac complications of diabetes mellitus include large coronary conduit arteries, epicardial coronary arteries, and the microvasculature. What is less considered and still controversial by some cardiologists is the concept that diabetes mellitus affects cardiac structure and function independent of high blood pressure or coronary artery disease (CAD). There are many experimental, pathological, epidemiological, and clinical studies that underline the existence of "diabetic cardiomyopathy". The Framingham study demonstrated the increased incidence of congestive HF independent of age, hypertension, obesity, CAD and hyperlipidaemia. Considering the increasing incidence of diabetes mellitus and its strong association with the development of heart failure, it is important to have in mind the evidence concerning the concept of "diabetic cardiomyopathy", which was first described nearly 30 years ago [14]. We have to understand the basic mechanisms leading to diabetic cardiomyopathic changes in order to treat these patients at early phases of the disease.

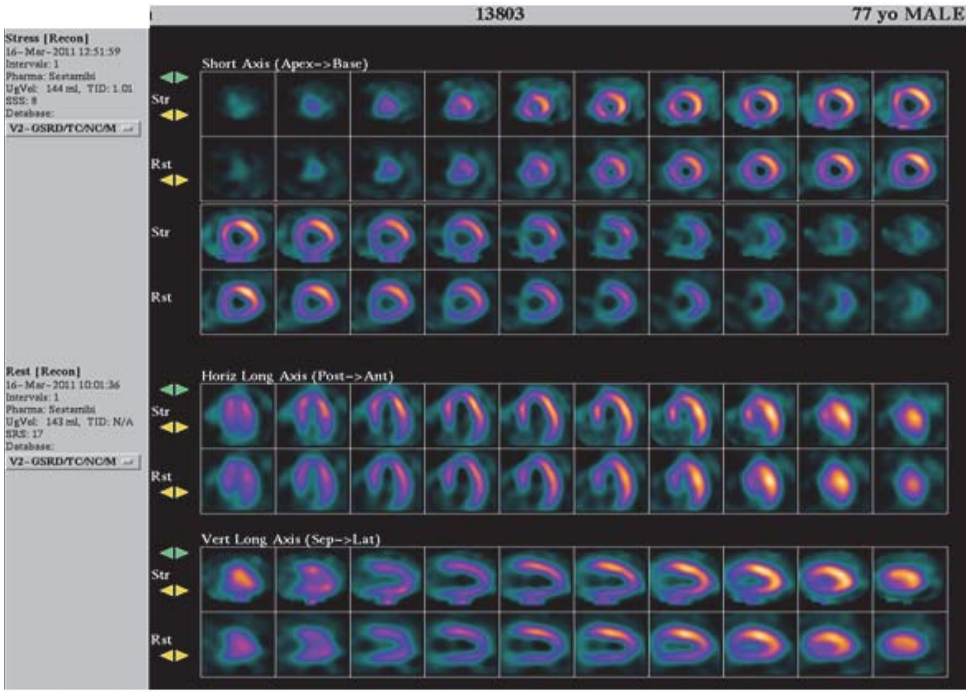

Fig. 1. Myocardial perfusion scintigraphy- SPECT scan with Tc-99m sestamibi. Mild reduction of radiotracer accumulation in the inferior wall, inferoseptal and small region of anteroseptal wall in both studies. Shortened septum. There are no signs of stress inducible ischemia. Increased left ventricular volumes with reduced global left ventricular function. Mild global hypokinesia. Scan results indicate cardiomyopathic changed myocardium in patient with DM type 2

Pathophysiology of diabetic cardiomyopathy

Diabetic cardiomyopathy is described as a disease process which affects the myocardium in diabetic patients causing a wide range of structural abnormalities that lead to left ventricular (LV) hypertrophy, and a combination of diastolic and systolic dysfunction. The condition is associated with structural and functional myocardial dysfunction not related to the presence of coronary artery disease (CAD), congenital heart diseases, valvular heart diseases or hypertension. The concept of diabetic cardiomyopathy is based on the concept that diabetes is the factor which causes changes at the cellular level, leading to structural myocardial abnormalities. Several pathological mechanisms have been described and connected with the pathogenesis of diabetic cardiomyopathy. Initial metabolic processes are postulated as triggers of mechanistic changes in myocardial structure, calcium signaling pathways and metabolism which may precede clinical manifestations of cardiac dysfunction. The other important factors include abnormalities in free fatty acid metabolism, increased oxidative stress, increased apoptosis, activation of the RAAS, autonomic neuropathy and, rarely, derangements in copper metabolism (Figure 1). Patients with hypertension and CAD may well have myocardial changes related to these disease processes, but a specific cardiomyopathy may also affect the myocardium secondary to diabetes causing a synergistic adverse effect as seen with a combination of diabetes and hypertension. The challenging clinical question is whether there are linking pathways between strict metabolic changes and coronary artery disease that cause cardiovascular complications and heart failure in more that 75% of diabetic patients.

Diabetes mellitus and heart failure have multiple common subcellular mechanisms that can be followed at different stages of impaired glucose tolerance and insulin resistance. Hyperglycemia is a causative factor that induces maladaptive mechanism, which leads to heart failure. Diabetic cardiomyopathy was originally descrybed in 1972 on the basis of observations in four diabetic patients who presented with heart failure without evidence of hypertension, CAD, valvular or congenital heart disease [4]. The review of the studies done since 1972 appears to support the concept of a diabetic cardiomyopathy independent of atherosclerotic cardiovascular disease. The exact mechanism is still questionable. Several mechanisms have been proposed including small and microvascular disease, autonomic dysfunction, metabolic derangements, and interstitial fibrosis, possibly caused by the accumulation of a peroxidase acid schiff (PAS)-positive glycoprotein, leading to myocardial hypertrophy and diastolic dysfunction.

Two phenotypes of diabetic cardiomyopathy have been described: restrictive or heart failure with preserved left ventricular ejection fraction (HFPEF) and dilated or heart failure with reduced left ventricular ejection fraction (HFREF). The pathophysiological mechanisms for left ventricular (LV) dysfunction consist of coronary microvascular endothelial dysfunction and cardiomyocyte cell death for both HFPEF and HFREF. Diabetes mellitus-induced metabolic changes such as hyperglycemia, lipotoxicity, and hyperinsulinemia induce development of diabetic cardiomyopathy (DCMP) with the restrictive/HFPEF type, which is more prevalent in obesity [14].

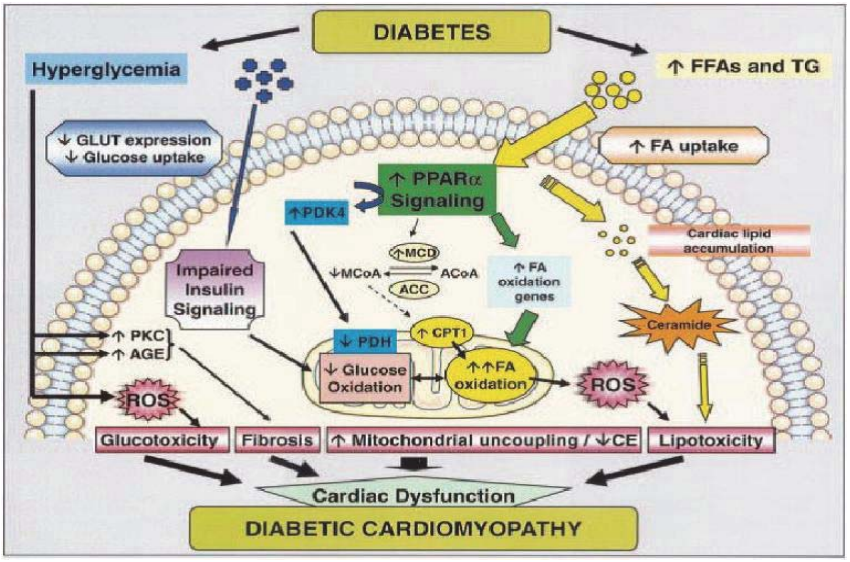

Fig. 1. Mechanisms leading to the development of diabetic cardiomyopathy. ACC: acetyl coenzyme A carboxylase; ACoA: acetyl coenzyme A; AGEs: advanced glycation end products; CE: cardiac efficiency; FA: fatty acids; FFA: free fatty acids; GLUTs: glucose transporters; MCD: malonyl coenzyme A; PDH: pyruvate dehydrogenase; PDK: pyruvate dehydrogenase kinase; PKC: protein kinase C; PPARα: peroxisome proliferator-activated receptor alpha; TG: triglycerides [2,5]

Diabetic cardiomyopathy consists of two major components, the first being a short-term, physiological adaptation to metabolic alterations, and the second represents degenerative changes for which the myocardium has only a limited capacity for repair. However, many factors such as treatments, metabolic characteristics, lipid profile, and other individual differences may affect the process of development of diabetic cardiomyopathy, and not all diabetic patients are affected by the same factors or to the same degree, which may result in marked variability in the clinical presentation of the diabetic cardiomyopathy.

Obesity, especially abdominal obesity is an independent risk factor for heart failure. Obese patients have increased myocardial collagen content and increased sympathetic function. Human adiposities seem to be capable of secreting a cardio-active substance that is negatively inotropic. One of the agents is leptin. Increased level of leptin is seen in obesity. The effects of long-term increased levels of leptin on cardiomyocites include structural and metabolic changes, which have mitogenic effect, myocardial hypertrophy and cardiomyocyte fatty acid loading. Increased levels of intracellular free acid can initiate the pathways of programmed cell death, termed lipoapoptosis.

In the course of diabetic cardiomyopathy, a spectrum of myocardial abnormalities develop and progress which include LVH and diastolic and systolic dysfunction. Left ventricular hypertrophy (LVH), systolic and diastolic dysfunction have distinct prognostic implications in the context of diabetic cardiomyopathy. The presence of LVH on the ECG is a poor prognostic indicator as seen by the results of the Framingham study [16]. The presence of LVH has been linked with increased markers of systemic inflammation [fibrinogen and CRP (C-reactive protein)] and microalbuminuria and, in a study of 1299 type II diabetic patients, increased albuminuria was a marker of endothelial damage and increased atherothrombotic risk [17].

In the context of diabetic cardiomyopathy, systolic dysfunction occurs late, often when patients have already developed a significant diastolic dysfunction. The prognosis in patients with depressed systolic dysfunction is poor with an annual mortality of 15-20%.

Little work has been done to assess the prognosis of asymptomatic isolated diastolic dysfunction, but there is one study which shows that echocardiographic evidence of subclinical contractile dysfunction and diastolic filling abnormalities are both predictive of subsequent CHF (chronic HF) [18]. Patients with diastolic HF have a significantly increased mortality of 58% annually compared to 1% for aged-matched controls [19].

Hyperglycemia, hyperlipidemia and increased ROS (reactive oxygen species) induce alterations in downstream transcription factors which result in changes in gene expression, myocardial substrate utilization, myocyte growth, endothelial function and myocardial compliance. Hyperglycemia may mediate its damaging effects through a series of secondary transducers. One of the principle abnormalities is the excess generation of AGEs (advanced glycation end-products), which deactivate NO (nitric oxide) and impair coronary vasodilation. Sustained hyperglycemia causes excess formation of mitochondrial ROS, which affects transcription, leading to contractile dysfunction [20,21]. An increase in ROS decreases NO levels, which leads to myocardial inflammation and endothelial dysfunction via PARP [poly (ADP-ribose) polymerase]) [22]. The severity of diastolic dysfunction correlates with HbA1c (glycated hemoglobin) levels and the likely cause is AGE induced formation of ROS, resulting in myocardial collagen deposition and fibrosis [23-25].

Independent of the effects of hyperlipidemia on coronary artery endothelial function, the increase in and dependence of diabetic myocardium on fatty acid supply results in several major cellular metabolic perturbations. Impaired glycolysis, pyruvate oxidation, lactate uptake and a greater dependence on fatty acids lead to a perturbation of myocardial bioenergetics and contraction/relaxation coupling [26]. Recent data from animal and human experimental studies have demonstrated the significant role of rennin angiotensin aldosterone system (RAS) in diabetes-induced myocardial dysfunction [27]. Hyperglycemia activates intra-cardiac RAS that has various effects on the myocardial cells. Intracellular angiotensin levels are assumed to be 3.4-fold higher in the cardiomyocytes of diabetic compared to nondiabetic patients [27].

Increased activation of the DAG (diacylglycerol)-activated PKC signal transduction pathway has been shown to induce many of the changes in diabetic cardiomyopathy which include a reduction in tissue blood flow, enhanced extracellular matrix deposition, capillary basement membrane thickening and increased vascular permeability with alterations in neovascularization. An inadequate angiogenic response to ischemia in the myocardium of diabetic patients could result in poor collateral formation and hence an increased propensity to infarction with a reduced reparative response.

Endothelial dysfunction is a precursor to and an effect of atherosclerosis. Anatomical and functional abnormalities of the vascular endothelium are commonly associated with diabetes [28]. The clinical implications of endothelial dysfunction are not limited to increased atherosclerosis. Endothelial cells also help collateral circulation development, which is reduced in patients with diabetes and may explain the increased infarct extension and congestive HF after MI in these patients.

The increased angiotensin II in diabetic myocardium and lipid metabolism abnormalities in diabetes may play a central role in early atherogenesis and progression to atherosclerotic plaque. Insulin resistance is also associated with accelerated atherosclerosis, especially coronary heart disease.

It is well known that hypertension and diabetes lead to a rise in arterial stiffness through endothelial dysfunction-

mediated fibrosis [29]. Vinereanu *et al.* demonstrated an association between conduit arterial stiffness and impaired LV function. Their results suggest that subendocardial function of the left ventricle may be depressed in patients with stiff and relatively noncompliant conduit arteries [30]. The net effect of these hemodynamic changes is ischemia,especially in the subendocardium, which, if chronic, can lead to interstitial fibrosis and the development of HF [31].

Cardiac autonomic neuropathy (CAN) may contribute to impaired diastolic function and is associated with an increased cardiovascular risk in diabetic patients. Diabetic autonomic neuropathy is associated with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation. Sympathetic dysfunction has been related to both systolic and diastolic dysfunction in type II diabetes [32]. Extremely high mortality rates have been associated with clinical findings of diabetic autonomic neuropathy.

Oxidative stress caused by toxic molecules may play a critical role in subcellular remodeling and abnormalities of calcium handling that lead to subsequent diabetic cardiomyopathy. Alterations in regulatory proteins and contractile proteins may be important contributors to abnormal myocardial carbohydrate and lipid metabolism in diabetes [33].

Structural and functional alterations of the small vessels in diabetes have been incriminated in the development of diabetic cardiomyopathy, although this remains controversial. There are studies indicating that abnormality of cardiac function described in diabetes is not associated with thickening of the myocardial capillary basal lamina [34]. According to Larghat's study, which used magnetic resonance imaging, patients with diabetes have increased left ventricular mass and torsion, and decreased perfusion reserve. Despite these findings, it has been proposed that such focal changes in microvessels are insufficient to account for the diffuse myocardial degeneration with interstitial fibrosis in diabetic cardiomyopathy.

Diagnostic algorithm in patients with suspected diabetic cardiomyopathy

Diagnosis of DCMP requires establishment of impaired glucose metabolism and clinical approach to exclude other causes of LV dysfunction: CAD, valvular disease, hypertension, congenital heart disease and infections such as viral myocarditis or toxins-induced, familial or infiltrative cardiomyopathies [35]. The following risk factors which might exacerbate DCMP need special attention: obesity, chronic high blood glucose, high blood pressure, dyslipidemia, smoking and alcohol consumption. The diagnostic should include a detailed history and a proper physical examination: urine analysis to test for the presence of proteinuria, stress test, chest X-ray, electrocardiography, echocardiography, myocardial perfusion SPECT imaging (Table 1). Invasive measures should also be considered in some situations including myocardial biopsy, cardiac catheterization to evaluate cardiac chamber blood flow, pressures and coronary blood flow.

Table 1. Diagnostic approaches used in the diagnosis of diabetic cardiomyopathy

Diagnostic methods	Parameters and clinical implications
Clinical	History of DM and family history of diabetes Physical examination, evaluation of symptoms and complications
Laboratory	Urine, for proteinuria Serum aminoterminal propeptide of type I and type III collagens B-natriuretic peptide (BNP), for increased ventricular pressure or heart failure
Transthoracic echocardiography	Evaluation of diastolic LV function (Transmitral Doppler analysis, for left ventricular mass and diameter; pulmonary venous blood flow), TDI, decreased tissue velocities for both diastolic and systolic dysfunction 2D/TDI, strain and strain rate, for systolic and diastolic dysfunction Evaluation of systolic LV function
Magnetic resonance imaging	MRI, for left ventricular mass and diameter Late gadolinium enhancement MRI, for diastolic and systolic dysfunction Magnetic resonance spectroscopy, for myocardial fibrosis, triglyceride content and myocardial phosphocreatine to ATP ratio
Myocardial perfusion SPECT	G-SPECT, differentiate ischemic from non-ischemic cardiomyopathy, assess both myocardial perfusion and ventricular function Quantitative myocardial perfusion SPECT, myocardial and coronary artery disease
PET	Radiotracer kinetics, quantitative assessment of myocardial blood flow

SPECT- single photon emission tomography; PET- positron emission tomography

Left ventricular dysfunction

Left ventricular (LV) diastolic dysfunction is the earliest manifestation in DCMP, which may evolve to symptommatic heart failure [36-37]. Doppler echocardiography imaging has emerged as an important non-invasive measure, which could easily reveal diastolic and systolic abnormalities [38]. The diastolic dysfunction in DCM is characterized by an increased ventricular wall stiffness and longer diastolic relaxation time, commonly at an early stage of the disease course.
Left ventricular systolic dysfunction is the later manifestation of the LV functional impairment continuum. There has been discrepancy regarding early detection of LV systolic dysfunction using left ventricular ejection function (LVEF) and LV fractional shortening (LVFS), attributable to load dependence and the relative insensitivity of LVFS in detecting subtle features of LV systolic dysfunction [39]. Currently, the more sensitive echocardiographic indices used to evaluate early LV systolic function include TDI and speckle tracking echocardiographic strain rate imaging which detect subclinical LV systolic dysfunction in DM [39].

Echocardiography

2D-TTE is unable to detect the subtle changes in myocardial function in DM. Newer technologies, such as TDI, look promising as they enabe an assessment of myocardial tissue velocities with relative ease. Strain and strain rate echocardiography is a unique technique for assessing myocardial systolic and diastolic function. It is a new advanced imaging tool which is highly sensitive and reproducible to evaluate early and subtle impairment of LV function.

Magnetic resonance imaging

Cardiac MRI is a useful imaging tool for assessment of structural and functional myocardial disorders. Gadolinium-enhanced cardiac MRI has been useful in predicting major adverse cardiac events in diabetic patients with no prior history of ischemic heart disease.

Stress single-photon emission computed tomography

Stress single-photon emission computed tomography (SPECT) is a validated imaging tool providing information on the physiological significance of flow-limitation and sarcolemmal membrane integrity. LV function analysis by SPECT enhances its prognostic and diagnostic ability, particularly in the prediction of cardiac death. Reliable automatic algorithms of SPECT provide semiquantitative assessment of myocardial perfusion, LVEF, LV volumes, regional myocardial wall motion and thickening. It also has high sensitivity in differentiating ischemic from non-ischemic cardiomyopathy. Nevertheless, factors other than CAD could play a role in the pathogenesis of myocardial dysfunction in diabetic patients, including endothelial dysfunction, interstitial fibrosis, impaired modulation of vascular growth and remodeling. As a result, SPECT could be helpful in these situations.

Positron emission tomography

Among the available imaging modalities, only positron emission tomography (PET) allows quantitative assessment of myocardial blood flow using radiotracer kinetics. PET provides a high spatial resolution detection of myocardial metabolic abnormalities and currently represents the most valuable imaging analysis for diagnosis and prognosis in DM.

Therapeutic options and clinical implications

High prevalence of CAD and cardiovascular complications in diabetic patients are cause of great concern and main treatment force in daily cardiology practice. The existence of specific diabetic cardiomyopathy is scientifically proved and is present, which urges us to think more carefully on metabolic changes that precede a disease and lead to long-term functional impairment. Strict metabolic control of glucose levels and all risk factors together with early screening for diabetes in high-risk population is most probably the way we should act in order to limit or postpone development of diabetic cardiomyopathy. Management approach should be aimed at CV prevention. This includes changes in lifestyle, improvement of diabetic control, lipid lowering therapy, management of coexistent hypertension and CAD if present, and management of heart failure with preserved and eventually reduced LVEF. Improvement of glycemic control (with HbA1c <7%) has been shown to be associated with lower diabetic microvascular complications, which has important pathogenic role in the development of DCMP. Additional development of hypertension and CAD should be treated based on latest disease guidelines.
The European Society of Cardiology and the European Association for the Study of Diabetes recommend ACE inhibitors (or Angiotensin-II-receptor-blockers) and Beta-blockers as first line therapy for patients with heart failure and diabetes (Class I, Level C). Diuretics are beneficial for symptomatic treatment of patients with heart failure. Great trials (SAVE, ATLAS, CONSENSUS, GISSI 3) have shown ACE inhibitors to be important in reduction of cardiovascular mortality and improvement of quality of life. Recommendation for the use of beta blockers is based on the results of diabetic subgroups in studies such MERIT-HF, CIBIS II, COMET and COPERNICUS [40,41].

Conclusions

In this review we present data that support the existence of diabetic cardiomyopathy as a distinct clinical entity. The pathophysiology of the condition still remains questionable, but includes interstitial fibrosis, cardiomyocyte loss, impaired energy utilization, small vessel disease, and neuropathy. Functional consequences of the above changes include diastolic and systolic dysfunction, which may manifest as dyspnea and exercise intolerance. Risk factors such as hypertension, atherosclerosis, and dyslipidemia are common in diabetic patients and further compromise cardiac status. Currently, no specific therapeutic strategies can be recommended for diabetic cardiomyopathy. Management of traditional risk factors and lifestyle modification established in the treatment of cardiac disease should be intensively applied. Further research of the molecular basis of diabetic cardiomyopathy is needed in order to introduce more appropriate therapies for these patients

Conflict of interest statement. None declared.

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Original article

SOME ASPECTS OF NEPHROTOXICITY OF PARACETAMOL AND KETOPROFEN IN PATIENTS WITH RHEUMATHOID ARTHRITIS

НЕКОИ АСПЕКТИ НА НЕФРОТОКСИЧНОСТ ОД ПАРАЦЕТАМОЛ И ОД КЕТОПРОФЕН КАЈ ПАЦИЕНТИ СО РЕВМАТОИДЕН АРТРИТИС

Dejan Spasovski[1], Sonja Genadieva-Stavric[2] and Tatjana Sotirova[2]

University Clinic of Rheumatology[1], University Clinic of Hematology[2], "Ss Cyril and Methodius" University, Medical Faculty Skopje, Republic of Macedonia

Abstract

Introduction. To determine the effect of initial therapy with Paracetamol and Ketoprofen on glomerular and tubular integrity in rheumatoid arthritis (RA), to quantify nephrotoxicity of these two drugs by measurement of enzymuria, which correlates with the damage of tubular epithelium. Microalbuminuria is used as a marker for glomerular damage, and urine excretion of N-Acetyl-b-D-glucosaminidase (NAG) as an indicator of proximal tubular damage.

Methods. Using colorimetric method for determination of NAG, and immunoturbidimetric method for microalbuminuria, samples of 70 participants were examined (35 RA patients treated with Paracetamol only, 35 RA patients treated with Ketoprofen). The follow-up was in 5 time-intervals in the course of 24 weeks.

Results. There was a moderate correlation between NAG and microalbuminuria (r=0.16) in the group of patients treated with Paracetamol only, and a moderate correlation (r=0.28) in the group of patients treated with Ketoprofen. NAG enzymuria in size, by number of patients Registered, and time of appearance, was greater and appeared earlier in the Ketoprofen group compared to the Paracetamol group.

Conclusions. Ketoprofen is more potent NAG inductor and provokes greater tubular enzymuria than Paracetamol. Results from our study confirm safety in use of Paracetamol and Ketoprofen in everyday clinical practice.

Keywords: N-acetyl-β–D-glucosaminidase, microalbumin, pheumathoid arthritis, paracetamol, ketoprofen

Апстракт

Вовед. Да се одреди ефектот на иницијалната терапија со парацетамол и со кетопрофен врз гломерулярниот и тубулярниот интегритет кај пациенти кои боледуваат од РА, да се квантифицира токсичноста на овие медикаменти преку мерење на ензимската екскреција, која колерира со степенот на оштетувањето на тубулярниот епител; Микроалбуминуријата е употребена како маркер за гломерулярно оштетување, а уринарната екскреција на N-Acetyl-β-D-Glukozaminidaza (НАГ) како индикатор за проксимално тубулярно оштетување.

Методи. Користејќи ја колориметриската метода за одредување НАГ, како и имунотурбидиметриска метода за детекција на мукроалбуминурија, испитани се примероци на 70 партиципанти (35 РА третирани само со парацетамол, 35 РА пациенти со кетопрофен), проследени во пет временски интервали, во тек на 24 недели. РФ е одреден со тест за аглутинација (латекс РФ тест) кај истите партиципанти.

Резултати. Постои умерена корелација меѓу НАГ и микроалбуминуријата (r=0,16) кај групата пациенти третирани со парацетамол, додека умерена корелација (r=0,28) кај групата со кетопрофен. НАГ ензимурија, по обем, по бројот на испитаници кај кои се регистрира и по времето на појавување е поголема и многу побрзо се јавува при употреба на кетопрофен, во однос на парацетамол.

Заклучок. Кетопрофенот е попотетен НАГ индуктор и дава поголема тубуларна ензимурија од парацетамолот. Добиените резултати во нашата студија ја потврдија безбедноста на парацетамолот и на кетопрофенот во секојдневната клиничка практика, во третманот на РА.

Клучни зборови: N-acetyl-β-D-glukozaminidaza, микроалбуминурија, ревматоиден артритис, парацетамол, кетопрофен

Correspondence to: Dejan Spasovski, University Clinic of Rheumatology, "Vodnjanska" 17, 1000 Skopje, R. of Macedonia; Phone: +389 2 31 47 668; E-mail: sdejan36@yahoo.com

Introduction

The use of drugs in the treatment of rheumatoid arthritis (RA) aims to shorten disease duration and prevent complications. Treatment with basic drugs somehow fulfils the expectations. There have been a lot of findings recently which show that drugs can damage certain organs caused by their toxic effect due to their accumulation in the organs.

Many experiments were realized in the previous two decades aimed to monitor the toxic effect of pharmacotherapy on kidneys. These results are used as a base to follow-up the influence of drugs in different kidney diseases. In these experiments, beside immunologic, radiologic and cytologic analyses, biochemical analyses also play an important role in detection of certain pathologic conditions caused in the course of treatment.

Among them, determination of the activity of enzymes and their isoenzymes in the serum, urine and renal tissue has an important role.

Very often, therapeutic drugs (NSAIDs, drugs that modify disease activity-(DMRADs), Paracetamol, immunosupressive and cytotoxic drugs, might have some nephrotoxic effect. The drug dose is very often not adjusted according to patient's condition that can cause some unwanted effects, especially those related to kidney failure due to their accumulation in the kidneys. This can be seen in long-term RA therapy.

Experiments done so far have shown that there is no indicator, tracer or marker that reveals on time the nephrotoxicity caused in the course of a disease. Efforts are made to detect these secondary (unwanted) effects by analysis of certain enzyme activity in the urine.

Diagnostic and prognostic significance of biotracers

In the contemporary medicine there is a tendency to find the most specific and most sensitive biomarkers as disease indicators and diagnostic tools for follow-up of the successful treatment.

Abundant research has been made in order to choose potential biomarkers that would be important in the clinical practice, giving the best diagnostic information. Especially important were biomarkers' analytical and clinical application and their cost-benefit.

Useful biomarker has to fulfil some criteria:

1. To have relatively high tissue-specific concentration, and low concentration in other tissues.
2. To be adequately distributed subcellularly, so that after the cell damage can be easily found in the examined fluid.
3. To be constant long enough for following its concentration.
4. To be able to be detected with sensitive analytical methods.
5. To be determined the cut-off values have to be determined, taking into consideration the clinical sensitivity and specificity.

Renal markers for estimation of renal dysfunction

Urine enzymes could originate from plasma, lymph nodes of the urinary tract, epithelial cells of the urinary tract, white blood cells, red blood cells and kidneys. There are about 40 different enzymes that belong to different groups: oxidoreductases, transferases, hydrolases, lyases. Only isomerases and ligases are not found in urine. Such a large amount of enzymes in the urine shows the dominant role of the kidney in their excretion.

Several classes of measurable proteins in the urine are used for estimation of the nephrotoxicity.

1. Enzyme with a high molecular weight, that is not usually filtrated in the glomerulus, originating from the proximal tubule (microsomal AAP, NAG, γ-GT).
2. Intermediary proteins that are usually filtrated in the glomerulus in very small amounts are reabsorbbed in the tubules in a large amount (microalbumin, transferrin).
3. Low-molecular weight proteins that are normally filtered in the glomerulus and are reabsorbed in the tubules (β2 microglobulin).

According to their subcellular location these enzymes could be divided into membranous **(**AAP, γ-GT,AF), lysosomal (NAG, β-GLU, β-GAL, lysozyme), mitochondrial (MDH, γ-LDH), and cytoplasmic (LDH). With the development of histochemistry a detailed insight was made in the enzyme distribution in different nephron structures. Their presence is lower in glomeruli than in tubules. The specific enzyme distribution in the nephron enables detection of the spot that is damaged as a sequel of nephrotoxic agents. Examination of the cell membranes of the brush epithelium of the proximal tubules prove the localisation of the alanine amnopeptidase (AAP) in 90%, alkaline phosphatase (AP) in 70% and γ-glutamyl transpeptidase (γ-GT) in 50% of the whole enzyme activity in the kidney. The examinations reveal that tubular part of the nephron is rich with enzymes. Brush border is very sensitive in changing in their physiological status, hence the release of the superficial enzymes could be used as a marker in primary and secondary renal impairments due to different drugs and toxins [1,2].

Of all the urinary enzymes, U-NAG **(**urinary) has been extensively examined. It belongs to the class of hydrolases present in a large amount in the lysosomes in the proximal tubular cells [8]. In the human body and biological fluids there are two major enzyme forms: A (Acid) and B (Basic) [3-5]. Percentage of A isoform (U-NAG-A) is the greatest in normal urine [6,7].

At the end of the cell maturation process it is found in soluble form in the cytosol. Thus, its excretion is associated with the exfoliative turnover and is noted as func-

tional enzymuria. B isoform (U-NAG-B) depends on the maturation and is closely connected with the basal membrane in which it is present. Due to this location of the B isoform (U-NAG-B), it is massively released in the tubular lumen only in the case of cytolytic tubular lesion. Its presence in the urine correlates with the cell lysis and is marked as lesion enzymuria [8,9]. NAG could also be detected in the circulation. But, plasma NAG could not pass over intact glomerular membrane because of its high molecular weight (140.000 daltons). Therefore, in healthy individuals the urinary NAG is a result of the enzyme amount released from the renal tubular cells [10] and is a very sensitive marker for renal tubular damage [11-14].

Urine albumin (microalbuminuria)

Albumin (molecular weight-66 KDa) is quantitatively the most important plasma and urine protein. Approximately 30% of urine proteins belong to albumin, and it is a good indicator for estimation of the changes in glomerular permeability. Such changes happen in patients with diabetic and hypertensive nephropathy, nephritic syndrome, preeclampsia and glomerulonephritis. Urine albumin excretion has high individual variability and depends on the physical activity and food variations. From pathophysiological point of view microalbuminuria could be caused by the increased glomerular permeability of albumin, increased glomerular pressure and/or decreased tubular albumin reabsorption. Renal endothelium is intimately involved in the regulation of these processes [15,16].

Renal impairment due to use of Paracetamol and Ketoprofen

If a drug is transported in proximal tubules via pinocytosis then the hypothesis that nephrotoxicity is caused by lysosomal dysfunction due to drug precipitation in lysosomes is proved. Vacuoles fulfilled with proteins are transported in the middle part of the cell, where they are united with the existing lysosomes. Hydrolytic enzymes catabolize proteins and the new products are suitable for recirculation.
In the mechanism of Methotraxate nephrotoxicity two moments are very important:

- Active secretion in proximal tubules with the same degree of reabsorption;
- Active transport inside the proximal tubules in the antiluminal side with restricted movement of tubular fluids. It is proved that the toxic agent can pass through cell membranes, entering the lysosomes in a non-ionised form, and thus it is trapped in these organels due to the low pH.
- Possible mechanism of nephrotoxicity could be due to interference of the normal lysosomal digestion which leads to lysis of the lysosomal membrane, and tranfer of the acid hydrolases in the cell cytosol of the proximal tubules, which is manifested later with necrosis.
- Possible pathways for entrance in the epithelial cells are as follows:
- Apical membrane transportation via pinocytosis with an adequate drug
- uptake (chemotherapeutics, aminoglicosides, cephalosporins, diuretics and other toxic drugs) inside the lysosomes.
- Apical membrane transportation via some unknown way which complements the process of pinocytosis.
- Basolateral membrane transportation.

Material and methods

The diagnosis of patients included in this study was based on the revised diagnostic criteria for classification of rheumatoid arthritis proposed in 1987 by the American Association for Rheumatism (ARA) [17]. In order to include the patient in the group with RA, he should fulfill at least 4 of the 7 criteria. Criteria 1-4 should persist for at least 6 months.
The study comprised 35 patients with RA (20 women, 15 men), treated with Paracetamol, and 35 patients with RA (22 women, 13 men) treated with Ketoprofen. Their average age was 55.53 years (±8.42), range (40-65 years), in the group treated with Paracetamol, and 53.24 years (±10.36) range (29-65 years) in the group treated with Ketoprofen. The mean disease duration from the begining was 40.11 months (±40.23 months), range (1-168 months). None of the patients had previous or current history of renal disease. None of the patients previously used NSAIDs. Other patients denied use of other drugs such as golden salts, antibiotics or diuretics. Specimens have been collected in the period of 2 years.
Inclusion criteria: Patients with RA, aged 18-65 years, previously not treated with NSAIDs or DMARDs were included in the study.
Exclusion criteria: We excluded patients with diseases or conditions that could have direct or indirect influence on the study results:

1. Patients younger than 18 years.
2. Patients with previous history of disease of the spleen, thyroid gland, liver, kidneys, hematological, cardiovascular, neurological, autoimmune and lung diseases.
3. Patients with diabetes mellitus, febrile conditions, acute infections, neoplasms.
4. Patients with uric arthritis, SLE, mixed connective tissue disease, vasculitis.
5. Patients with history of blood transfusion and patients with body overweight.
6. Patients with history of use of drugs from the baseline.

7. Patients that in 0 point had an increased level of glucose, serum and urine urea and creatinine, blood hypertension, smokers and blood and enzyme disorders.
8. Patients previously treated with salycilates, antibiotics, golden salts or diuretics.
9. All patients took part in this study voluntary, so the ethics criteria for this study were fulfilled.

Clinical estimation of disease activity

Clinical estimation was made by a subspecialist rheumathologist. Disease activity was estimated using DAS 28 index (Disease Activity Score-DAS 28) [18-20]. The index uses mathematical formula to obtain unique composite quantitative score, which consists of: palpabile painful joints (maximal number 28), swollen joints (maximal niumber 28), erythrocyte sedimentation rate (ESR) and patient's estimation of disease activity (0-100 mm), Visual Analogue Scale (VAS) and morning stiffness (minutes).
DAS 28 index ranges from 0 to 10 and score <3.2 qualifies the disease as low active.

Laboratory estimation

For clinical estimation of the disease it is necessary to examine the following laboratory variables: complete blood count, reactants of the acute phase, ACPA-antibodies, C-reactive protein (CRP), rheumatoid factor (RF) and erythrocyte sedimentation rate (ESR), alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), lactate dehydrogenase (LDH), serum urea, and serum creatinine. Urine samples are taken not only for routine analyses, but also for determination of NAG and microalbuminuria.

Detection of microalbuminuria with immunoturbidimetric assay (Randox Laboratories limited)

Principles:

Undissolved sample is added to the puffer with antibodies specific for human serum albumin. The absorbance (340 nm) is proportional with the albumin concentration in the urine sample. With the construction of the standard curve from the standard absorbance, one can determine the albumin concentration in the sample. Determination is automatic with the use of DAKO tests.
Urine sample and its storage:
The middle stream from the morning urination is taken. It is centrifuged before the use in order to use purified supernatant.
Reference values: microalbuminuria 2.0-20.0 mg/L.

Determination of the activity of N-acetyl-β-D-glucosaminidase (NAG): colorimetric assay (roche)

Principles:
3-cresolsulfonphthaleinyl-N-acetyl-β-D-glucosaminide as sodium salt is hydrolyzed from NAG releasing 3-cresol-sulfonephthalein, sodium salt (3-cresol purple) which is measured photometrically on 580 nm wavelength (Roche Mancheim tests). The examined urine is centrifuged and the supernatant is taken.
Reference values: NAG in urine 0.27-1.18 U/mmol creatinine.
Serum urea was determined with the "Kassirer" method.
Reference values: serum urea 3-7.8 mmol/L.
Serum creatinine was determined with the "Jaffe" method.
Reference values: serum creatinine 45-109 μmol/L; urine creatinine 7-17μmol/dU.
C-reactive protein (CRP) was determined with the agglutination assay (Latex CRP test) (BioSystems S.A. Reagens &Instruments Costa Brava 30, Barcelona, Spain).
Reference values: <6 mg/L CRP in serum
Rheumatoid factor (RF) was determined with the agglutination assay (Latex RF test) (BioSystems S.A. Reagens& Instruments Costa Brava 30, Barcelona, Spain).
Reference values: <8 IU/ml inserum.
For determination of erythrocyte sedimentation rate (ESR) the quantitative method Westergren test was used.
Reference values: for men 7-8mm, for women 11-16 mm.

Statistical analysis

To test the significance of the differences between two arithmetic means i.e. proportions the Student's t-test was used. To compare the mean values of certain numeric parameters between the two groups the Wilcoxon matched test for independent parameters was used. Sensitivity and predictivity for positive and negative test of the examined markers was determined with the sensitivity and specificity test. P-value between 0.05 and 0.1 was considered statistically significant. Data analysis was performed with the Statistica 7.0 statistical package.

Results

The analysis of the group of patients treated with Paracetamol in comparison with the distribution of patients according to NAG values in the four samples has shown that NAG values were registered in 20 patients in the 12^{th} week, when the degree of the mean urine NAG value was highest (1.20±1.04) (Table 1).

Table 1. NAG, microalbuminuria in the group of patients with Paracetamol and Ketoprofen

	GROUP PARACETAMOL N=35		GROUP KETOPROFEN N=35	
	*NAG + >1.18 (U/mmol/crea) value (M±SD)	Microalbuminuria + >20 (mg/L) value (M±SD)	NAG + >1.18 (U/mmol/crea) value (M±SD)	Microalbuminuria + >20 (mg/L) value (M±SD)
0	1.13±0.54	12.91±10.07	0.93±0.48	16.35±7.41
time	13	5	13	5
4	1.17±0.48	14.1±1.07	1.27±0.47	18.80±0.33
weeks	18	5	18	7
8	1.19±0.67	11.91±11.23	1.58±1.40	16.50±9.69
weeks	19	4	23	4
12	1.20±1.04	12.08±10.68	1.80±0.33	15.50±8.58
weeks	20	2	26	2

*NAG-positive value (>1.18 U/mmol/crea); Microalbuminuria - positive value (>20mg/L);
** Data are expressed as mean values M±SD and as number of patients with values in normal range or above normal

The analysis of the group of patients treated with Paracetamol in comparison with the distribution of patients according to NAG values in the four samples has shown that NAG values were registered in 26 patients in the 12th week, when the degree of the mean urine NAG value was highest (1.80±0.33) (Figure 1).

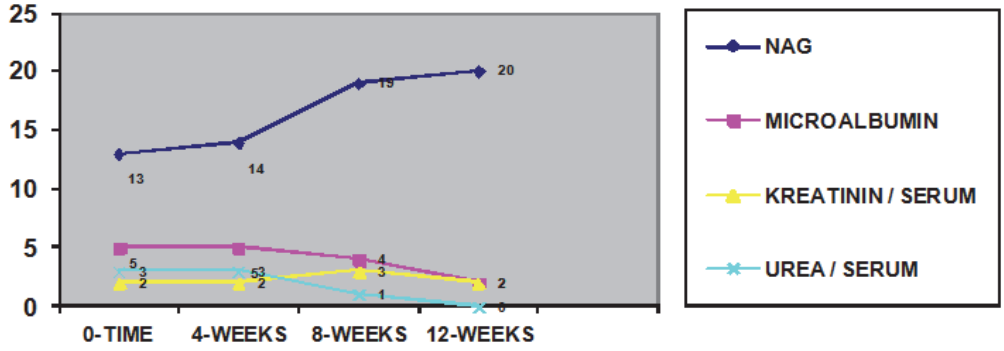

Fig. 1. Distribution of patients in the group with Paracetamol according to the increased values of NAG, microalbuminuria and other laboratory variables in the four samples.

Testing the significance of the differences in both groups in the 0 (zero) sample in the group of patients treated with Paracetamol, the mean value of the NAG enzymuria was in the range 0.93±0.48, while in the group of patients treated with Ketoprofen in the range 1.59±0.67. This result has demonstrated that Ketoprofen is more potent NAG indicator in comparison with Paracetamol both in range and in time of appearance.

In the group of patients treated with Paracetamol, regarding the distribution of patients according to the values of microalbuminuria in the four groups, increased values of microalbuminuria were registered in 5 patients in the 4th week, when the degree of microalbuminuria was highest 14.1±1.07.

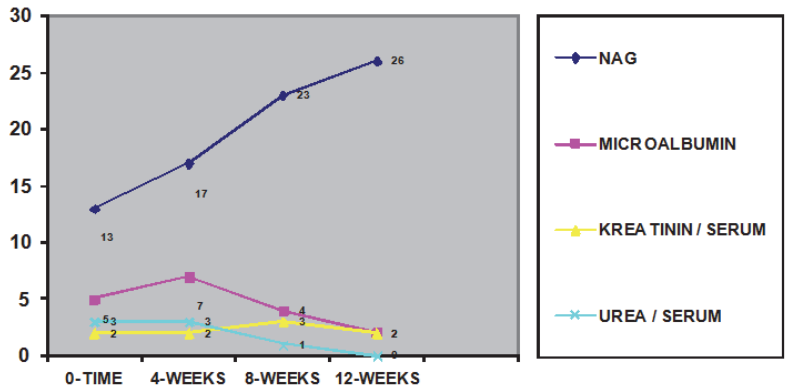

Fig. 2. Distribution of patients in the group with Ketoprofen according to initial values of NAG, microalbuminuria and other laboratory variables in the four samples.

The analysis of the distribution of patients according to microalbuminuria values in the four samples, in the group of patients treated only with Ketoprofen, can conclude that micrioalbuminuria is present at 7 patients in the 4th week, when the degree of microalbuminuria is highest 18.80±0.33 (Figure 2).

Testing the significance of the differences in both examined groups in the zero sample, mean value of microalbuminuria was in the range 0.53±0.48 in the group of patients treated with Paracetamol, while in the group of patients treated with Ketoprofen it was 0.67±0.57. Paracetamol had identical values of microalbuminuria compared to Ketoprofen.

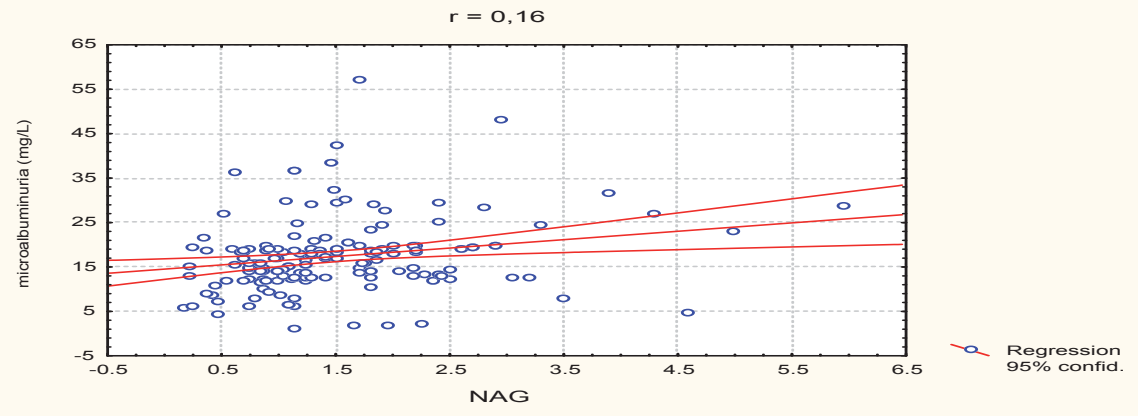

Fig. 3. Pearson's coefficient of correlation (r) between values of NAG and microalbuminuria in the group treated with Paracetamol. There is weak correlation between NAG and microalbuminuria (r=0.16)

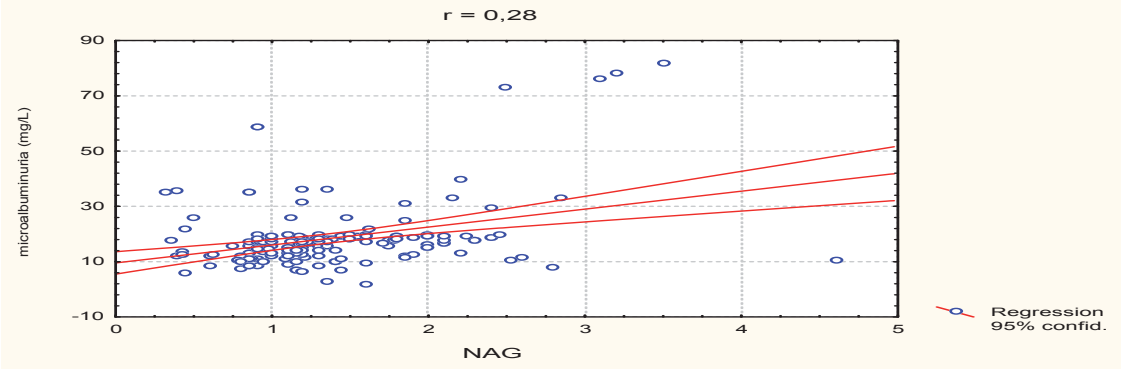

Fig. 4. Pearson's coefficient of correlation (r) between values of NAG and microalbuminuria in the group treated only with Ketoprofen. There is moderate correlation between NAG and microalbuminuria (r=0.28)

Pearson's $\chi 2$ test showed a moderate correlation between NAG and microalbuminuria (r=0.28) between the increase of the NAG values and microalbuminuria in the four samples in the follow-up period of 12 weeks in the group of patients treated with Ketoprofen alone (Figure 3).

Pearson's $\chi 2$ test showed a statistically significant correlation (r=0.16) between the increase of the NAG values and microalbuminuria in the four samples in the follow-up period of 12 weeks in the group of patients treated with Paracetamol alone (Figure 4).

Discussion

Traditional treatment of RA includes non-steroid anti-inflammatory drugs (NSAIDs), drugs that modify the disease (DMARDs), steroids, imunosuppressive and cytotoxic drugs. Methotrexate in a low dose regime is the most frequent drug from the group of DMARDs, while from the group of NSADs the most used drugs are Ketoprofen (Niflam^R, Ketonal^R), and Paracetamol.

The approach for estimation of the drug nephrotoxicity is possible only with drugs that have dominant proximal tubular excretion, such as Methotrexate, Ketoprofen, Paracetamol and golden salts.

Such approach for estimation of the drug nephrotoxicity is not applicable for other drugs from the baseline used in the treatment of RA, such as resochin, sulphasalazine and leflunomide, due to the predominant hepatobiliary secretion. There are no literature data about the toxic effect of these drugs on proximal tubular dysfunction.

In untreated RA tubular and much less gromerular function are primarily affected [21]. Glomerular integrity is basically intact in the examined groups of RA patients with the use of Paracetamol and Ketoprofen. The initial increase in the activity is a result of the changes in cell synthesis and enzymuria cannot be always the result of the lytic or necrotic processes.

Paracetamol does not trigger a significant damage of the renal proximal tubules in most of the examined patients. Nephrotoxicity of Ketoprofen is higher in comparison with Paracetamol.

Ketoprofen is more potent NAG inductor in comparison with Paracetamol. NAG induction is higher and appears earlier when using Ketoprofen versus Paracetamol.

Our results correspond with the findings in the literature [22-26]. Early detection of the increased NAG enzymuria or appearance of the microalbuminuria before the beginning of the drug use could be useful compared with the possible toxicity probably related with impared renal clearance.

There are no changes in the clinical indicators of the renal function compared to degradation products of the nitrogen metabolism (serum creatinine, serum urea) in the course of the disease. The least sensitive markers for early nephrotoxicity caused by Ketoprofen and Paracetamol are the serum creatinine and urea concentration, as well as the level of calculated creatinine clearance. These tests point out to the changed, decreased glomerular filtration, but not to changes in the renal tubular function. We think that the use of these parameters could be applicable in the clinical practice in cases with long-term therapy with Ketoprofen, Methotrexate and Paracetamol combined with antibiotic therapy, when they can show impairment of the gromerular filtration.

Conclusion

Results obtained in our study proved the safety of Paracetamol and Ketoprofen in the treatment of RA patients.

Measures taken for prevention of nephrotoxicity are: follow-up of the renal function by regular check- of the enzyme activity in the urine, estimation of the effecttivness of the exfoliative turnover on tubular cells, avoidance of frequent use of drugs and individual adjustment of the drug dosage.

Complementary diagnostic tools are determination of the urine NAG together with urinary creatinine excretion as more sensitive tests for renal damage in patients with RA.

Conflict of interest statement. None declared.

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Original article

LASER LABIAL FRENECTOMY IN PEDIATRIC PATIENTS

ЛАСЕРСКА ЛАБИЈАЛНА ФРЕНУЛЕКТОМИЈА КАЈ ПАЦИЕНТИ НА ДЕТСКА ВОЗРАСТ

Marina Kacarska[1], Maja Gjorovska[2] and Biljana Dzipunova[3]

[1]Department of Oral Surgery, Faculty of Dentistry, University Ss.Cyril and Methodius, [2] Department of Oral Surgery, University Dental Clinical Center St. Pantelejmon, [3]Department of Orthodontics, Faculty of Dentistry, University Ss. Cyril and Methodius Skopje, Republic of Macedonia

Abstract

The paper presents the specifics of a laser-assisted labial frenectomy in a pediatric patient, with emphasis on the surgical technique, the laser parameters, patient's compliance and postoperative outcome. A 9-year-old girl was referred to the University Department of Oral Surgery for labial frenectomy for orthodontic reasons. The clinical examination and evaluation revealed the presence of an aberrant labial frenum (class IV according to Placeket *et al*.) and a 3 mm wide medial diastema. A penetrating frenum caused a significant problem in the closure of the diastema during the orthodontic treatment, and a frenectomy was indicated. A conventional frenectomy is carried out with a scalpel excision followed by placement of few stitches. Some degree of post-operative discomfort as well as the need for a return visit to remove the stitches can be anticipated. The patient was in good general health but anxious about the surgical intervenetion, and hence Er. YAG laser frenectomy was suggested. The surgery was performed with Er.YAG laser (Fotona Fidelis III) and a non-contact hand piece, working with long pulse mode (LP), energy (E) of 120 mJ, frequency of 15 Hz and power of 1.80 W. The surgery was fast and easy to perform. The cooperation with the patient during treatment was excellent. The bleeding was scarce and the visibility was not compromised. Sutures were not necessary. The postoperative period was uneventful, pain-free, without swelling or signs of infection. No painkillers or antibiotics were used**.** A fibrin coating was visible the following day. The wound healing process was completed three weeks after surgery, with minimal scar. This laser is suitable to be used in soft-tissue proceduresin pediatric patients.

Keywords: labial frenum, frenectomy, laser, Er.YAG laser, pediatric patient

Апстракт

Во овој труд авторите ги презентираат спецификите на ласерски изведена хируршка интервенција-френулектомија, со особен осврт на хируршката техника, применетите ласерски параметри, соработката и постоперативниот исход. Пациентка на 9 годишна возраст беше упатена на Универзитетската клиника за орална хирургија за изведување на френулектомија во склоп на ортодонтската терапија. Со клинички преглед констатиравме присуство на девијантен максиларен лабијален френулум (класа IV според Placek *et al*.) и медијална дијастема со ширина од 3мм. Пенетрирачкиот френулум значително го отежнуваше ортодонтскиот третман, затварањето на дијастемата и претставуваше индикација за френулектомија. Конвенционално, френулектомијата се изведува со скалпел, а раната потоа се сутурира. Оваа техника вообичаено во постоперативниот период е проследена со одредена болка, оток, и потреба од повторна посета за отстранување на конците. Токму поради овие особености, како и поради плашливоста на пациентката, беше предложена и прифатена хируршка интервенција со Er. Yag ласер. Операцијата беше изведена со Er.YAG ласер (Fotona Fidelis III), без контактен насадник, долг пулс (LP), со енергија (E) од 120mJ, фреквенција од 15Hz и сила од 18W. Интервенцијата беше брза и едноставна за изведување со овие параметри. Соработката со пациентката беше одлична за време на третманот. Крварењето беше оскудно и не ја компромитираше прегледноста на хируршкото поле. Немаше потреба од поставување сутури. Постоперативниот тек беше спокоен, без болка, оток или други знаци на инфекција. Пациентката не користеше аналгетици ниту антибиотици. Веќе следниот ден оперативното поле беше прекриено со беличасти фибрински налепи. Заздравувањето беше финализирано по три недели, со формирање на дискретна лузна.

Correspondence to: Marina Kacarska, Department of Oral Surgery, 1000 Skopje, R. Macedonia; Phone: 072 247-438; E-mail: marina_kacarska@yahoo.com

Поради горе наведените атрибути, овој ласер е особено пригоден за мекоткивни процедури кај пациенти на детска возраст.

Клучни зборови: лабијален френулум, френулектомија, Er. YAG ласер, пациент на детска возраст

Introduction

The labial frenum is a fold of mucous membrane that consists of connective tissue with elastic and collagen fibers and at times muscular fibers originating from the orbicularis oris. This fold contains vascular structures with thin peripheral nervous ramifications and is covered by stratified layered epithelium [1]. The insertion of the frenum should be at the mucogingival junction, so as not to interfere with the adhesion of the attached gingiva.
Based on its anatomical situ of insertion the labial frenum was classified as mucosal, gingival, papillary, and penetrating [2,3]. A papillary, or penetrating frenum can cause a significant problem if tension from lip movement pulls the gingival margin away from the tooth, or if the tissue inhibits the closure of a diastema during orthodontic treatment. In such cases a frenectomy may be considered. The best time for a frenectomy is shortly after the beginning of the eruption of the permanent canines.
Conventional frenectomy is carried out with ascalpel elliptical excision around the frenum with a muscle dissectionfrom the periosteum, and a wound reapproximation with sutures. Some degree of postoperative discomfort as well as the need for a return visit to remove the stitches can be anticipated. Because many dental patients, in particular children would rather not suffer the pain and discomfort generally associated with conventional surgery, an alternative approach to traditional surgical procedure is warranted.
Lasers have been utilized in surgery because they are capable of executing precise surgical incisions and offer hemostatic control. The results of the laser interaction depend on the type of laser used and the targeted tissue (whether the tissue has a high collagen, hemoglobin, or water content) [4,5].
Er:YAG laser currently has the highest absorption peak in water of any commercially available, FDA-approved dental laser. The Er:YAG laser emits infrared optical energy at 2.94 microns in the mid-infrared electromagnetic spectrum. The high water content in the oral soft tissues makes Er:YAG a useful tool in oral soft surgery, while the finest low-pulse energy and high-repetition rates make this laser an extremely precise tool suitable for delicate procedures [6].
When operating in a pulsed mode with 200-400 ms pulse widths, 5-40 microns (1 micron=1,000 millimeters) of the thermal mechanical tissue ablation (tissue removal) with as little as 5 microns of residual thermal damage is the norm. These unique characteristics of the Er:YAG laser allow for very narrow layers of thermal mechanical tissue ablation with minimal collateral thermal consequences [7].
In this article the specifics of a laser-assisted labial frenectomy in a pediatric patient is presented, with emphasis on laser parameters, surgical technique, patient's cooperation andpostoperative outcome.

A case presentation

A 9-year-old girl was referred to the University Department of Oral Surgery for upper labial frenectomy for orthodontic reason. The patient was in good health, but very anxiousabout the surgical intervention.The clinical examination and evaluation revealed existence of an aberrant labial maxillary frenum (class IV according to Placek *et al.*) and a 3mm wide medial diastema. The frenum was strong, wide-based and papilla penetrating (Figure 1).

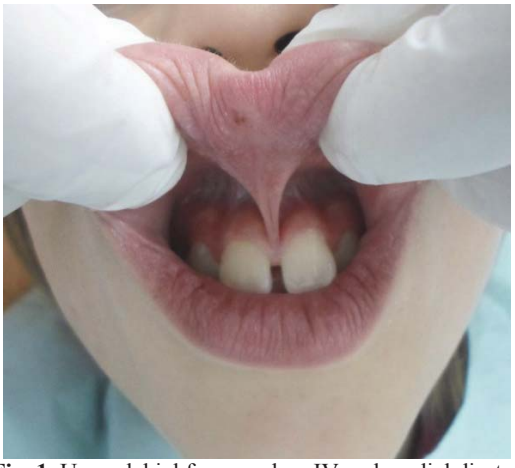

Fig. 1. Upper labial frenum class IV and medial diastema

Keeping in mind our patient's sensitivity and fear of surgical treatment, we suggested Er.YAG laser surgery for frenum removal. Numbness of the surgical field was obtained with infiltrative terminal anesthesia. Small amounts (0.2-0.3ml) of scandonest 2% with epinephrine were injected bilaterally to the frenum, and on the palatal aspect. The surgery was performed with Er.YAG Fotona

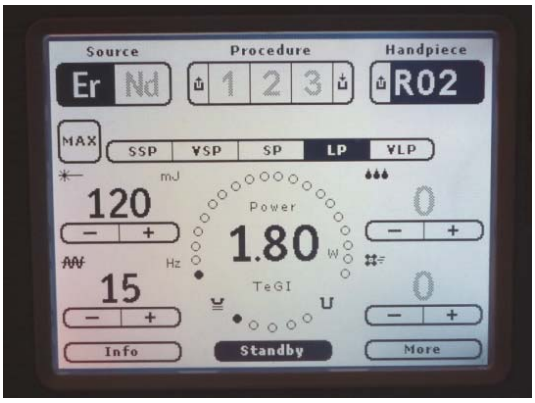

Fig. 2. Laser display with actual parameters

Fidelis III laser, non-contact hand piece, long pulse mode (LP), energy (E) of 120 mJ, frequency of 15 Hz and power of 1.80 W (Figure 2).
Stretching the lip outwards distended the frenum and the laser ablation started at the lowest point of frenum insertion (Figure 3).

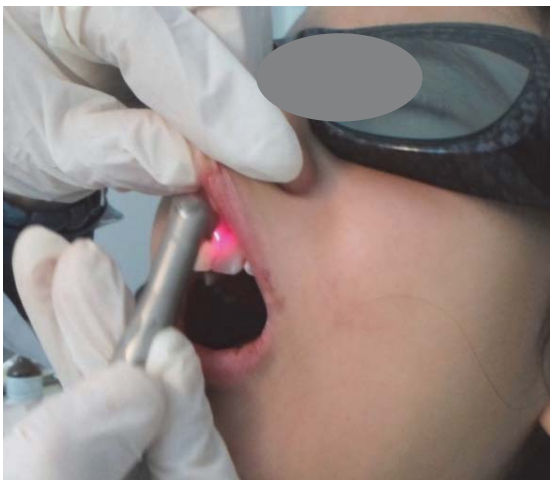

Fig. 3. Non-contact hand piece targeted the lowest point of the frenum attachment

As the tissue detached, further ablation alongside the frenum created a rhomboid-like wound, which extended towards the fornix vestibule. Careful inspectionof the woundwas followed by deeper ablation of the vertical fibers which run towards the periosteum (Figure 4 and 5).

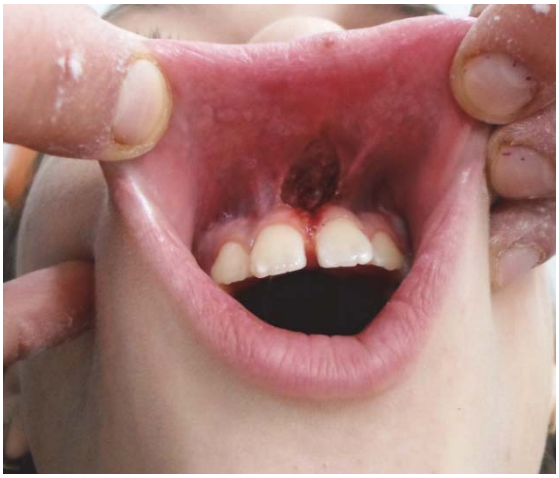

Fig. 4. Rhomboid laser wound (lateral view)

To end with, the surgical site was coagulated with a very long pulse (VLP) used in defocused mode. The bleeding was scarce, and no sutures were placed. After surgery, the patientwas advised to avoid hot and sour beverages, and to use pain killers if necessary. Usual daily oral hygiene was to be maintained, with avoidance of the trea ted area. Postoperative check-ups were conducted on the following day, seven and twenty-one days after surgery. The postoperative period was uneventful, pain-free**,** without swelling or signs of infection. No pain killersor antibiotics were used**.** A fibrin coating was visible the following day (Figure 6).The wound healing process was completed three weeks after surgery, with minimal scar (Figure 7).

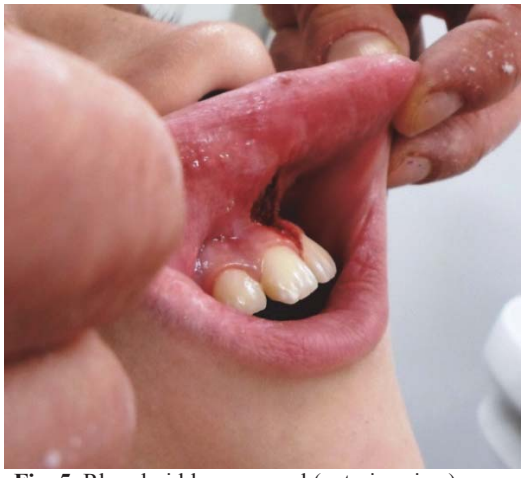

Fig. 5. Rhomboid laser wound (anterior view)

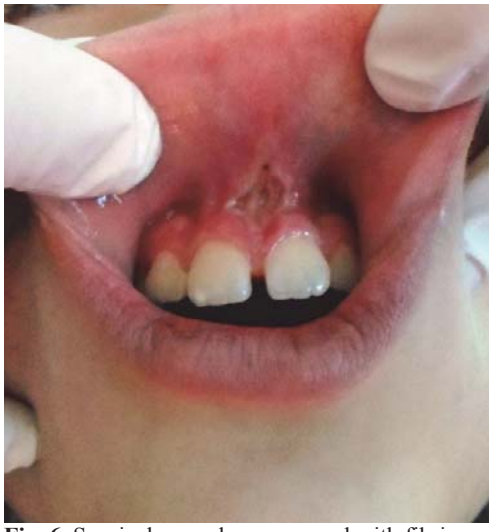

Fig. 6. Surgical wound was covered with fibrin coating the following day

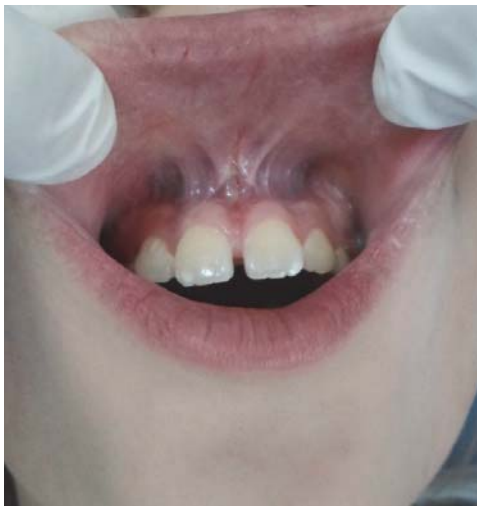

Fig. 7. Complete healing 21 days after surgery

Discussion

Labial frenectomies for orthodontic purposes are usually performed when hypertrophic labial frenum provokes diastema or hindersthe orthodontic treatment with mobile appliances. Although the current trend seems to suggest that surgical intervention is indicated mainly for patients between the ages of 9 and 11, surgical treatment may also be recommended for younger children (aged 7-8 years) to prevent possible malpositioning of teeth during the final phase of maxilla development. While some may consider this approach to be overtreatment, it should be noted that a single laser intervention performed by experienced clinicians can reduce or minimize additional orthodontic treatment at a later age [8].

In the treatment of low and overactive labial frenulum Er: YAG laser surgery has an inherent characteristic outcome of minimal bleeding, a reduced need for anesthesia and an excellent healing process [9]. Postoperative findings showed no complications. The healing process was very fast, showing fibrin coating on the following day [10]. Venugopalan V. first described the erbium tissue ablation mechanism in 1995 [11]. If water is the dominant chromophore, the mechanical integrity of the extracellular matrix (collagen) is not targeted directly. To achieve material removal, the heated water (intracellular steam) must expand first straining and then fracturing the extracellular matrix components (collagen). Hence, because Er: YAG energy has such a high absorption peak in water, the thermal damage to the tissue is kept to a bare minimum as the thermal mechanical ablation takes place (i.e. no char). The healing capacity of the laser-irradiated tissue when looked at with this logic is profound. Neev J *et al*. [12] in a thermo-optical skin conditioning study stated that less thermally induced damage means less collagen remodeling is necessary. With less collagen damage and remodeling, faster and easier healing with minimal scarring is the norm. The main benefit of the Er: YAG frenectomy for the patient is its simplicity, speed and minimal discomfort both during and after surgery. Keeping in mind our patient's sensitivity, and after discussing other treatment options, we suggested the Er.YAG laser surgery as the most convenient one. The frenum's anatomy (strong and wide-based) required infiltrative anesthesia for painless surgery, but smaller amounts of scandonest were injected (0.2-0.3ml) in comparison to conventional frenectomy. Initially we started the frenectomy with long-pulse mode (LP) and energy of 120 mJ, and then we increased the energy to 150 mJ to speed up the treatment. The LP hascutting, coagulation and disinfection purposes. The surgery was fast and easy to perform. Because the frenum penetrated the interincisal papilla, this portion was ablated also (Figures 5 and 6). The scarce bleeding did not compromise the visibility. Sutures weren't necessary. The cooperation of the patient during treatment was excellent. Postoperative findings showed no complications. No bleeding, pain or swelling appeared. These can be due to certain reported properties of Er.YAG laser. C. Walkinski [13] reported that sealing of the blood and lymph vessels minimized the postoperative swelling, while sealing of the nerve endings reduced pain and discomfort. The healing was promoted.

There was no need of another surgery. To our great satisfaction we gained the patient's trust, because the intervention was concluded the way we predicted.

Conclusion

The Er.YAG laser-assisted frenectomy is a minimally invasive surgical procedure, easy to perform and very comfortable for the patient, during and after surgery. No pain, sutures or signs of infection were present in our patient. The postoperative recovery was uneventful with promoted healing. This is a particularly suitable laser to be used in soft-tissue procedures in pediatricpatients.

Conflict of interest statement. None declared.

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Original article

THROMBOPHILIA IN PATHOLOGICAL PREGNANCIES

ТРОМБОФИЛИЈА КАЈ ПАТОЛОШКА БРЕМЕНОСТ

Jani Angelovski

Institute of Transfusion Medicine in Skopje, Republic of Macedonia

Abstract

Introduction. Many situations in pregnancy create a thrombophilia, which is believed to have a protective function, which is the result of the hormone influence, primarily by gestagenic hormones. This is a physiological condition and it helps in successful implantation of the embryo and prevention of bleeding. The presence of additional, hereditary or acquired cause of thrombophilia disrupts the natural balance and creates conditions for venous thromboembolism and consequences for pregnancy, such as miscarriage, intrauterine fetal death, delayed intrauterine growth, eclampsia and abruption of the placenta.
Methods. The study was designed as a retrospective epidemiological cross-sectional study and was conducted at the Institute of Transfusion Medicine in Skopje in the period from June to October 2016. The study included patients with current pathological pregnancies.The following laboratory analyses were conducted in all patients: hemostasis, D-dimer, antithrombin III, protein C, protein S, antiphospholipid antibodies, lupus anticoagulant, MTHFR, factor V Leiden and prothrombin mutation.
Results. The study included 41 patients, of whom 3 were excluded due to an insufficient medical history, 3 who were receiving corticosteroid therapy, 2 due to incomplete laboratory analyses and one patient with proven systemic lupus. Data analysis showed that family history of thrombophilia was present in 25%. The most common MTHFR mutation was recorded in 26 (82%) patients, followed by the factor V mutation present in 18 (55%) of the examined patients.
AT III deficiency was detected in only one patient (2%). In 12 patients (35%) a disturbed ratio of DD vs. markedly shortened APTT or inappropriately low levels of DD was registered, which is an indirect indicatorof hypofibrinolysis.
Conclusion. Pathologic pregnancy is a condition that is often associated with thrombophilia. Advanced age of a patient, family and personal history of thrombotic conditions indicate a high risk of complications in pregnancy. Due to the current increased frequency of high risk pregnancies associated with circulation problems with the placenta, there is a need for more frequent hemostatic examinations in pregnancy.

Keywords: pathological pregnancy, thrombophilia, intrauterine gestation-which halts the growth of the fetus, placental insufficiency, hemostatic tests

Correspondence to: Jani Angelovski, Institute of Transfusion Medicine in Skopje, Clinical Center "Mother Teresa" 1000 Skopje, R. Macedonia; E-mail: angelovskijani@yahoo.com

List of abbreviations DD-D-Dimers, MTHFR- methylenetetrahydrofolate reductase, FM-Fetus mortus (Foetusmortus), AT III-antithrombin 3, APTT-activated partial thromboplastin time, IUGR-gestational intrauterine growth retardation of the fetus

Апстракт

Вовед. Низа промени во бременоста креираат една хиперкоагулабилност, за која се верува дека има заштитна функција, која е резултат на хормонското влијание, пред сè од гестагенските хормони. Оваа состојба е физиолошка и помага за поуспешна нидација на плодот, како и за превенција од крварења. Присуството на дополнителна, хередитарна или аквирирана причина за тромбофилија го нарушува овој природен баланс и создава услови за венски тромбоемболизам и последици по бременоста, како што се спонтан абортус, интраутеринска смрт на плодот, забавен интраутерински раст, прееклампсија и абрупција на плацента
Методи. Студијата е дизајнирана како епидемиолошка ретроспективна студија на пресек и е спроведена на Институтот за трансфузиона медицина во Скопје, во периодот од јуни до октомври 2016 година. Во студијата беа вклучени пациентки со актуелна патолошка бременост. Кај сите пациентки беа иследувани следните лабораториски анализи: Хемостаза, Д-димери, антитромбин III, протеин C, протеин S, антифосфолипидни антитела, лупус антикоагуланс, MTHFR, фактор V Laiden и протромбин мутација.
Резултати. Во студијата беа обработени 41 пациентка, од коишто три беа исклучени поради нејасни анамнестички податоци, три поради примање кортикостероидна терапија, две поради некомплетни лабораториски анализи и една поради докажан системски лупус. Анализата на пода-

тоците покажа дека семејната анамнеза за тромбофилија е застапена кај 25%. Од лабораториеските анализи, најзастапена беше MTHFR мутацијата, регистрирана кај 26(82%), по што следеше Фактор V мутацијата, присутна кај 18(55%) од испитуваната популација.
АТ III дефицит беше регистриран кај само една пациентка (2%). Кај 12 пациентки (35%), беше регистриран нарушен сооднос на ДД, наспроти скратено АПТТ, односно несоодветно ниски вредности на ДД, што е индиректен показател за хипофибринолиза.
Заклучок. Патолошката бременост е состојба која е често асоцирана со тромбофилија. Напредната возраст на пациентката, семејната и личната анамнеза за тромботични состојби укажуваат на висок ризик за компликации во бременост. Поради зголемената фреквенција на ризични бремености, заради проблеми со циркулацијата на постелката, се наметнува потребата за почести хемостатски испитувања кај бремените.

Клучни зборови: патолошка бременост, тромбофилија, интраутеринскиот гестациски застој во растот на плодот, плацентарна инсуфициенција, хемостатски тестови

Introduction

Many situations in pregnancy create a thrombophilia, which is believed to have a protective function, and which is the result of the hormone influence, primarily by gestagenic hormones. This is a physiological condition and it helps in successful implantation of the embryo and prevention of bleeding. The presence of additional, hereditary or acquired cause of thrombophilia disrupts the natural balance and creates conditions for venous thromboembolism and consequences for pregnancy, such as miscarriage, intrauterine fetal death, delayed intrauterine growth, eclampsia and abruption of the placenta [1]. A growing number of studies indicate the connection of different thrombophilias and pregnancy complications. Robertson *et al.* have analyzed previous studies on this link and have confirmed that women with thrombophilia are at an increased risk of venous thromboembolism and pregnancy complications. However, clinical studies presented controversial results. So far, there are no controlled and randomized studies about the impact of antithrombotic therapies on reducing complications in pregnancy. Also, there are no strict recommendations on conducting a rigorous screening for thrombophilia in each pregnancy [2]. The aim of our study was to determine the presence of thrombophilia in patients with pathological pregnancies.

Materials and methods

The study was designed as a retrospective epidemiological cross-sectional study and was conducted at the Institute of Transfusion Medicine in Skopje in the period from June to October 2016. The study included patients with current pathological pregnancies. Criteria for exclusion were having another cause of secondary thrombophilia (systemic diseases such as systemic lupus erythematosus, Hashimoto's thyroiditis, rheumatoid arthritis), extreme obesity, nephrotic syndrome, dyslipidemias. The study also excluded patients already taking corticosteroid and other hormonal therapy. Demographic data (age, place of residence), gynecological history (spontaneous abortions, stillbirths, unsuccessful in vitro fertilization, EPH gestosis, preeclampsia, live births with deformities), history of deep vein thrombosis and other thromboembolic events, and family history of thrombophilia were collected. The following laboratory analyses were conducted in all patients: hemostasis, D-dimer, antithrombin III, protein C, protein S, antiphonspholipid antibodies, lupus anticoagulant, MTHFR, factor V Leiden and prothrombin mutation.

Results

The study included 41 patients, of whom 3 were excluded due to an insufficient medical history, 3 who were receiving corticosteroid therapy, 2 due to incomplete laboratory analyses and one patient with proven systemic lupus. Thus, the analysis included 32 patients aged 25 to 45 years (Figure 1). The majority of patients (27

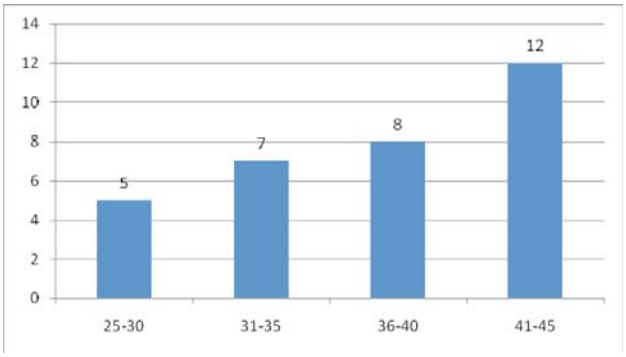

Fig. 1. Distribution by age

Table 1. Relevant data from the history of disease

	Yes	No
Family history of trombophilia n (%)	8(25)	24(75)
History of thrombotic events n (%)	5(20)	27(80)
History of miscarriages n (%)	18(55)	14(45)
History of prematurity n (%)	14(45)	18(55)
Live births with deformities n (%)	2(5)	30(95)
FM in utero n (%)	10(29)	22(71)
History of hypertension in pregnancy n (%)	7(23)	25(77)

or 84%) were over 30 years of age, of whom 12 (37%) were over 40 years of age. Seventeen of them live in rural areas and 15 in the city. Data analysis showed that family history of thrombophilia was present in 25%.
Of gynecological history, the most common complication in previous pregnancies was miscarriage registered in 18(55%) patients and premature delivery in 14(45%). Hypertension in previous pregnancies was reported in 7(23%) patients.
The most common MTHFR mutation was recorded in 26(82%) patients, followed by the factor V mutation present in 18 (55%) of the examined patients.
AT III deficiency was detected in only one patient (2%). In 12 patients (35%) a disturbed ratio of DD vs. markedlyshortened APTT or inappropriately low levels of DD was registered, which is an indirect indicatorof hypofibrinolysis.

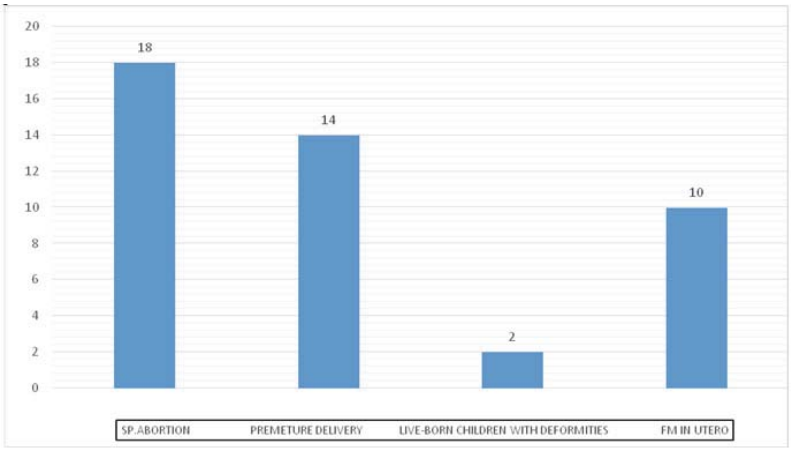

Fig. 2. Complications in pregnant patients

Table 2. Laboratory test findings

	Yes	No
AT III deficiency n (%)	1(2)	31(98)
MTHFR mutation n (%)	26(82)	6(18)
Protein C deficiency n (%)	6(22)	26(78)
Protein S deficiency n (%)	4(17)	28(83)
Factor V Laiden n (%)	18(55)	14(45)
Prothrombin mutation n (%)	7(23)	25(77)
DD / APTT (↓ Inappropriate values of DD vs. markedly shortened APTT)	12(35)	20(65)

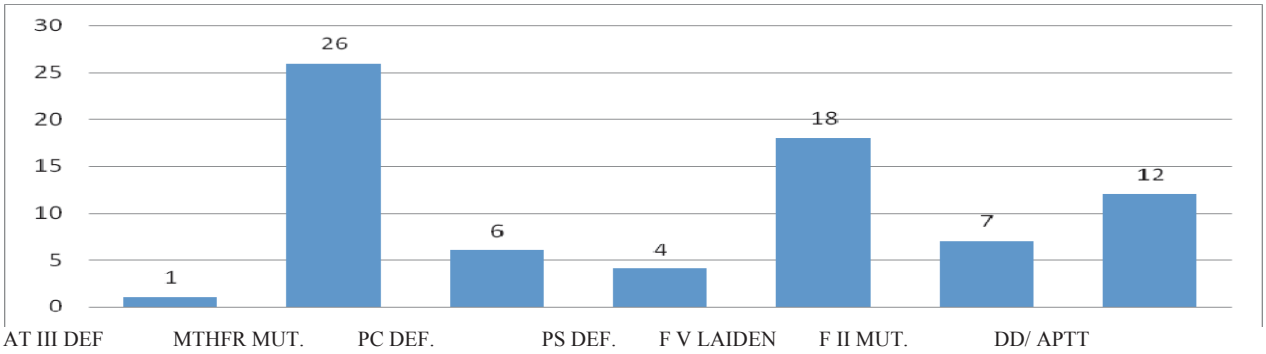

Fig. 3. Detected laboratory variances

Discussion

Thrombophilia is a hereditary or acquired condition which may be a predisposing factor for thromboembolism [1]. There are three important factors for congenital thrombophilia responsible for thromboembolic conditions in patients who have no other risk factors for thrombosis: homozygous mutation in the MTHFR, mutation Factor V Leiden and the state of hypofibrinolysis.

Preeclampsia, abruption of the placenta, intrauterine growth retardation of the fetus (IUGR) and intrauterine fetal death (IUFD) cause morbidity and mortality of the mother and the fetus. All these conditions may be associated with abnormal blood vessels in the placenta and disorders of hemostasis [3,4].
The results of our study showed that patients with current pathological pregnancy, who were referred to the Institute for Transfusion Medicine in Skopje, had a history of miscarriages (55%), premature births (45%) and

hypertension in previous pregnancies (23%). The age of the patients (84% were over the age of 30), as well as a family or personal history of thrombotic conditions indicate a high risk of placental hypoperfusion. In the case of three of the study group patients, they possessed an increased risk of abruption of the placenta due to a history of repeated miscarriages or premature births, along with one patient who experienced fetal mortality (FM) in the late stage of pregnancy. These conditions are most likely the result of thrombogenic complications in the later months of pregnancy.

In normal pregnancy, trophoblastic acted of the spiral arteries lose their muscular wall and become more elastic allowing maximum blood flow in the placenta. Abnormal interaction between the mother and the fetus leads to abnormal trophoblastic invasion of the spiral arteries, resulting in constricted blood vessels, which causes inadequate perfusion of intervillous spaces. Placental pathologists use the term placental vasculopathy to describe changes characterized by superficial endovascular abnormalities in spiral arteries, atherosclerosis thrombotic processes in spiral arteries and/or intervillous spaces. Clinically, placental vasculopathy is associated with preeclampsia, IUGR, placental abruption and in some cases fetal loss and premature birth [5].

Analysis of laboratory variances in our research has shown that the MTHFR mutation was present in 82% of respondents, the majority of which were found to have homozygous mutation. In 35% of patients, they were shown to have inappropriately low levels of D-dimer i.e. the condition of hypofibrinolysis. We Registered a significantly higher percentage of patients with a mutation in factor V Leiden than in the general population. These patients were observed to be hyperthrombogenic. Resistance to activated protein C caused by adenine, guanine 506 (A506G) and mutation of the factor V Leiden is associated with an increased risk of venous thromboembolism [6]. Heterozygosity for factor V (FV) Leiden mutation is detected in about 5% of the population and the mutation is responsible for 20-30% of venous thromboembolism. 20210 guanine adenine prothrombin mutation is associated with higher plasma concentrations of prothrombin, and increased risk of venous thromboembolism [7] and cerebral venous thrombosis [8]. Homozygosity for thymine to cytosine 677 (C677T) mutation methylenetetrahydrofolate reducetase (MTHFR) results in decreased synthesis of 5-methyltetrahydrofolate, the primary methyl donor in the conversion of homocysteine to methionine and the resulting increase in the plasma concentration of homocysteine is a risk factor of thrombosis [9]. The mutation is responsible for the reduction of MTHFR activity and is the most common cause of mild hyperhomocysteinemia, which can be found in 5-15% of the population. Concentration of homocysteine is influenced by diet. Lack of folic acid, B-6, and/or B-I2 causes an increase of homocysteine. The levels of homocysteine can be affected by a lack of cystathionine beta synthase and MTHFR C677T gene mutation [10]. Many vascular endothelial changes associated with hyperhomocysteinemia can be found in preeclampsia [11]. Candidates for anticoagulant therapy are women currently with thrombosis, history of thrombosis, thrombophilia and history of bad outcomes in previous pregnancies, or postpartum risk of VTE. Recommended treatments for these conditions are heparins, in particular low-molecular weight heparins. There is a small number of studies on the use of anticoagulants in pregnancy, and the recommendations are based on smaller series and expert opinions. However, according to present knowledge, it is believed that anticoagulant therapy improves prognosis in women with related risks [12]. The Institute of Transfusion Medicine has a long-term good experiences in preventing thrombogenic complications in patients with risk pregnancy and risk for thrombogenic complications, primarily by using low-molecular weight heparins and methylated form of folic acid.

Conclusion

Pathologic pregnancy is a condition that is often associated with thrombophilia. Advanced age of a patient, family and personal history of thrombotic conditions indicate a high risk of complications in pregnancy. Due to the current increased frequency of high risk pregnancies associated with circulation problems with the placenta, there is a need for more frequent hemostatic examinations in pregnancy, along with examinations that might identify genetic mutations that result in thrombophilia. In our effort to find the best solution for this problem, (realizing the important role that hemostatic imbalance can have in pathological pregnancies) our findings have shown excellent results in using low-molecular-weight heparins to improve placental blood flow.

Conflict of interest statement. None declared.

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Original article

PROGNOSTIC FACTORS AFFECTING SURVIVAL OF PATIENTS AFTER LIVER RESECTION DUE TO COLORECTAL LIVER METASTASES

ПРОГНОСТИЧКИ ФАКТОРИ КОИ ШТО ВЛИЈААТ НА ПРЕЖИВУВАЊЕТО НА ПАЦИЕНТИ ПОСЛЕ РЕСЕКЦИЈА НА ЦРНИОТ ДРОБ ПОРАДИ КОЛОРЕКТАЛНИ МЕТАСТАЗИ

Stefan Petrovski[1], Elena Arabadzhieva[2], Saso Bonev[2], Dimitar Bulanov[2], Valentin Popov[2] and Violeta Dimitrova[2]

[1]Department of Surgery-Clinical Hospital Shtip, PhD candidate at the Department of General and Hepato-pancreatic Surgery, University Hospital "Aleksandrovska"-Sofia, Medical University-Sofia, [2]Clinic of General and Hepato-pancreatic Surgery, University Hospital "Aleksandrovska"-Sofia, Medical University-Sofia, Bulgaria

Apstract

Introduction. Colorectal liver metastases have a poor prognosis and only 2% have an average 5-year survival if left untreated. In recent decades there has been a development in the diagnosis, treatment and palliative treatment of patients with colorectal liver metastases, and despite radical resection the average five-year survival is between 25% and 44%.
Aim. To explore the experience of the Clinic in the treatment of colorectal liver metastases, comparing it with data from the literature and based on the comparison to determine the prognostic factors that affect survival after radical surgical treatment of patients.
Methods. A retrospective study was conducted at the Clinic of General and Hepato-pancreatic Surgery at the University Hospital "Aleksandrovska"-Sofia. The study comprised the period between 01.01.2006 to 31.12.2015. It included a total of 239 cases, of whom: 179 patients underwent radical interventions, 5 palliative and 55 patients underwent explorative interventions due to liver metastases. Clinical and pathological materials were analyzed using SPSS-19 to determine the prognostic significance of a number of factors in relation to the survival: gender, age, type and localization of metastases, postoperative stage of the primary tumor, type and volume of liver resection, extrahepatic metastases, preoperative values of CEA, postoperative values (AST, ALT).
Results. Factors that correlated with lower survival type: metastases (synchronous or metachronus), localization of metastases (uni-or bilobar), presence of the regional lymph node metastases and metastases to other distant organs and the impossibility of radical resection of liver were statistically significant with multivariant analysis. Elevated preoperative value of CEA, the value of hemoglobin and stage IV disease also affected the survival of patients.
Conclusion. In patients with colorectal liver metastases only resection has potentially curative character. The surgical strategy for resection in context of increasing the percentage of patients with resectable potential is the only possible factor for long-term survival.

Keywords: colorectal metastases, radical resections, prognostic factors, survival, stage of the disease

Correspondence to: Stefan Petrovski, Department of Surgery at Clinical Hospital-Shtip, R. Macedonia; E-mail: stefan.petrovski@ugd.edu.mk

Апстракт

Вовед. Колоректалните метастази на црниот дроб имаат лоша прогноза и само 2% имаат средно 5-годишно преживување ако не се лекуваат. Во последните неколку декади се забележа развој во дијагностицирањето, лекувањето и палијацијата на пациенти со колоректални метастази на црниот дроб, но и покрај радикалната ресекција средното петгодишно преживување е помеѓу 25% и 44% .
Цел. Да се проучи искуството на Клиниката во лекувањето на колоректални метастази на црниот дроб, споредувајќи ги со податоците од светската литература, и врз основа на тоа да се определат прогностичките фактори кои што влијаат на преживувањето после радикално хирушко лекување на пациентите.
Методи. Во клиниката по општа и црнодробно-панкреатична хирургија во УМБАЛ "Александровска"-Софија е направено ретроспективно проучување помеѓу 01.01. 2006 до 31.12.2015, вклучувајќи 239 случаи претставени во Табела 1, подложени соодветно на 179 радикални интервенции, 5 палијативни и 55 експлоративни по повод колоректални метастази на црниот дроб. Клиничкопатолошкиот материјал се анализираше со помош на SPSS-19, за да се определи прогностичката значајност во однос

на преживувањето на редица фактори: пол, возраст, тип и локализација на метастазите, постоперативен стадиум на примарниот тумор, тип и обем на ресекцијата на црниот дроб, екстрахепатални метастази, предоперативни вредности на CEA, постоперативни вредности на (AST, ALT).
Резултати. Фактори кои што корелираат со пониско преживување се типот на метастазите (синхрони или метахрони), локализацијата (уни- или билобарни), присусвото на метастази во регионалните лимфни жлезди и во други далечни органи како и неможноста за радикална ресекција на црниот дроб се статистички значајни со мултиваријантната анализа. Покачени предоперативни вредности на CEA, вредноста на Hgb и IV стадиум на болеста исто така имаат влијание на преживувањето на пациентите.
Заклучок. Кај пацинетите со колоректални метастази на црниот дроб само ресекцијата има потенцијално лечебен карактер. Хирушката стратегија за ресекција во контекст на зголемувањето на процентот на пациенти кои имаат ресектабилен потенцијал е единствен можен фактор за долгогодишно преживување.

Клучни зборови: колоректални метастази, радикални ресекции, прогностички фактори, преживување, стадиум на болеста

Introduction

Colorectal cancer CRC is the third most common cancer worldwide after lung cancer and breast cancer [1,2]. A large percentage of 50-70% of patients develops colorectal liver metastases (CRLM) because of hematogenous dissemination of primary cancer [3-7]. Synchronous metastases are diagnosed in 15-25% [8-10] during the primary diagnosis of CRC and in 20-25% [11-15] in the first five years metachronous metastases develop. They represent the most common cause of death caused, so that 77% of untreated patients die in the first year, and only 14-23% survive more than three years [16-19]. Surgical resection represents the only curative treatment approach to patients with CRLM; in larger series patients treated with resection have a mean 5-year survival from 25% to 44% [15,20,21], but only 15-25% [22] of metastasis of liver are initially resectable. Poor prognosis of the disease is the cause of looking for opportunities to improve postoperative results which corresponds with defining determinants of survival.
Aim. To explore the experience of the Clinic in the treatment of colorectal liver metastases, comparing them with data from the literature, and based on the comparison to determine the prognostic factors that affect survival after radical surgical treatment of patients.

Methods and materials

A retrospective study was conducted at the Clinic of General and Hepato-pancreatic surgery at the University Hospital "Aleksandrovska"-Sofia. The study comprised the period between 01.01.2006 to 31.12.2015. It included a total of 239 patients (Table 1), of whom: 179 patients underwent radical interventions, 5 palliative and 55 patients underwent explorative interventions due to liver metastases. In addition, 119(49.8%) patients were diagnosed with synchronous metastases, 120(50.2%) patients with metachronous metastases, including 7(2.9%) with metachronous metastases with recurrence on the colon. With regard to sex structure of the patients there were 93(38.91%) women and 146(61.08%) men. Majority of patients were aged 61 to 70 years-88(36.82%), while a small percent belonged to the youngest age group under 40 years-9 (3.77%).

Table 1. Types of radical and palliative surgical interventions used for resections of patients with colorectal liver metastases, included in our study

Type of operation			
Radical N=179 (74.9%)		**Palliative / biopsy N = 60 (25.1%)**	
atypical resection	57	biopsy	55
resection of 2 segments	24	biopsy+biliary drainage	2
resection of 3 segments	18	thermoablation	1
resection of >3 segments	10	alcoholization	2
left lobectomy	15		
left hemihepatectomy	4		
right hemihepatectomy	12		
Metastasectomy	20		
resection+another procedure	19		
atypical resection+metastasectomy	9		
left lobectomy +atypical resection	5		
atypical resection+thermoablation	4		
atypical resection+alcoholization	1		

The follow-up period of the patients operated on for colorectal liver metastases in the Clinic, was 5 years after resection of the liver according to the method of Kaplan-Mayer. Statistical analysis of the collected material to determine the factors for survival was done using SPSS-19, and it included sex, age, type and localization of metastases, postoperative stage of primary tumor, type and amount of resection of the liver, extrahepatic metastases, preoperative CEA values and postoperative values (AST, ALT).

Results

The cumulative overall survival is shown in Table 2, and it was 79.6% in the first year, 25.9% in the third year, and 19.2% in the fifth year.

Table 2. Cumulative survival of patients after radical resection of colorectal liver metastases

	Cumulative survival % (Std.Error)		
	1-year	3-year	5-year
Total survival	80 (0.029)	25.9 (0.03)	19.2 (0.025)

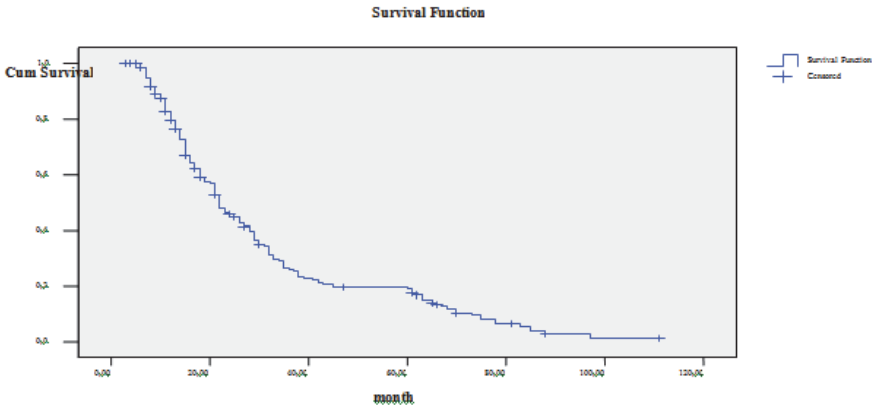

Fig. 1. Curve of survival in patients with colorectal cancer and liver metastases

Survival analysis by gender indicated that within the group of female patients 68 died (81.93%), while in the male patients group death occurred in 101(80.8%). The median survival for women with CRLM was 31.9 months and for men shorter-30.8 months. The median survival was 25 months in female patients with CRLM and 22 months in male patients. However, the results did not show statistical significance (p = 0.69, p = 0.7).

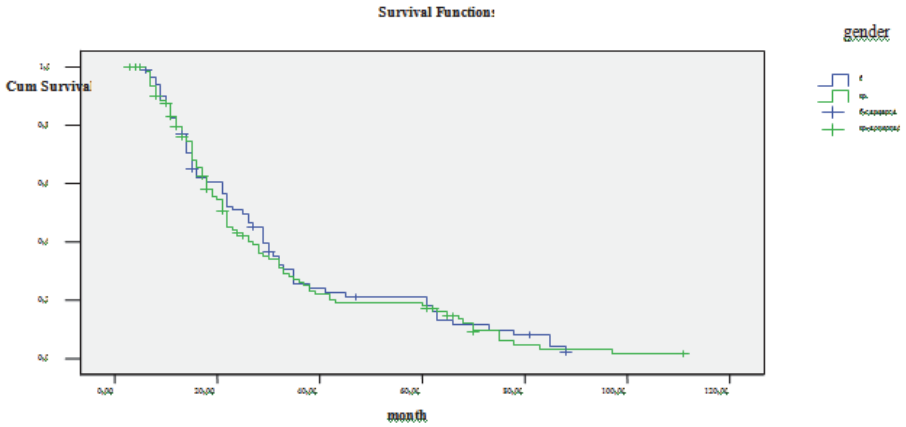

Fig. 2. Curve of survival according to sex of patients, Log Rank (Mantel-Cox) p = 0.69 Breslow p = 0.7

The analysis by age showed that the median survival was 34.3 months in patients under 40 years, 29.8 months in the age group 41-50 years, 29.2 months in patients aged 51 to 60 years, 34.1 months in patients aged 61 - 70 years and 29.2 months in patients over 70 years. However, these differences were not statistically significant (Figure 3).

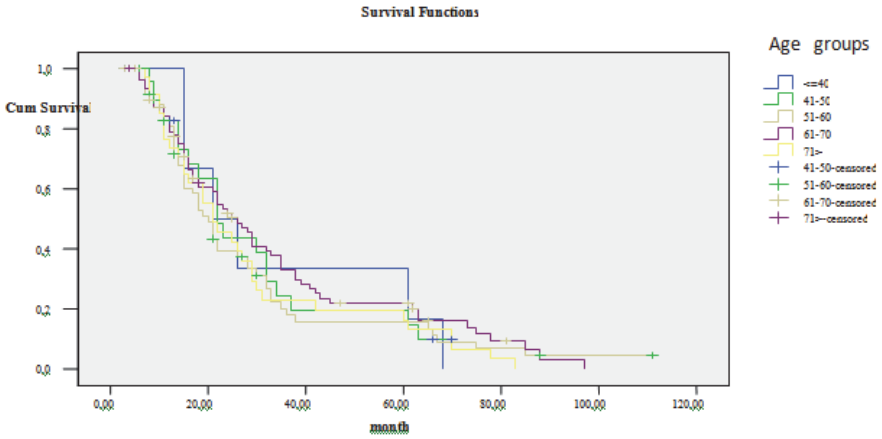

Fig. 3. Survival curves according to age, LogRank (Mantel-Cox) p = 0.78 Breslow p = 0.74

The analysis showed that the hazard ratio-Exp (B) for liver metastases was 1.49 95% CI (1.098-2.022), p=0.01. These factors suggest that the type of liver metastases in patients with colorectal cancer is a significant prognostic factor for survival. Statistical analysis showed that there was a significant difference in survival time depending on the type of liver metastases (p=0.008, p=0.002). Patients with colorectal cancer and metachronous metastases had a significantly longer survival time.

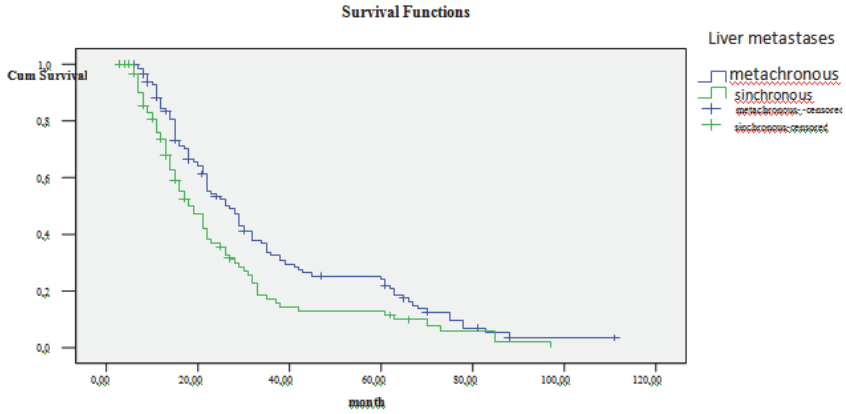

Fig. 4. Curve of survival depending on type of liver metastases

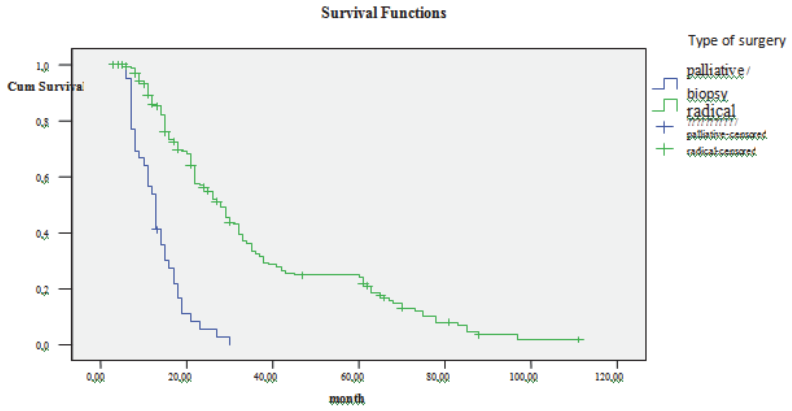

Fig. 5. Curves of survival depending on type of surgical resection

Radical intervention was also proved to be a significant factor for survival with Lesser Cox-regression analysis (p <0.0001).

The value of HP of 0.203 95% CI (0.135 - 0.306) suggests that the risk of fatal outcome in patients treated with radical intervention was 79.7% lower than in patients treated palliative or with biopsy.

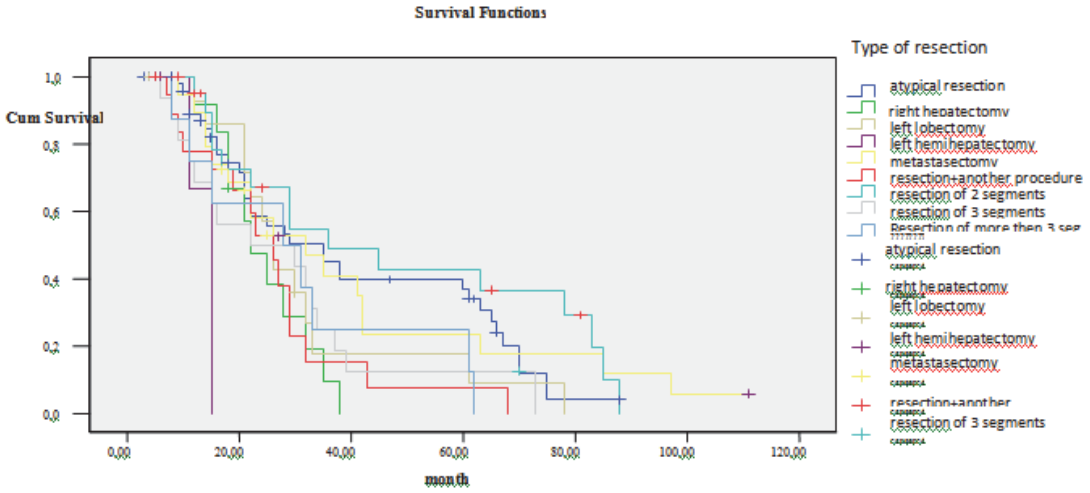

Fig. 6. Curves of survival depending on type of resection

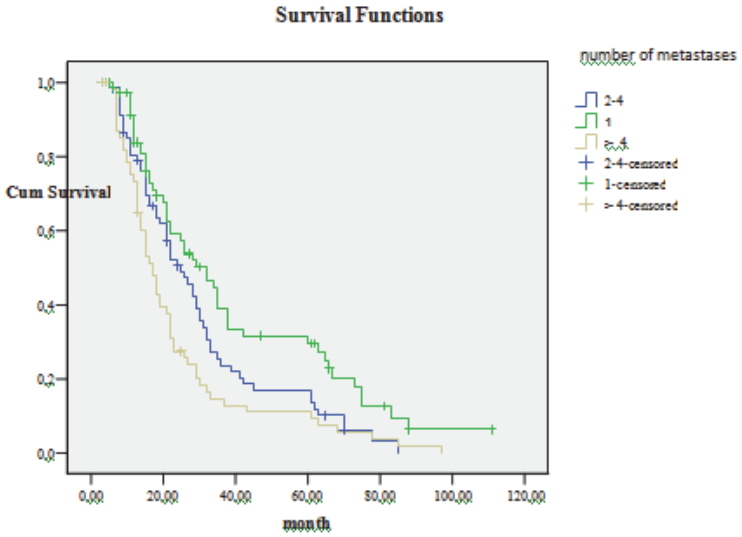

Fig. 7. Survival depending on metastases number

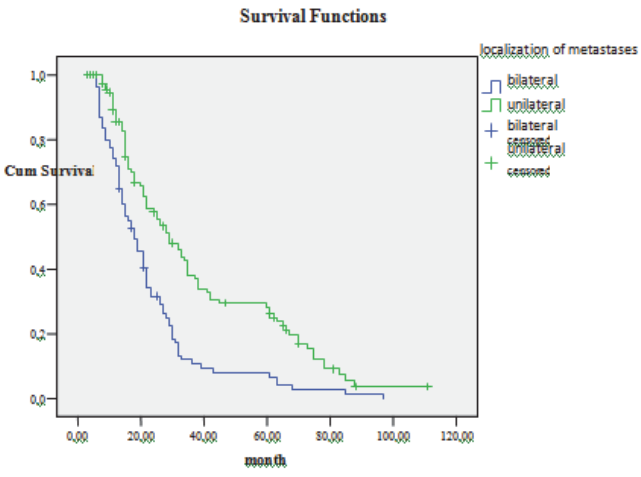

Fig. 8. Survival depending on localization of colorectal metastases

The statistical analysis of survival time showed that median survival was lowest in the group with left hemihepatectomy (about 14 months), and the highest in the group with resection of two segments (48 months). Statistical tests confirmed the difference in the length of survival among the types of liver resections as significant (p=0.004, p=0.043), and type of resection in relation to the other factors in terms of survival as non-significant. Extent of resection was also not proved as a significant factor in terms of survival.

The number of metastases was proved to be a significant predictor of survival in patients with colorectal cancer metastases of the liver. Patients with 2 to 4 metastases had a 1.5 times higher risk of fatal outcome compared to patients with one metastasis. Patients with more than 4 metastases had a twofold higher risk compared to patients with one metastasis. Statistical tests Log Rank and Breslow confirmed the difference in the length of survival time as significant (p <0.0001). Patients with bilateral localization of liver metastases survived significantly shorter compared to patients with unilateral localization of metastases.

Table 3. Cox-regression analysis on the relationship between laboratory parameters and survival of patients with colorectal metastases

	p	Exp (B)	95% CI for Exp (B)
AST	0.069	1.004	1.00-1.008
ALT	0.894	1.00	0.996-1.004
GGT	0.129	1.001	1.000-1.001
direct bilirubin	0.266	1.027	0.98-1.007
total bilirubin	0.737	0.995	0.969-1.023
PRT	0.357	1.016	0.982-1.054
INR	0.16	1.372	0.882-2.134
HGB	0.007**	0.989	0.981-0.995
CA 199	0.117	1.00	1.000-1.001
CEA	0.008**	1.001	1.000-1.002
AFP	0.621	1.038	0.896-1.201
operative time	0.631	0.999	0.997-1.002
blood loss	0.084	1.001	1.000-1.001

Values of Hgb (p=0.007) and values of the tumor marker CEA (p=0.008) were confirmed as significant predictors. The risk of a fatal outcome was reduced by 11% by increasing the HGB by 1. Increasing tumor marker CEA 1 increased the risk of a fatal outcome by 0.1%.

Discussion

The surgical resection represents the only curative treatment approach in patients with CRLM; in larger series the treated patients with resection have mean 5-year survival rate of 25% to 44% [15,20,21], but only 15-25% [22] of liver metastases are initially resectable. Numerous publications indicate that gender and age do not significantly affect the survival of patients after resection of CRLM [23-25]. Many authors who compared synchronous with metachronous metastases, found superior results in favor of metachronous metastases [26-29], and others showed similar survival rates for both types of CRLM [30,31]. Tumor size of potentially resectible CRLM has been studied as a prognostic factor with contradictory results [32]. Ercolani *et al*. [33] demonstrated that the total tumor volume of liver metastases had a stronger impact on the survival compared to the number and location of metastases. In the multifactorial prognostic model described by Rees *et al.* [34] the number of CRLM>3 represents an independent prognostic factor for low rate of survival. Better survival of patients with four or more metastases was observed by Pawlik *et al.* [35], 5-year OS median survival of 50.9%, and Kornprat *et al.* [36], 5-year survival of 33% OS. The prognostic significance of bilobar distribution of colorectal metastases became controversial. Some studies indicate the bilobar distribution as a poor prognostic factor, while others are reporting that it does not affect survival [37,38]. Tomlinson *et al*. [39] report five and ten percent survival OS of 29% and 25% with bilateral resection. Type of resection of the liver does not affect the survival of patients with CRLM. Non-anatomical resection is inferior compared to the anatomical resection regarding the marginal status, recurrent rate and survival [40]. Our study showed that the type of metastases, localization and inability to radical resection has a statistical significance in terms of survival. The type and extent of liver resection does not affect the survival, but the presence of metastases in the regional lymph glands, extrahepatic distant metastases, the elevated amount of CEA and stage IV disease have also significant effects on survival of patients after liver resection. Fong *et al*. [41] created a clinical risk score (CRS) using a regressive analysis of multiple clinical factors of patients resected due to colorectal liver metastases. They found five clinical criteria that have prognostic significance for survival: lymph node - initially positive, CEA>200 ng/ml, >1 lesion liver, lesion>5 cm, DFI less than 1 year from the initial resection. They noticed that patients with CRS of 0, 1, 2 have a fondness for survival and surgical resection is a rational therapy. Patients with CRS 3, 4 and 5 have low survival and therefore surgical resection should be planned in the context of chemotherapy.

Conclusion

There are several ways for treatment of patients with colorectal liver metastases: radiofrequent ablation, transarterial chemoembolization, chemo-and radiotherapy as well as in selected cases liver transplantation, but only liver resection has curative sense. The surgical strategy for resection in context of increasing the percent of patients with resectable potential is the only possible factor for long-term survival.

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Original article

SUBCLINICAL DIASTOLIC DYSFUNCTION IN DIABETIC POPULATION

СУБКЛИНИЧКА ДИЈАСТОЛНА ДИСФУНКЦИЈА КАЈ ДИЈАБЕТИЧНАТА ПОПУЛАЦИЈА

Slavica Mitrovska

Public Health Organization, Polyclinic Chair, Department of Internal Medicine-Cardiology, Skopje, Republic of Macedonia

Abstract

Introduction. Left ventricular dysfunction is very frequent in asymptomatic diabetic population. Tissue Doppler Imaging (TDI) is a new echocardiographic technique, able to record early changes of left ventricular dysfunction and to identify asymptomatic diabetic patients at high risk of developing heart failure.
Aim. To assess the role of TDI in early detection of diastolic dysfunction in asymptomatic diabetic patients.
Methods. Cross-sectional study that involved a total number of 48 subjects. The target group consisted of 25 asymptomatic diabetic patients and control group was composed of 23 subjects without diabetes. All subjects underwent echocardiography (conventional 2D and Pulsed-Wave Doppler and contemporary-TDI) to analyze left ventricular function. We compared the results from both echo-techniques and analyzed the relation of echocardiographic parameters with risk factors.
Results. We found statistically significant difference between TDI and PW Doppler (E/E´vs E/A) in target ($Z=-3.17$, $p<0.001$) and control group ($Z=-2.4$, $p<0.003$). There was no significant difference in E/A between the groups ($Z=0.0$, $p<1.0$). TDI identified significantly lower E´ ($Z= 2.03$, $p<0.04$) and higher E/E´ ($Z= -2.12$, $p<0.03$) in target vs control group.
LVDD strongly correlated with duration of DM ($p< 0.00001$), age ($p<0.00001$), female gender ($p<0.0001$) and obesity indices (BMI, BSA) ($p<0.00001$, $p<0.00001$) in both groups.
Conclusion. TDI unmasks the presence of subclinical LV dysfunction in asymptomatic diabetic patients and has a valuable prognostic importance.

Keywords: tissue doppler Imaging, PW doppler echocardiography, diabetic cardiomyopathy, left ventricular diastolic dysfunction, diabetes mellitus type 2

Correspondence to: Slavica Mitrovska, "Dzole Stojcev"1-2/8, 1000 Skopje, R. Macedonia; Phone: 00 389 71 38 52 67;
E-mail: mitrovska2000@yahoo.com

Апстракт

Вовед. Дисфункцијата на левата комора е многу честа појава, дури и кај асимптоматските пациенти со дијабетес. Новата ехокардиографска техника-Ткивна доплер анализа (ТДА), ги бележи отстапките во функцијата на левата комора во најраниот стадиум и дава можност за идентификација на пациентите кои имаат висок ризик од развој на срцева слабост.
Цел на трудот. Процена на улогата на ТДА во раната детекција на дијастолната дисфункција на левата комора кај асимптоматски пациенти со дијбетес.
Материјал и методи. Студија на пресек, којашто вклучува вкупно 48 испитаници (целна група-25 асимптоматски пациенти со дијабетес и контролна група-23 пациенти без дијабетес).
Испитаниците беа подложени на ехокардиографска анализа на левата комора (пулсна доплер анализа-ПДА и ТДА). Гиспоредуваме резултатите од двете техники и ја анализираме нивната асоцијација со факторите на ризик.
Резултати. Најдовме статистички значајна разлика меѓу ТДА и PDA (E/E vs E/A) кај целната ($Z= -3.17$, $p<0.001$) и кај контролната група ($Z=-2.4$, $p<0.003$). Не најдовме статистички сигнификантна разлика во E/A меѓу двете групи ($Z=0.0$, $p< 1.0$). Со ТДА бележевме значително помал E бран ($Z=2.03$, $p<0.04$) и поголем E/E сооднос ($Z=-2.12$, $p<0.03$) кај целната vs контролната група.
И кај двете групи-ДД покажа силна позитивна корелација со должината на дијабетичниот стаж ($p<0.00001$), возраста ($p<0.00001$), женскиот пол ($p<0.0001$) и параметрите на обезност (БМИ, БСА) ($p<0.00001$, $p<0.00001$).
Заклучок. ТДА покажа предност, во споредба со ПДА, во поглед на раната детекција на супклиничката дисфункција на ЛК кај асимптоматски пациенти со дијбетес и има голема прогностичка важност.

Клучни зборови: ткивна доплер анализа, пулсна доплер анализа, дијабетична кардиомиопатија,

дијастолна дисфункција на левата комора

Introduction

Left ventricular diastolic dysfunction (LVDD) is very common in diabetic population even in the absence of coronary artery disease, valve pathology and hypertension. It is an indicator of myocardial damage before heart failure become apparent, and serves as a predictor of adverse cardiac events. Hence, the early identification of myocardial dysfunction and correction of potentially modified risk factors, are very important in order to delay the onset of heart failure. Unfortunately, subclinical cardiomyopathy still remain unrecognized in asymptomatic diabetic patients [1].

The conventional Pulsed-Wave (PW) Doppler echocardiography is dependent on multiple factors, the influence of volume changes on transmitral flow, heart rate, left atrial pressure, that make the method inadequate for the diagnosis of diastolic dysfunction.

Tissue Doppler Imaging (TDI) is a non-invasive cardiac imaging technique, relatively independent to the loading conditions and provides comprehensive assessment of myocardial tissue velocities [2]. It measures the velocity of the longitudinal motion of the mitral annulus. Systolic wave (S) corresponds to LV ejection and diastolic waves-E´ reflects the LV relaxation (elongation) while A'-wave reflects the left atrial (LA) contraction and late LV filling (shortening). E'-wave progressively decreases with decreasing longitudinal lengthening (relaxation) in various pathological conditions. It is the earliest marker of diastolic dysfunction and is present in all its stages.

Therefore, the concept of Tissue Doppler Imaging should be introduced into daily clinical practice as an integral part of echocardiographic evaluation. It would be useful in identifying diabetic patients who may benefit from earlier treatment to prevent heart failure [3].

Aim: To assess the role of TDI in the early detection of diastolic dysfunction in asymptomatic diabetic patients.

Materials and methods

This cross sectional study included 48 subjects. Twenty-five asymptomatic patients with diabetes mellitus type 2 comprised the target (diabetic) group, and the control group included 23 subjects without diabetes. Inclusion criteria were type 2 diabetes mellitus (insulin dependent or non-dependent) with duration of diabetes (between 1 to 10 years), free of coronary artery disease (normal resting 12-lead ECG), hypertension and valve diseases. Exclusion criteria were systolic dysfunction (ejection fraction <55%), significant arrhythmia and any stage of renal failure. All patients underwent transthoracic echocardiography (conventional 2D and PW Doppler echocardiography) and Pulsed-Wave TDI images. Echocardiography was performed using Philips HD7 system echocardiography machine with 3,5 MHz probe.

LV morphology and function (LVEDd, LVESd, LVEDV, LVESV, EF, WMSI) were assessed by the conventional 2D echocardiography, according to the recommendation of the American Society of Echocardiography. The ejection fraction (EF) >55% was considered as normal systolic function.

PW Doppler echocardiography was carried out to assess LV diastolic function. In the apical 4-chamber view, with the sample volume placed at the mitral valve leaflet tips, transmitral flow velocities (early-E and late-A diastolic filling velocities, DT-deceleration time, IVRT-isovolumic relaxation time, E/A ratio) were recorded. Diastolic function was classified into 4 groups: 1-Normal (E/A=0,7-1.3, DT=140-240 ms, IVRT=76±13 ms), 2-Mild LVDD (E/A <1, DT>240 ms, IVRT>90 ms), 3-Moderate LVDD (E/A=1.0-1.5, DT=160-240 ms, IVRT=76 ±13 ms), 4-Severe LVDD (E/A>2, DT< 160 ms, IVRT<60 ms) [4].

During the longitudinal LV movement, the apex remains relatively stationary and measurement of peak velocities of mitral annular motion by Pulsed-Wave TDI give us data of overall longitudinal motion. A 2 mm sample volume was placed on septal corner of mitral annulus. An average of 3 to 5 consecutive cardiac cycles was taken for the calculation of all echo-Doppler parameters and systolic velocity (S'), early diastolic velocity (E') and myocardial velocity associated with atrial contraction (A') were measured.

E' velocity ≤8 cm/s was an indicator of diastolic dysfunction. The E/E' ratio was used to estimate LV filling pressures. The value E/E' <8 indicated normal LV end-diastolic pressure, whereas E/E' >10 was accepted as an elevated LV end-diastolic pressure [5].

All patients underwent lab-biochemical analyses and anthropometric measurements. Thus, we analyzed glycemic (fasting plasma glucose and glycosylated hemoglobin-HbA1c) and lipid profiles (total cholesterol, triglycerides, low-density lipoprotein (LDL-c) and high-density lipoprotein (HDL-C). We followed the guidelines given by the American Diabetes Association (ADA), and the level of HbA1c <7% and fasting plasma glucose of <6.7 mmol/l were criteria for good glycolregulation. Regarding the lipid profile, diabetic patients have characteristic high level of LDL-c and TG and low level of HDL-c. According to the ADA statin therapy should be started to achieve target LDL-c level of 1.8 mmol/l in patients with very high risk and 2.58 mmol/l in high risk patients. Regarding HDL-c, target level is 2.58 mmol/l in very high risk and 3.36 mmol/l in high risk patients [6].

Anthropometric measurements included BW, BH, BMI, BSA and waist-hip ratio. According to NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases, normal BMI is between 18-25 kg/m^2, overweight is

between 25-30 kg/m^2, and BMI ≥30 kg/m^2 is considered as obesity [7].
Obesity should be defined, if the male individual has waist-hip ratio (WHR) ≥94 cm and female has WHR ≥ 80 cm [8].

Statistical analysis

The statistical analyses were performed by using the commercial statistical package, Statistica for Windows, version 7.0. Continuous parameters were expressed as mean+SD. The Mann-Whitney U-test was used for two independent variables and Wilcoxon Matched Pairs Test for two dependent samples. A p value < .05 was considered to indicate significance.

Results: A total of 48 subjects were enrolled in this study. Diabetic group consisted of 25 asymptomatic patients with diabetes mellitus type 2. Fifteen of them (60%) were on insulin, and 10 (40%) patients were on oral hypoglycemic medications. Thirteen patients (52%) were female, mean age 41.8±5.9 and 12 (48%) were male, mean age 41.5±7.8.
The control group was composed of 23 apparently healthy subjects. Ten patients (43.5%) were female, mean age 39±6.33, and 13(56.5%) were male, mean age 45±6.29.

Table 1. Demographic and clinical characteristics of the study patients

Parameters	Study group (n=25)				Control group (n=23)				p
	Mean	Min	Max	SD	Mean	Min	Max	SD	
Age (years)	42	30	53	6.56	43	30	54	7.5	NS
Duration of diabetes (years)	6.0	1	10	3.10	/	/	/	/	
HbA1c (%)	6.8	4.5	9.1	1.31	/	/	/	/	
Fasting plasma glucose (mmol/l)	8.1	5.2	11	1.3	/	/	/	/	NS
Weight (Kg)	68.6	47	92	11.6	71.3	45	95	12.2	NS
Height (cm)	168.6	152	196	10.8	171.1	155	183	7.84	NS
BMI (Kg/m^2)	24	19.2	27.9	2.56	24.1	16.9	28.4	3.02	NS
BSA (m^2)	1.74	1.4	2.1	0.20	1.77	1.4	2.1	0.18	NS
Waist-to-hip ratio	0.84	0.70	0.98	0.10	0.85	0.70	1.00	0.07	NS

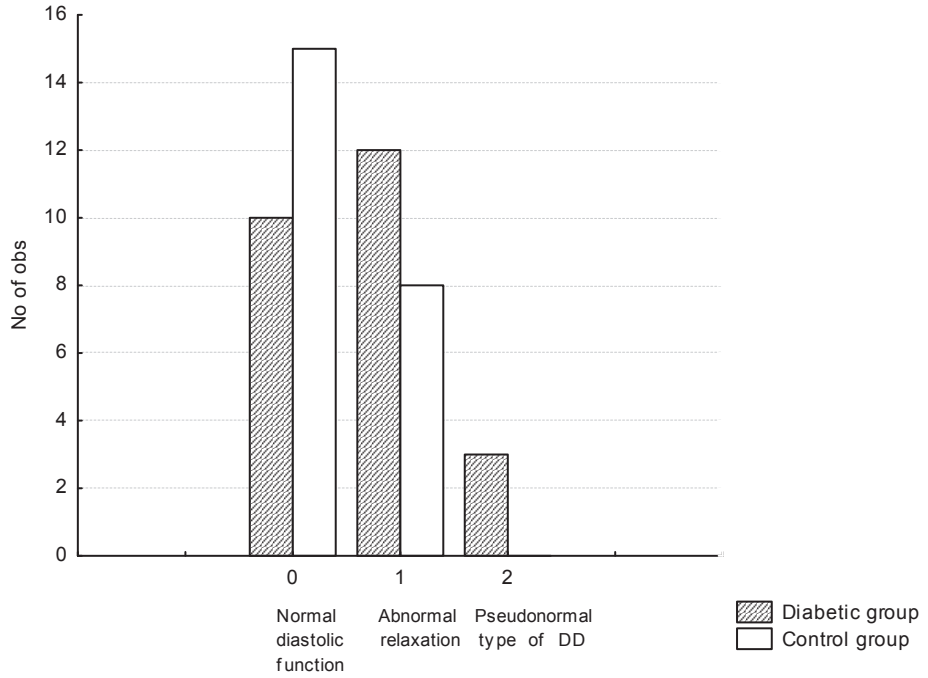

Fig. 1. Diastolic function assessed with PW Doppler in both groups

Demographic and clinical characteristics are summarized in Table 1.
Both groups were homogeneous in terms of demographic and clinical parameters.
We did not find statistically significant difference between groups in terms of lipid profile. Biochemical analyses showed 10(40%) patients from target group and 8 (34.7%) from control group to have dyslipidemia (Z=0.32, p<0.7).

Echocardiographic findings. Pulsed-Wave Doppler analyses

All patients underwent conventional 2D, PW Doppler echocardiography and Tissue Doppler assessment of myocardial tissue velocities.

In the study group, 15 patients (60%) had diastolic dysfunction, assessed by PW Doppler technique and 10 (40%) had normal transmitral flow velocities. Twelve (80%) patients with DD had abnormal relaxation and 3 (20%) patients had pseudonormal type of DD (Figure 1).

Table 2. Lipid profile of the study patients

Parameters	Target group (n=25)				Control group (n=23)				p
	Min	Max	Mean	SD	Min	Max	Mean	SD	
Cholesterol (mmol/l)	3.6	7.7	4.6	1.0	3.4	7.2	4.2	0.9	0.6
LDL-c (mmol/l)	1.5	5.8	3.7	1.2	1.4	5.4	3.5	1.2	0.7
HDL-c (mmol/l)	0.7	2.8	2	0.2	1.3	2.3	2	0.3	0.7
TG (mmol/l)	1.1	3.4	2.1	0.9	0.9	3.2	2.1	0.7	0.8

Table 3. Transmitral flow velocities derived from Pulsed-wave Doppler techniques

PW Doppler	Study group (n=25)				Control group (n=23)				p
	Mean	Min	Max	SD	Mean	Min	Max	SD	
E (cm/s)	0.5	0.3	0.9	0.16	0.8	0.4	0.9	0.13	NS
A (cm/s)	0.6	0.3	1.2	0.21	0.8	0.4	1.3	0.29	NS
E/A	0.8	0.3	1.2	0.31	0.9	0.6	1.3	0.22	NS
DT (ms)	178	132	247	42.6	194	75	276	52.5	NS
IVRT (ms)	80.1	55	120	16.2	74.4	56	120	14.5	NS

In control group PW Doppler noted 15 (65.2%) patients with normal mitral flow parameters, and 8 (34.7%) patients with abnormal relaxation.

The values of transmitral flow variables derived from Pulsed-wave Doppler techniques are given in Table 2.

In our study we found no statistically significant differences in mitral inflow velocities (E, A, E/A, DT and IVRT) between two groups ($Z=0.0$, $p<1.0$).

Tissue Doppler Imaging

Tissue Doppler parameters (E´ and E/E´) pointed out diastolic dysfunction in 18 (72%) diabetic patients. Seven (28%) patients had normal diastolic function.

In the control group, 13(56.5%) patients had diastolic dysfunction and 10(43.4%) had normal diastolic function (Figure 2).

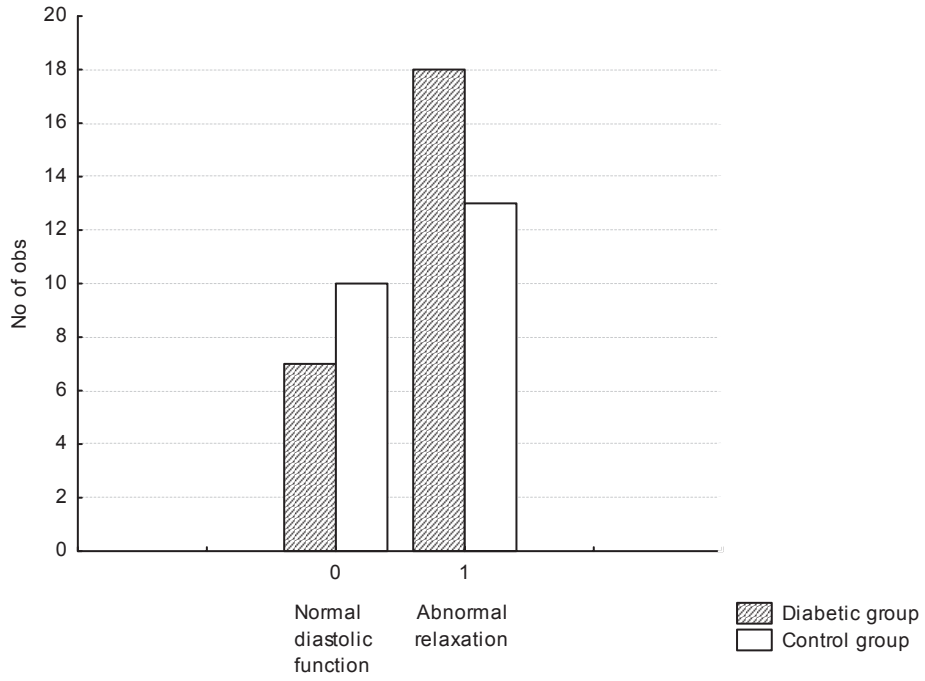

Fig. 2. Diastolic function assessed with Tissue Doppler Imaging in both groups

E' velocities obtained at the septal side of mitral annulus were significantly lower in the target group (diabetic patients) vs control group (Z=2.03, p< 0.04).
TDI identified statistically significant higher E/E´ in diabetic group vs control group (Z= -2.12, p<0.03).
Mann-Whitney U-test showed statistically significant difference between the two echocardiographic techniques, TDI vs PW Doppler, in terms of detection of diastolic dysfunction (E/E´ vs E/A) in both groups. In diabetic group, E/E´ vs E/A showed statistical significance for Z=-3.17 and p<0.001. In the control group, the value was Z= 2.4 and p<0.003.
The velocities of the mitral annular motion measured at a septal corner by Tissue Doppler imaging are given in Table 4.

Table 4. Mitral annular velocities measured at septal corner by Tissue Doppler Imaging

TDI	Study group (n=25)				Control group (n=23)				p
	Mean	Min	Max	SD	Mean	Min	Max	SD	
E´ (cm/s)	3.9	2	8.0	2.54	9.5	8	10	0.59	p<0.04
E/E´	12.9	7.0	16.0	3.46	8.0	4.0	11.0	1.75	p<0.03

Relation of diastolic parameters (PW and TDI) with risk factors

Thirteen (52%) patients with diabetes mellitus had poor glycemic control (HbA1c>7%) and had higher prevalence of DD than patients with HbA1c<7% (Z=-4.3, p<0.0004).
Diastolic dysfunction was significantly higher in patients with longer duration of DM, between 5-10 years vs 1-5 years (p<0.00001), in patients older than 40 years (p<0.00001), in female gender (p<0.0001) and obesity indices-BMI and BSA (p<0.00001, p<0.00003).
In the control group we also found a statistically significant relation of DD with age, female gender and obesity indices-BMI and WHR (p<0.0002, p<0.0004, p<0.0002 and p<0.0003).

Discussion

Diagnosis of diabetic cardiomyopathy is a challenge for cardiologists. Current technology and methods are still subjects of modification and they do not have routine use in daily practice. Echocardiography is a diagnostic method of choice, from practical and economic point of view, but conventional Pulsed Doppler analysis has limitations and provides inconclusive results. A new Tissue Doppler Imaging is more sensitive method that measures the velocity of the longitudinal motion (shortening and lengthening) of the mitral annulus and has the capability for early detection of diastolic dysfunction.
In our study we compared the results from the two echocardiographic techniques and demonstrated that TDI is superior to PW Doppler in early detection of subclinical diastolic dysfunction. Kibar *et al.* also demonstrated that TDI of the septal corner of mitral annulus provided better estimation of diastolic dysfunction than PW Doppler parameters [9].
Omen *et al.* in their catheterization study concluded that the ratio of mitral velocity to early diastolic velocity of the mitral annulus (E/E') correlated better with LV filling pressures than other Doppler variables [10].
E'-wave reflects the LV relaxation and progressively decreases with decreasing longitudinal lengthening in patients with diabetes mellitus. In our study we noted a statistically significant reduction of E´ wave in diabetic group vs control group (p< 0.04).
Jong-Won in his study examined the changes of E´ in diabetic patients during the exercise, and found significantly smaller changes in magnitude of E´ in diabetic group during the exercise compared to control group (p<0.032) [11].
Also, we evaluated the relation of diastolic dysfunction with various risk factors (age, gender, duration of DM, HbA1c, lipid profile and obesity indices-BMI, and WHR). There were statistically significant associations of DD in both groups (p<0.00).
Our findings are comparable to other studies. Thus, Patil *et al.* noted higher prevalence of DD in patients with longer duration of diabetes (more than 5 years) (p<0.02), bad glycemic control (HbA1c>7%) (p<0.02), and in obesity (WHR) (p<0.002) [12].
Shrestha NR. *et al.* also confirmed strong association between diastolic dysfunction and age, duration of DM and female gender [13].
Although many studies suggest correlation between hyperlipidemia and diastolic dysfunction, our analysis did not confirm this relationship in both groups (p<0.1 for diabetic and p<1 for control group) [14].
Most common dyslipidemia in diabetic population is high level of TG and LDL-c (low density lipoproteins) and low level of HDL-high density lipoproteins. In our study, in most of the patients, the level of the lipids was in the normal range. Thus, in the target group 15 patients (60%) had normal lipid level, whereas in the control group,the percent was 65% (15 patients).
We have no clear explanation about this, but if we take into consideration the fact that patients with good glucose regulation (<7%) have a lower rate of diastolic dysfunction, then we can assume that it may be due to the treatment. Namely, the majority of study subjects with dyslipidemia were already receiving statins (23 patients - 92% from target group and 20(87%) from control group). These data support our assumption that early treatment of potentially modifiable risk factors will delay the progression to heart failure and will improve the outcome of diabetic cardiomyopathy.

Conclusion

TDI unmasks the presence of subclinical LV dysfunction in asymptomatic diabetic patients and has valuable prognostic importance.

Conflict of interest statement. None declared.

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Original article

SINGLE DOSE OF MAGNESIUM SULFATE AS AN ADJUVANT TO GENERAL ANESTHESIA IMPROVES PAIN CONTROL, DISCOMFORT AND QUALITY OF SLEEP POSTOPERATIVELY

ЕДИНЕЧНА БОЛУС ДОЗА НА МАГНЕЗИУМ СУЛФАТ КАКО АДЈУВАНТ НА ОПШТАТА АНЕСТЕЗИЈА, ВЛИЈАЕ ВРЗ ПОДОБРУВАЊЕТО НА КОНТРОЛАТА НА БОЛКАТА, ДИСКОМФОРОТ И КВАЛИТЕТОТ НА СОНОТ, ПОСТОПЕРАТИВНО

Biljana Kuzmanovska[1], Marija Donevska Tolevska[1], Andrijan Kartalov[1], Marija Jovanovski Srceva[1], Mirjana Shosholcheva[2] and Nikola Jankulovski[3]

[1]University Clinic for Anesthesiology, Reanimation and Intensive Care Medicine, Clinical Campus "Mother Teresa", [2]University Surgical Hospital "St Naum Ohridski", [3]University Clinic for Digestive Surgery, Clinical Campus "Mother Teresa", Skopje, Republic of Macedonia

Abstract

Introduction. As a N-methyl-D-aspartate receptors antagonist, magnesium may play a role in prevention of pain. The aim of this study was to assess the effects of single dose magnesium sulfate preoperatively on postoperative pain scores, discomfort and quality of sleep.
Methods. Forty patients scheduled for elective laparoscopic cholecystectomy were randomized in two groups. Group A received 20 mg/kg magnesium sulfate after the anesthesia induction, prior to surgical incision, and Group B was the control group. Assessment was made for pain at rest in both groups according to VAS (0-10), analgesic consumption, discomfort and quality of sleep during first 48 hours postoperatively.
Results. Compared to control group, magnesium-treated patients had lower postoperative pain at rest according to VAS score ($p< 0.05$) and consumed less analgesic drugs during the first 48 hours ($p<0.05$). The magnesium-treated group experienced less discomfort during the first and the second postoperative day. The magnesium-treated group reported no changes in sleeping pattern compared to preoperative sleeping pattern, while the control group showed an increase in insomnia during the first and the second postoperative night, compared to that preoperatively.
Conclusion. Perioperative use of magnesium sulfate as an adjuvant to general anesthesia is associated with lower postoperative pain, less analgesic consumption, less discomfort and better sleep in the postoperative period.

Keywords: magnesium sulfate, anesthesia, pain control, sleep

Correspondence to: Kuzmanovska Biljana, University Clinic for Anesthesiology, Reanimation and Intensive Care Medicine, Clinical Campus "Mother Teresa", Skopje, Republic of Macedonia; Email: kuzmanovskabibi@gmail.com

Апстракт

Вовед. Магнезиумот е доминантен антагонист на рецепторите Н-метил-Д-аспартат (НМДА) и игра голема улога во превенција на болката. Цел на оваа студија е анализирање на влијанието на поединечната болус доза на магнезиум сулфат врз пероперативните и постоперативните наоди за болка, како и неговото влијание врз нивото на постоперативен дискомфор и врз квалитетот на сон.
Метод. 40 пациенти закажани за елективна лапараскопска холецистектомија поделени во две групи (по метод на случаен избор). Групата А, по воведот во општа анестезија, но пред хируршката инцизија, доби 20мг/кг магнезиум сулфат додека групата Б беше контролна група и не доби магнезиум сулфат. Во студијата се одредуваше и нивото на болка, според Визуелната аналогна скала (ВАС од 1-10), нивото на искористени аналгетици, нивото на дискомфор и квалитетот на сон во првите 48 часа.
Резултати. Пациентите коишто добија магнезиум по воведот во анестезија, во споредба со контролната група, покажаа ($p<0.05$) понизок степен на болка (според ВАС) и помала употреба на постоперативни аналгетици ($p<0.05$). Нивото на дискомфор, првиот и вториот постоперативен ден било помало кај пациентите од испитуваната група. Кај контролната група се регистрираше и зголемено ниво на несоница, споредено постоперативно, додека во групата која доби магнезиум сулфат не се регистрирани промени во спиењето.
Заклучок. Периоперативната употреба на магнезиум сулфат, како додаток на општата анестезија, резултира со намалување на постоперативната болка, понизок степен на употреба на аналгетитици, помало чувство за дискомфор и подобар сон кај хируршките пациенти.

Клучни зборови: магнезиум сулфат, анестезија,

постоперативна болка, сон

Introduction

Current understanding of postoperative pain has demonstrated its association with sensitization of central nervous system (CNS) that clinically elicits pain hypersensitivity. Acute perioperative pain can produce structural and functional changes in the pain pathway, resulting in hyperalgesia and central sensitization. N-metyl-D-aspartate (NMDA) receptors play a role in synaptic plasticity and are implicated in facilitation of pain processing in the CNS. NMDA receptor antagonists, specifically ketamine is commonly used in clinical practice in perioperative pain management [1].

As a part of a multimodal anesthesia, ketamine is used as a preemptive analgesic agent in low, subanesthetic doses. Its use as a preemptive analgesic proved to be efficient in reduction of intraoperative opioid consumption, reduction of postoperative pain and postoperative opioid and non- opioid analgesic consumption [2-8].

Magnesium sulfate is a natural antagonist of N-metyl-D-aspartate (NMDA) receptors. As NMDA antagonist, magnesium sulfate may play a role in prevention of pain. Magnesium depresses CNS, blocks peripheral neuromuscular transmission, produces anticonvulsant effects, decreases amount of acetylcholine released at end-plate by motor nerve impulse. Magnesium also stabilizes excitable membranes. Tramer MR, *et al.* in 1996 conducted the first clinical study regarding the role of magnesium sulfate as an adjuvant to general anesthesia on postoperative analgesia [2].

The aim of this study was to assess the effects of single dose magnesium sulfate preoperatively on postoperative pain scores, discomfort and quality of sleep.

Materials and methods

Forty patients scheduled for elective laparoscopic cholecystectomy were randomized in two groups. Group A received 20 mg/kg magnesium sulfate after the anesthesia induction, prior to surgical incision, and Group B was the control group. The patients in both groups received a standardized general endotracheal anesthesia; midazolam 0.02 mg/kg, remifentanyl 0.75 microgr/kg, propofol 2 mg/kg, rocuronium 0.6 mg/kg. The anesthesia procedure consisted of a balanced anesthesia technique with continuous infusion of remifentanyl 0.1-0.5 mg/kg/min, 1.24% end-tidal sevoflurane, with a mixture of gases in ratio of 50% O and 50% air. The standard monitoring procedure included continuous ECG record, measurement of the blood pressure every 5 minutes, pulse oximetry, heart frequency and capnography.

Postoperative assessment of the severity of pain was made at rest in both groups according to Visual Analog Scale (VAS), from 1 to 10, consumption of analgesics, discomfort and quality of sleep during the first 48 postoperative hours.

Pain assessment was made at rest in the first postoperative hour, and then on every 6 hours in the 48 hours postoperatively, using VAS.

Patient discomfort was assessed on every 6 hours during the first 48 postoperative hours, by answering the questionnaire designed to evaluate patients comfort.

The quality of sleep was assessed during the first two postoperative nights, by answering the questionnaire designed to detect the changes in the patients sleep patterns.

The obtained data were analyzed statistically with the SPSS statistical program.

Results

Postoperative pain and analgesics consumption: Compared to control group, magnesium-treated patients had lower postoperative pain at rest according to VAS score in the first postoperative hour, and during the first postoperative 48 hours (Table 1). The magnesium-treated group consumed less analgesic consumption (NSAID and tramadol) during the first 48 hours ($p<0.05$). Tramadol was given only to patients who reported pain at rest to be 4 or higher according to VAS.

Patient discomfort: The magnesium-treated group reported that experienced less discomfort during the first and the second postoperative day (12 patients in the control group reported discomfort against only 5 patients in the magnesium-treated group).

Quality of sleep: The magnesium-treated group reported no changes in sleeping pattern compared to preoperative sleeping pattern, while the control group showed an increase in insomnia during the first and the second postoperative night, compared to that preoperatively.

Table 1. VAS scores in magnesium-treated group and control group during first 48 hours postoperatively

Main VAS Score	1st hour	6th hour	12th hour	18th hour	24th hour	30th hour	36th hour	42nd hour	48th hour
MgSO4 Group	4*	4*	2*	2*	2*	1*	1*	1*	1*
Control Group	7*	6*	5*	5*	4*	3*	3*	3*	3*

* Statistically significant, $p< 0.05$

Discussion

In our study magnesium-treated patients had lower postoperative pain at rest according to VAS score in the first postoperative hour, and during the first 48 hours postoperatively, and consumed less analgesics (NSAID and tramadol) during the first 48 hours. The magnesium-treated patients experienced less discom-

fort during the first and second postoperative day and reported no changes in sleeping pattern compared to preoperative sleeping pattern.

Tramer *et al*. published the first clinical study presenting many benefits of perioperative magnesium sulfate application had [2].

Seyhan *et al*. [3] in his study used three different dose regimens of magnesium on propofol requirements, hemodynamic variables and postoperative pain relief in patients undergoing gynecological surgery. Magnesium groups (magnesium 40 mg/kg bolus followed by 10 mg/kg/h infusion required significantly less propofol and atracurium and morphine consumption was significantly lower on the first postoperative day.

In a randomized, double-blind, prospective study, Hwang *et al.* [4] evaluated the effect of i.v. infusion of magnesium sulfate (50 mg/kg for 15 minutes and then 15 mg/kg/h by continuous i.v. infusion until the end of the surgery), during spinal anesthesia on postoperative analgesia and postoperative analgesic requirements in forty patients undergoing total hip replacement arthroplasty. Postoperative pain scores were significantly lower in magnesium group at 4, 24, and 48 hours after surgery and cumulative postoperative PCA consumptions were also significantly lower at 4, 24, and 48 hours after surgery. Intravenous magnesium sulfate administration during spinal anesthesia improves postoperative analgesia.

Taheri *et al*. [5] in his study used single dose of magnesium sulfate (50 mg/kg in 100 ml of normal saline solution i.v. as single dose, 15 minutes before induction of anesthesia) for postoperative analgesia in hysterectomy patients receiving balanced general anesthesia. Postoperative pain score was significantly lower in magnesium group at 6, 12, and 24 hours after surgery and pethidine requirement was significantly lower in the same group throughout 24 hours after the surgery. Single dose of magnesium sulfate could be considered as an effective and safe method to reduce postoperative pain and opioid consumption after total abdominal hysterectomy.

Kocman *et al*. [6] in his study determined the effect of preemptive i.v. low-dose magnesium sulfate on early postoperative pain after laparoscopic cholecystectomy. Patients who received magnesium sulfate 7.5 mg/kg had significantly lower VAS scores at 1 and 3 hours postoperatively, but there was no effect on pain reduction at 6, 9 and 24 hours after surgery.

A meta-analysis by Albrecht *et al*. [7] evaluated whether perioperative administration of i.v. magnesium can reduce postoperative pain. Perioperative magnesium reduced cumulative i.v. morphine consumption by 24.4% at 24 h postoperatively. Numeric pain scores at rest and on movement at 24 h postoperatively were reduced by 4.2 and 9.2 out of 100, respectively. It was concluded that parioperative i.v. magnesium reduced opioid consumption, and pain scores in the first 24 hours postoperatively, without any reported serious adverse effects.

Bhatia *et al*. [8] examined the role of magnesium sulfate on analgesic requirement, pain, discomfort and sleep during perioperative period in patients scheduled for elective open cholecystectomy. Patients in magnesium group received 50 mg/kg in 100 ml saline i.v. during the preoperative period followed by 50 ml/h infusion of magnesium sulfate (15 mg/kg/h) until the end of the surgery. Patients in the magnesium and control groups had similar morphine requirement during the first 24 hours postoperatively. Patients in the magnesium group experienced less discomfort during the first hour after surgery and had better sleep quality during the first postoperative night.

The results of our study correlate with the findings of other authors who have used magnesium sulfate as an adjunct to anesthesia.

Intraoperative use of magnesium sulfate may also play a role in diminishing the cognitive impairment caused by anesthesia. Corsonello *et al*. [9] in his cross-sectional case control study investigated the association between low serum magnesium levels and cognitive impairment in 1058 hypertensive hospitalized patients. Twenty-nine percent of the selected hypertensive patients were classified as having cognitive impairment. Older age, female sex, and low educational level showed a significant trend for association to cognitive impairment. Their results demonstrated the existence of a significant association between magnesium imbalance and cognitive impairment.

Conclusion

Perioperative use of magnesium sulfate as an adjuvant to general anesthesia is associated with lower postoperative pain, less analgesic consumption, less discomfort and better sleep in the postoperative period.

Conflict of interest statement. None declared.

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ММП

Original article

CHRONIC KIDNEY DISEASE AS A LONG-TERM CONSEQUENCE OF PREECLAMPSIA AND HYPERTENSIVE DISORDERS IN PREGNANCY

ХРОНИЧНА БУБРЕЖНА БОЛЕСТ КАКО ДОЛГОРОЧНА ПОСЛЕДИЦА ОД ПРЕЕКЛАМПСИЈА

Biljana Gerasimovska Kitanovska and Vesna Gerasimovska

University Clinic for nephrology, University "Ss. Cyril and Methodius" Medical Faculty, Skopje, Republic of Macedonia

Abstract

Introduction. Preeclampsia is a condition characterized by hypertension, proteinuria after 20th week of gestation, dysfunction of other maternal organs or uteroplacentary dysfunction and is associated with short-term renal damage. Recent studies report on potential association of preeclampsia with chronic kidney disease in later life. The aim of this study was to determine this potential association by literature review and our results.
Methods. A Pubmed (Medline) literature search on the association of preeclampsia and subsequent chronic kidney disease was carried out. Our study was conducted at the Department of Nephrology of the University Clinical Centre Skopje in 2010 and included women who consulted the Clinic due to hypertension or impaired renal function and who had either preeclampsia or hypertensive disorders in pregnancy. Thirty patients with decreased glomerular filtration that occurred 1-28 years after pregnancy with hypertensive disorder were included in the study.
Results. Literature search yielded 227 abstracts, of which 19 papers were selected, and they referred only to chronic kidney disease in the period after delivery in patients with preeclampsia. Various risks for emergence of chronic kidney disease in later life were reported in recent literature, varying from 1.2 to 14 for preeclampsia and in patients with superimposed preeclampsia, the risk was 45 times higher. In our study, risk of reduction in glomerular filtration rate was highest in the first 5 years (OR 3.6, 95% CI 1.06-22.5). Delivery before 27 weeks of gestation insignificantly increased the risk of reduced glomerular filtration in the later period (OR 1.33 95% CI 0.2-8.5). Preeclampsia is not a direct risk factor for chronic kidney disease, however, proteinuria over 0.3 g/24h in the group of patients with hypertension or preeclampsia in pregnancy, increased the risk of reduced glomerular filtration rate by 28 times (OR 28.5, 95% CI 2.7-30.9).
Conclusions. Patients with preeclampsia need careful monitoring in postpartal and long-term period, not only for cardiovascular but for chronic kidney disease.

Keywords: preeclampsia, chronic kidney disease, proteinuria

Correspondence to: Biljana Gerasimovska Kitanovska University Clinic for nephrology, "Vodnjanska" 17, 1000 Skopje, R. Macedonia; E-mail: bgerasimovska@yahoo.com

Апстракт

Вовед. Преeклампсијата е состојба која се карактеризира со хипертензија и со протеинурија по 20. гестациска недела и постоење дисфункција на други органи кај мајката или со утероплацентарна дисфункција, и е поврзана со краткорочно бубрежно оштетување. Поновите сознанија соопштуваат можна поврзаност на преeклампсија со хронична бубрежна болест во натамошниот живот. Целта на студијата е да се испита таа поврзаност со преглед на литературата и со нашите резултати.
Методи. Пребарувањето на литературата за асоцираноста на преeклампсија и подоцнежна хронична бубрежна болест е спроведено во Pubmed (Medline). Нашата студија е спроведена на Универзитетската клиниката за нефрологија и вклучува пациентки за кои е консултирана Клиниката заради хипертензија и намалена бубрежна функција и кои имале претходна преeклампсија во гравидитет или хипертензивно пореметување во гравидитетот. Вкупно беа вклучени триесет испитанички, кои се јавиле во период една до 28 години, по гравидитетот со хипертензивно пореметување.
Резултати. Со пребарување на литературата се најдени вкупно 19 труда, кои се однесуваат само на хронична бубрежна болест во период по породувањето кај пациентки со преeклампсија. Соопштени се различни ризици за настанување хронична бубрежна болест во подоцнежниот живот (од 1,2 до 14 пати). Во нашата студија, во периодот од една до 28 години по породување, ризикот за намалување на гломеруларната филтрација бил најголем во првите пет години (OR 3.6, 95% CI 1.06-22.5).

Породувањето пред 27 гестациска недела незначително го зголемило ризикот за намалена гломеруларна филтрација во подоцнежниот период (OR 1.33, 95% CI 0.2-8.5). Прееклампсијата не е директен фактор за хронична бубрежна болест, но протеинуријата над 0.3 г/24ч во групата на пациентки со хипертензија во гравидитет или со прееклампсија го зголемила ризикот за намалена гломеруларна филтрација за 28 пати (OR 28.5, 95%, CI 2.7-30.9).
Заклучоци. Прееклампсијата не е комплетно реверзибилна состојба и е потребно внимателно следење на пациентките во постпородилниот период, како и долгорочно, не само за кардиоваскуларна, туку и за хронична бубрежна болест.

Клучни зборови: прееклампсија, хронична бубрежна болест, хипертензија

Introduction

Preeclampsia is a condition of hypertension in pregnancy and proteinuria above 300 mg/24 hours, occurring after 20th week of gestation, characterized by dysfunction of maternal organs, or uteroplacentary dysfunction [1]. It may cause acute renal failure during pregnancy or immediately after pregnancy due to an edema of the endothelial cells in the glomeruli, and the glomerular function may decrease by 40% [2]. Although these changes are significant, most frequently renal function is completely restituted in the period 3-6 months after delivery and rarely in the period up to 12 months after delivery [3].
Former studies found no association of hypertension in pregnancy with chronic kidney disease in later life. In one meta-analysis of studies [4], no difference was found in the glomerular filtration, serum creatinine, creatinine clearance in patients with former preeclampsia compared to healthy controls in a period up to 5 years after delivery.
Recent studies report that there are long-term consequences after preeclampsia, such as cardiovascular complications and chronic kidney disease. The interest on potential association of preeclampsia and chronic kidney disease without existence of glomerulopathy re-emerged after publication of the study by Vikse, who found an increased risk of chronic kidney disease in patients with preeclampsia [5,6]. Chronic kidney disease that occur much later after delivery may be due to glomerular disease, which existed before or during pregnancy, or to newly emerged proteinuria, which does not persist after delivery in patients with preeclampsia [7-10].
The aim of this study was to make a cross-section of current knowledge on association of preeclampsia and later chronic kidney disease by literature review and a summary of results obtained in our study.

Material and methods

Literature search

The association of preeclampsia and later chronic kidney disease was investigated by a Pubmed (Medline) literature search. The search was conducted by the use of combining the following key words: "maternal renal disease after preeclampsia or maternal long-term renal disease and preeclampsia or maternal end-stage renal disease and preeclampsia or maternal progression of chronic renal disease after preeclampsia or consequent maternal kidney disease and preeclampsia". The result was 227 abstracts, which were reviewed independently by two researchers. Studies that referred to systemic diseases (e.g. systemic lupus erythematodes, diabetes mellitus), preexisting chronic kidney disease and acute renal injury immediately after pregnancy were excluded. Abstracts selected independently by the two researchers were reviewed jointly, a decision on contentious abstracts was reached, and 19 studies were selected, which pertained only to chronic kidney disease in a long-term period after delivery in patients with preeclampsia.

Cross-sectional study of patients with hypertensive disorder in pregnancy

The study was conducted in 2010 in the Department of Nephrology at the University Clinical Centre in Skopje and included patients who came for consultation about hypertension and decreased renal function and who had preeclampsia or hypertensive disorders in pregnancy. A total of 30 patients who came in the period between 1-28 years after pregnancy were included.
Logistic regression of risk factors that were found to be significant for glomerular filtration (age, time after delivery, preeclampsia, delivery before 37 weeks of gestation and birth weight less than 2500 g) was made by the use of the SPSS program.

Results

Literature review

From the selected 19 studies, 9 studies were reviews or systematic reviews, 6 studies were cross-sectional and 4 were prospective studies (Table 1). Most of the prospective studies were an intersection between registries of delivered patients and registries of patients with kidney biopsy or chronic kidney disease in later life. The study of Vikse from 2006 was the largest and included a total of 756420 patients that were delivered and 588 of them had renal biopsy in later life, in a period up to 38 years after delivery.
Chronic kidney disease after delivery in all studies was reported between 1-39 years. Studies have shown that several years after preeclampsia, microalbuminuria emerged, which is an independent risk factor for cardiovascular and renal diseases [6-8].

Table 1. Review of the literature on association of preeclampsia with later chronic kidney disease

Author of the study, year of publication (reference)	Type of study/ design of the study	Number of patients	Renal outcomes after delivery
1. Paauw, 2016[10]	Review	NA	Higher risk (5-12 times) of chronic kidney disease in patients with preeclampsia
2. Van Balen 2016[15]	Cross-section study	775 delivered patients	In 13.7% annual follow-up of renal function was needed and in 1.4% there was a risk of progression to chronic kidney disease
3. Alvarez, 2016[24]	Review	NA	Risk of chronic kidney disease increased 10 times in patients with hypertension in pregnancy
4. Kessous R, 2015[11]	Population study	7824 patients with preeclampsia	Risk of renal hospitalizations (3.7 times more) in patients with preeclampsia
5. Wu CC, 2014[14]	Prospective study	13633 patients with hypertension in pregnancy	Risk of chronic kidney disease in surperimposed preeclampsia – 44.72 (95% CI 22.59-88.51) Risk of chronic kidney disease after hypertension in pregnancy – 10.64 (95% CI -15.05)
6. Mannisto T, 2013[20]	Prospective study	10314 delivered patients with registered high blood pressure	Risk of chronic kidney disease and preeclampsia -3.08 times higher
7. Wang 2013[13]	Population study	213397 delivered patients 26651 patients with hypertensive disorders in pregnancy	Risk of chronic kidney disease increased 14 times in patients with preeclampsia
8. Hawfield 2012[26]	Review	NA	Low total risk, but preeclampsia may be considered as an independent risk of kidney disease
9. Hennesy and Makris 2011[19]	Review	NA	Preeclampsia left sequelae on renal function
10. Mac Donalds, 2010[4]	Systematic reviews and meta-analysis	273 patients with preeclampsia	Risk of chronic kidney disease increased 10 times
11. Vikse 2010[6]	Cross-sectional study (birth registries and registries of renal biopsy)	582 delivered patients	Risk of end-stage renal disease -1.2 in preeclampsia and 2.1 in women with pre-term birth
12. Spaan, 2010[25]	Cross-sectional study	34 patients	Chronic kidney disease in a longer period after preeclampsia was due to previously decrease renal function
13. Hamano 2009[23]	Review	NA	Although the risk of CKD after preeclampsia was low, follow-up after preeclampsia was needed for kidney disease
14. Vikse, 2008[27]	Cross-sectional study (birth registries and registries of renal biopsy)	570433 delivered patients, 477 with end-stage kidney disease	Risk of CKD increased 4 times
15. Hertig, 2008[3]	Review	NA	Follow-up of urinary ratio protein/creatinine was recommended, and after 4 and 8 weeks referral to renal biopsy was needed if proteinuria did not subside
16. Suzuki, 2008[22]	Review of 3 studies	52, 48 and 127 patients with preeclampsia included in 3 studies	There was an association between chronic kidney disease and preeclampsia
17.Vikse, 2006[5]	Cross-sectional study (birth registries and registries of renal biopsy)	756420 delivered patients, 588 patients with renal biopsy	Risk of renal biopsy was increased 17 times in women with preeclampsia who gave birth to a child weighing below 1.5 kg
18. Van Pampus 2005[28]	Review	NA	Preeclampsia did not affect long-term renal function
19. Nissel 1995[7]	Cross-sectional study	45 patients with preeclampsia and 49 with pregnancy- induced hypertension	Microalbuminuria was registered in 20% at long-term follow-up in patients with prior preeclampsia

NA- Not applicable

Chronic kidney disease after delivery occurred after a shorter time (3.8 years) in women with hypertensive disorders in pregnancy than in women without hypertension in pregnancy (5.74 years on average) [11].
The risk of hospitalizations for kidney disease in later life in patients with preeclampsia was 3.7 times higher compared to patients without preeclampsia [12]. Patients with preeclampsia who gave birth to a child with low birth weight (below 1500g) had 17 times higher risk of renal biopsy in later life [5]. Emergence of chronic kidney disease in later life was more frequent (1.2-14 times) in patients with preeclampsia [5,13], while in patients with superimposed preeclampsia the risk was 44 times higher [14]. Recommendations for follow-up of renal function [15] were given in a study with 775 patients with history of preeclampsia who were offered renal screening after delivery, and to whom, according to the calculated creatinine clearance and KDIGO guideline, advice for renal follow-up was given. This study recommended annual follow-up of renal function since in 13.7% of patients with and in 1.4% there was a risk of progression of kidney disease.

Results of the study

The study included thirty patients, who had either preexisting hypertension in pregnancy (58%) vs. hypertension in pregnancy or preeclampsia (84%) vs non-preeclampsia, and who came for consultation in the Clinic due to hypertension and reduced kidney function. 38% gave birth before 37 weeks of gestation. The largest number of patients (71%) were followed 5-10 years after delivery, and fewer(16%) were followed for more than 10 years, or 13% less than five years after delivery.
At the control visit at the Clinic, after different period from delivery, proteinuria was found in 32% of patients, and reduced glomerular filtration rate was observed in 22.6%. 71% had hypertension, antihypertensive therapy was given to 58% and uncontrolled hypertension was found in 38% of patients (Table 2).

Table 2. General characteristics of patients with hypertension in pregnancy or preeclampsia and later chronic kidney disease

	Number and percentage of total number
Total number of patients	30
Average age (yrs.)	33(23-53)
Time after delivery (yrs)	(1-25)
1-5	4/31(13%)
5-10	22/31(71%)
Above 10	5/31(16%)
Data on the pregnancy and outcome	
Preexisting hypertension before pregnancy	18/31(58%)
Preeclampsia	26/31(84%)
Delivered before 37 gw	12/31(38%)
Condition after delivery (period 1-28 years)	
Proteinuria (new)	10/31(32%)
GFR	7/31(22.6%)
Antihypertensive therapy	18/31(58%)
Uncontrolled hypertension	12/31(38%)
Current hypertension	22/31(71%)
Gw-gestational week, GFR-glomerular filtration rate	

In the period 1-28 years after birth, the risk of reduction of glomerular filtration rate was highest in the first 5 years (OR 3.6, 95% CI 1.06-22.5). Renal biopsy was performed only in one patient and the diagnosis was membranoproliferative glomerulonephritis. Delivery before 27 weeks of gestation slightly increased the risk of reduced glomerular filtration in the later period (OR 1.33, 95%

Table 3. Risk of decreased glomerular filtration in patients with hypertension in pregnancy or preeclampsia in a period 1-28 years after delivery

Risk factor for decreased GFR	OR	95% CI
Time after delivery (years)		
1-5 yrs	3.6*	1.06-22.5*
5-10 yrs	0.24	0.03-2.2
over 10 yrs	0.12	0.02-0.98
Preeclampsia	0.9	0.08-10.3
Delivery before 37 gw	1.33	0.2-8.5
Proteinuria >0.3 g/du	28.5*	2.7-309*

CI 0.2-8.5). However, proteinuria over 0.3 g / du in the group of patients with hypertension or preeclampsia in pregnancy, increased the risk of reduced glomerular filtration for 28.5 times (OR 28.5, 95%, CI 2.7-30.9).

Discussion

In our study, the risk of chronic kidney disease and de novo proteinuria in patients with preeclampsia increased 28 times and was highest in the first 5 years, which is similar to the findings of Vikse [5]. Preeclampsia in our study did not occur as a direct risk factor, however, it may lead to subsequent emergence and proteinuria in chronic renal disease.

Gene theory explains that there are several susceptibility genes for preeclampsia likely to interact with hemostatic and cardiovascular system as well as inflammatory response, which may have an impact on long-term renal impairment [16]. In addition, preeclampsia can cause permanent damage to the glomeruli by emergence of glomerulopathy, which may be monitored by the presence of podocytes in the urine [17-18]. Persistent endothelial damage can cause new microalbuminuria [19]. In some cases, part of the pathophysiologic mechanisms associated with preeclampsia can continue after delivery -impaired immune system with increased inflammatory markers, angiogenic imbalance, increased activity of the sympathetic system and changes in extracellular volume, and some of the risk factors for hypertension may match risk factors for future cardiovascular and renal disease [2].

According to various studies, the risk of chronic kidney disease in hypertensive disorders in pregnancy and preeclampsia increased by 3-17-fold in patients with preeclampsia. The longest follow-up after pregnancy was 39 years after delivery and the risk of chronic kidney disease was 1.9 times higher [20]. In 37% of multiparas [21] classical glomerular lesions or other lesions were found on renal biopsy after delivery. Focal glomerulosclerosis, nephroarteriosclerosis and IgA nephropathy dominated in renal biopsies done 10 years after previous preeclampsia [22]. Comparing renal biopsy data with data on previous preeclampsia, Vikse (6) found that the risk of performance of renal biopsy in later life was 17 times higher in women with preeclampsia.

Recommendations for long-term follow-up in patients with preeclampsia in pregnancy

Proteinuria should be reduced continuously from the second to the sixth week after birth [2]. If proteinuria (urinary protein ratio to urinary creatinine) recovered over a period of 8 weeks after delivery, the patient should be referred to a nephrologist for renal biopsy. In terms of long-term follow-up in patients where proteinuria is normalized after delivery, it is recommended to make an assessment of proteinuria, serum creatinine, glomerular filtration rate and lipid status, glucose fasting assessment of overall cardiovascular risk every five years, recommendations for modification of lifestyle, including smoking cessation and maintaining a body mass index <25 kg / m2 [15,23].

Although the risk of cardiovascular disease much later after delivery is known, knowledge of possible renal impairment is relatively new. Careful monitoring of patients for chronic cardiovascular and renal disease with previous preeclampsia is needed in a long-term period.

Conflict of interest statement. None declared.

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Original article

NON-INVASIVE PRENATAL DETERMINATION OF FETAL MATURITY

НЕИНВАЗИВНА ПРЕНАТАЛНА ДЕТЕКЦИЈА НА ФЕТАЛНА ЗРЕЛОСТ

Elena Dzikova[1], Goran Dimitrov[1] and Olivera Stojceva-Taneva[2]

[1]University Clinic for Gynecology and Obstetrics, [2]University Clinic of Nephrology, Medical Faculty, University Ss. "Cyril and Methodius", Skopje, Republic of Macedonia

Abstract

Aims. The prenatal prediction of fetal maturity is very important, since neonatal respiratory distress syndrome (RDS) is one of the biggest causes of neonatal mortality. Our aim was to investigate a new non-invasive method for prediction of fetal maturity and to determine in which group according to gestational age of the fetus, the treatment works the best and in which cases it is necessary to be repeated.

Methods. We examined 60 patients (30 with impending preterm delivery, divided in 3 groups: 28-30, 30-32, and 32-34 gestational weeks and 30 controls), at the University Clinic for Gynecology and Obstetrics, Medical Faculty, University "Ss. Cyril and Methodius", Skopje, R. Macedonia. Fetal maturity was examined using ultrasound histogram from fetal lungs and liver, correlated with gestational age and postpartum RDS. Where possible, we performed amniocentesis for lamellar body count (LBC) to correlate our results with the current invasive method for prediction of fetal maturity.

Results. Pre-therapy investigation showed a strong fetal immaturity in 28-32 weeks of gestation and less evident fetal immaturity in 32-34 weeks of gestation. Seventy-two hours post-treatment, fetal maturation was low in the first group, higher in the second and the highest in the third group. Amniocentesis for LBC showed correlation with the ultrasound results. Postpartum results were correlated with pre-delivery ultrasound and showed significance of $p < 0.05$.

Conclusion. The results obtained in our study were with high significance, and they were in correlation with other similar studies. However, more extensive investigations should be made to replace the current invasive technique.

Keywords: prenatal non-invasive method, ultrasound, histogram, fetal maturity, respiratory distress syndrome

Correspondence to: Dzikova Elena, Bul. Ilinden No.59, 1000 Skopje, R. Macedonia; Phpone: +389 70 58 52 22; E-mail: elena.dzikova@gmail.com

Апстракт

Вовед. Пренаталната предикција на феталниот матуритет е извонредно важна, особено што респираторниот дистрес синдром (РДС) е еден од најголемите причинители за неонатален морталитет.

Нашата цел беше да се испита нова неинвазивна метода за предикција на фетална зрелост и да се утврди во која група, според гестациската возраст на плодот, третманот најдобро делува, и каде е треба тој да се повтори.

Методи. Испитавме 60 пациенти (30 со претечко предвремено породување, поделени во три групи: 28-30, 30-32 и 32-34 гестациска недела и 30 контролни случаи), на Универзитетската клиника за гинекологија и акушерство, Медицински факултет, Универзитет „Св. Кирил и Методиј"- Скопје.

Феталната зрелост беше испитана преку споредба на ултразвучниот хистограм меѓу феталното белодробие и црниот дроб на плодот, корелирано со гестациската возраст (г.н.) и РДС, каде што постоеше можност беше направена и амниоцентеза за испитување ламеларни телца (ЛБЦ), со цел нашата метода да се спореди со инвазивната метода, која рутински се користи за таа цел.

Резултати. Претерапиското испитување покажа голема незрелост од 28 до32 г.н., и нешто помала од 32 до 34 г.н, а 72 часа по третманот, испитувањето покажа ниска фетална зрелост во првата група, средна-во втората, и највисока во третата група. Амниоцентезата покажа корелација со ултразвучните резултати. Постпарталните показатели на РДС корелираа со препарталните резултати со сигнификантност П<0,05.

Заклучок: Нашата студија покажа сигнификантни резултати, но сепак се потребни поекстензивни испитувања за да може оваа техника да се воведе како рутинска метода.

Клучни зборови: пренатална не-инвазивна метода, ултразвук, хистограм, фетална зрелост, респираторен дистрес синдром

Introduction

Respiratory distress syndrome (RDS) is one of the biggest causes of fetal mortality. In immature newborn, the lack of surfactant causes increased surface tension of the alveoli. That process reduces the possibility of their expansion thus preventing the establishment of the process of breathing, described as a major etiological factor for hyaline membrane disease in the study of Avery and Mead by 1959. [1]; Mahaffey et al. in 1959. [2]; Adams et al. 1967. [3]; Northway et al. 1967. [4]. In the process of maturation, fetal lungs are the most important organ for survival in extra uterine environment. Therefore, it is very important to predict the fetal maturity prenatally, in order to provide adequate treatment to improve fetal maturity, and thus postpartum adaptation of the fetus, as well as to reduce morbidity and mortality in the newborn. One of the oldest techniques and still one of the gold standards for determining fetal maturity is the ratio between lecithin and sphingomyelin (L/S) in the amniotic fluid; these two being predictors of generated surfactant, necessary for the process of respiration. L/S should be greater than 1.5, preferably 2, or more, to achieve full fetal lung and fetal maturity in general. This technique was mentioned for the first time in the study of Gluck *et al.* 1971 [5] and Whitfield *et al.* 1972 [6].

Later, a simple method with high sensitivity and specificity was described, which counted the lamellar bodies in the amniotic fluid (LBC). For the first time in the literature this method was described by Dubin SB in 1989 [7], Bowie *et al.* in 1991 [8] and Ashwood *et al.* in 1993 [9]. This method almost completely replaced the method of determining the L/S ratio in the amniotic fluid.

Today there are several attempts to find the most adequate non-invasive method for prenatal prediction of fetal maturity. One of them is the method of detecting fetal maturity by determining the ratio between the density in fetal lungs and fetal liver using MRI. This method gives good results, but is too expensive to be introduced into the routine practice.

Aims

To examine a new method, which will provide timely prediction of fetal maturity and timely treatment; and that would be non-invasive, inexpensive, accessible, simple, repeatable, sensitive, specific, and can be performed routinely in any hospital facility available good ultrasound device and educated staff.

To determine in which group of patients according to gestational age of the fetus, the treatment works the best and in which cases it is necessary to be repeated for assessing a good fetal maturity, and thus to reduce fetal mortality and morbidity, which are among the main objectives of the action Plan of the World Health Organization from 2012 [10] and Healthy people 2020 [11].

Material and methods

The study was designed as a prospective observational-interventional clinical study. It included 60 patients, of whom 30 were impending preterm deliveries, and 30 control patients from the University Clinic for Gynecology and Obstetrics, Medical Faculty, University Ss. “Cyril and Methodius” in Skopje, Republic of Macedonia. Patients with premature ruptured membranes (PPROM), pain and expected early preterm birth (PPI), or with an expected early caesarean section (PSC) were included in the study. Exclusion criteria were: abnormalities of the fetus, multiple pregnancy, and the presence of a disease in the mother.

The protocol for the research project was approved by the Ethics Committee of the Medical Faculty, University Ss. “Cyril and Methodius”, and the protocol conformed to the codes of the Declaration of Helsinki (Ethics Board approval number 03-5515/5).

The ultrasound machine Voluson expert E8 and semi-convex ultrasound probe of 3.5 MHz, transabdominally were used. Histogram examined the density of the fetal lungs in patients selected according to the inclusion and exclusion criteria and compared to the degree of postpartum respiratory distress syndrome (RDS), (Figure 1).

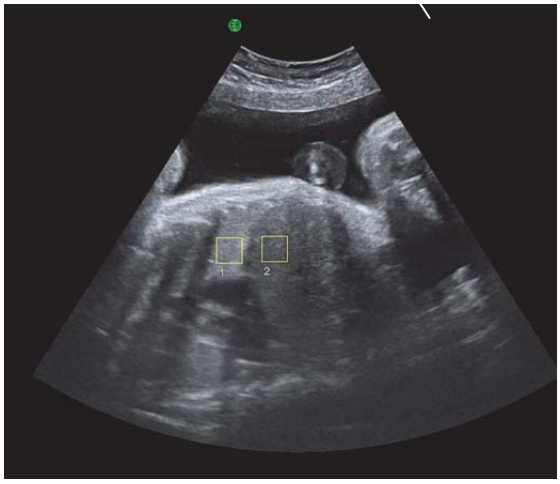

Fig. 1. Ultrasound histogram of fetal lungs and liver

If there was an opportunity to investigate LBC in the amniotic fluid, then amniocentesis was performed as a standard procedure. The examination was made before and 72 hours after administration of the therapy, Amp. Betamethasone a 14 mg / II dose / 24h, a protocol for fetal lung maturation. The results were followed up to 72 hours after the last dose of Betamethasone, and then if the patient was delivered, they were compared with the extent of postpartum respiratory distress syndrome (RDS).

If the patient was not delivered within 72 hours of measurement, she was excluded from the study.

Statistical analyses were done using standard statistical procedures for data processing, mean, standard deviation,

correlation, analysis of variance, Student's t-test for paired analysis and determination of p value for statistical significance. Statistical significance was defined as a p value <0.05. The correlation was made using Spearman's Rho Calculation test. For testing the diagnostic accuracy of our method we measured sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratio.

Results

Of the 60 patients analyzed so far, 30 were the examined cases and 30 control ones. Control patients were over 39 weeks of gestation, with expected full maturity of the fetal lungs. Of the examined 30 patients, 16 were with premature ruptured membranes (PPROM) and 14 were expecting prematurity (PPI). Ten of them were within 28-30 gestational weeks (g.w.); 14 were in 30-32 weeks of gestation and 6 were in 32-34 weeks of gestation. The ultrasound measurement protocol made before therapy for fetal lung maturation showed a strong fetal immaturity in the first two groups (28-32 weeks of gestation). In the first group from 28-30 weeks of pregnancy, the average ultrasound histogram signal intensity was 1.89±0.25; and in the second group from 30-32 weeks of pregnancy the average ultrasound histogram signal intensity was 1.43±0.05. The third group from 32-34 weeks of pregnancy showed less obvious fetal immaturity with an average histogram intensity ultrasound signal of 1.23±0.03. Seventy-two hours after the administered therapy we repeated the measurements, which showed a low fetal maturation in the first group, with a mean histogram intensity ultrasound signal of 1.62±0.14; intermediate in the second, with an average histogram intensity ultrasound signal of 1.35; SD=0.05; and most significant in the third group, with an average histogram intensity ultrasound signal of 1.11±0.02. After completion of therapy in those patients where there was an opportunity to perform the amniocentesis test for LBC, it showed a strong negative correlation (R=-1 in the first group; R=-0.99 in the second group and R=-0.87 in the third group). The results of the ultrasound were with significance of p<0.05 in all three groups of patients. Postpartum results correlated with the results of predelivery ultrasound, with a strong positive correlation (R=0.87 in the first group; R=0.81 in the second group and R=1 in the third group) and significance of p<0.05. In control patients, the histogram ultrasound signal intensity correlated with the gestational age of the fetus and postpartum establishing process of breathing, were with a significance of p <0.05 (Tables 1, 2, 3, 4).
Statistical analysis showed that the ratio between the intensity signals of fetal lungs and fetal liver, correlated with the gold standard (determination of the LBC in amniotic fluid by amniocentesis) and the postpartum respiratory distress syndrome, were with significance of p <0.05.

Table 1. Results for postpartum RDS, LBC and DZ before and after Th

G.A.	Postpartum RDS M±SD	LBC M±SD	DZ (M± SD) Before Th.	DZ (M± SD) After Th.
28-30 g.a.	2.6±0.55	18.8±5.17	1.89±0.25	1.62±0.14
30-32 g.a.	1.86±0.69	32.9±4.30	1.43±0.05	1.35±0.05
32-34 g.a.	1.33±0.58	45±2	1.23±0.03	1.11±0.02

Legend: RDS-respiratory distress syndrome; LBC-lamellar body count; M-mean; SD-standard deviation; Th.-treatment; R-correlation; DZ-intensity of density; p-significance; g.a.-gestational age

Table 2. Results in different weeks of gestation before and after therapy

G.A.	DZ before Th. (M±SD)	DZ after Th. (M±SD)	p
28-30 g.a.	1.89±0.25	1.62±0.14	0.01
30-32 g.a.	1.43±0.05	1.35±0.05	0.0016
32-34 g.a.	1.23±0.03	1.11±0.02	0.0086

Legend: RDS-respiratory distress syndrome; LBC-lamellar body count; M-mean; SD-standard deviation; Th.-treatment; R-correlation; DZ-intensity of density; p-significance; g.a.-gestational age

Table 3. Overview of the results of calculated correlation between DZ and LBC

G.A.	DZ after Th. (M±SD)	LBC (M±SD)	R	p
28-30 g.a.	1.62±0.14	18.8±5.17	-1	0.000
30-32 g.a.	1.35±0.05	32.9±4.30	-0.99	0.00001
32-34 g.a.	1.11±0.02	45±2	-0.87	0.03

Legend: RDS-respiratory distress syndrome; LBC-lamellar body count; M-mean; SD-standard deviation; Th.-treatment; R-correlation; DZ-intensity of density; p-significance; g.a.-gestational age

Table 4. Overview of the results of calculated correlation between DZ and RDS

G.A.	DZ after Th. (M±SD)	RDS (M±SD)	R	p
28-30 g.a.	1.62±0.14	2.6±0.55	0.87	0.057
30-32 g.a.	1.35±0.05	1.86±0.69	0.81	0.03
32-34 g.a.	1.11±0.02	1.33±0.58	1	0.000

Legend: RDS-respiratory distress syndrome; LBC-lamellar body count; M-mean; SD-standard deviation; Th.-treatment; R-correlation; DZ-intensity of density; p-significance; g.a.-gestational age

Also, this method showed that there was a significant difference ($p<0.05$) between fetal maturity before and after treatment.

The sensitivity of the test was 86.67% with 95% CI 59.54%-98.34%; specificity was 93.33% with 95% CI 68.05%-98.83%; positive likelihood ratio was 13.00 with 95% CI 1.94-87.26; negative likelihood ratio was 0.14 with 95% CI 0.04-0.52; disease prevalence was 50.00% with 95% CI 31.30%-68.70%; positive predictive value was 92.86% with 95% CI 66.13%-99.82%; negative predictive value was 87.50% with 95% CI 61.65%-98.45%.

Discussion

When expecting preterm birth, fetal lung evaluation is particularly important because of its significant impact on neonatal prognosis and fetal morbidity and mortality. In our study we examined the fetal maturity by comparing the density between fetal lungs and fetal liver according to the gray scale. Fetal lungs density depends on the presence of liquid in it. In early pregnancy, fetal lungs due to lack of fluid have hyperechoic density. It changes with fetal maturity. By forming surfactant the density of the fetal lungs changes, as well as the expansion of the alveoli, and its histogram becomes close to the signal of the fetal liver. Therefore, the histogram signal intensity of the liver is used for measurement standardization of the intensity of the signal in the fetal lungs, particularly because they contain other elements necessary for the standardization of measurement which are: similar size, close position, homogeneity and stability during pregnancy. Although the intensity of the signal in the fetal liver can be discretely variable during pregnancy, Duncan *et al.* 1997 [12] and Li *et al.* 2013 [13], showed that fetal liver meets most all these requirements.

Fetal lungs development can be divided into five stages [14]:

1. Embryonic stage (4-6 weeks)
2. Pseudo-glandular stage (6-16 weeks)
3. Canalicular stage (16-26 weeks)
4. Saccular stage (26-36 weeks)
5. Alveolar stage (36+ weeks)

The first stage is the embryonic stage, where fetal lungs are formed. Then, in the process of maturation, fetal lungs become secreting organ, passing into second pseudo-glandular stage. In this stage, future air space becomes filled with fluid rich in Cl^-, K^+, H^+, which is produced by epithelial cells, thus moving through the trachea and being excreted into the amniotic cavity. The balance in this process is an important factor in the maturation of the fetal lungs [15]. Because the fluid in the fetal lungs is produced by the epithelial cells, production begins in late canalicular stage, when epithelial cells are formed. This production increases with the maturity of the fetal lungs, and it becomes a rich body fluid. With increasing in gestational age, epithelial surface and microcirculation is growing, and thus the production of liquid. The detection of fetal maturation with our non-invasive method is enabled by the fact that the fetal lungs in maturation process increase its hypoechoicity, which is becoming close to the density of fetal liver [16]. Our results showed significance in the testing of this method for prenatal non-invasive determination of the fetal maturity through ultrasonography histogram, by determining the intensity of the signal in fetal lungs correlated with the fetal liver, taken as a standard of comparison, and in terms of gold standard, we took determination of the LBC in amniotic fluid by amniocentesis and the postpartum extent of respiratory distress syndrome or respiratory fetal maturity. We used the same method before and after the administration of the treatment protocol for fetal maturation, to determine whether the treatment is fully effective in the fetus and if it is necessary to retreat after 7-14 days of treatment. The results obtained by our method were highly significant. Also, the calculations for diagnostic accuracy of our method using STARD guidelines showed that our method had high sensitivity, specificity, and positive and negative predictive value. All results were compared with those obtained in the control group, and showed a high level of significance. Since this is a new method for non-invasive predicting of fetal maturity, there are few published data regarding this issue. Nevertheless, we have compared all our results with other similar studies that we have found [17].

In conclusion, the results of our study showed a signifycant correlation between the histogram intensity signal of the fetal lungs and gestational age of the fetus, a significant correlation of fetal lungs maturity before and after therapy given in fetal maturation protocol, a signifycant correlation with the gold standard for examination of LBC in the amniotic fluid as well as a correlation with the postpartum degree of respiratory distress syndrome or respiratory function in the fetus. However, more exten-

sive investigations should be made for this technique to replace the gold standard and be included in the routine use as a noninvasive method for prediction of fetal maturity.

Conflict of interest statement. None declared.

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Case report

DANDY WALKER AND EXTREME MACROCEPHALY CAUSED BY ENORMOUS OCCIPITAL ENCEPHALOCELE

СИНДРОМ НА DANDY WALKER И МАКРОЦЕФАЛИЈА ПРИЧИНЕТА ОД НЕЛЕКУВАНА ОКЦИПИТАЛНА ЕНЕФАЛОЦЕЛА

Vladimir Mirchevski[1], Elizabeta Zogovska[2], Aleksandar Chaparoski[1], Milenko Kostov[1], Michun Micunovic[3], Jasna Bushinoska[4], Marija Srceva[4], Mirko Mishel Mirchevski [5] and Blagoj Shuntov

[1]University Clinic of Neurosurgery, Clinical Center "Mother Teresa" Skopje, [2]University Clinic of Plastic, Esthetic and Reconstructive Surgery, Clinical Center "Mother Teresa" Skopje, [3]Special Hospital for Ortopedic Surgery and Traumatology "St. Erazmo"-Ohrid, [4]Clinic of Anesthesiology, Reanimation and Intensive Care, Clinical Center "Mother Teresa" Skopje, [5]Medical Faculty of Skopje, Skopje, Republic of Macedonia

Abstract

Introduction. Dandy-Walker syndrome is a congenital brain malformation involving cerebellum with partial and complete vermian agenesis, enlargement of the fourth ventricle and surrounding fluid spaces, cyst formation in posterior cranial fosse pushing tentorium upward [1,2]. Hydrocephalus or an increase in the pressure of the fluid spaces may also be present or other malformation as corpus calosum hypoplasia or agenesia, occipital encephalocele, malformation of the heart, face, limbs fingers and toes [3-5].
The symptoms often occur in early infancy and include slow motor development and progressive enlargement of the skull. The diagnostic is done by ultrasound, CT and MRI [6-11].
The treatment of this syndrome may be complex and sometimes includes various experts such as pediatrician, pediatric neurosurgeon, physiatrist, psychologist, sociologist or others. The treatment consists of treating the associated problems such as hydrocephaly [12-15]. Prognosis of Dandy-Walker syndrome is variable and the morbidity and mortality depends on severity of the syndrome and associated malformations [16].
Aim. The aim of this paper was to demonstrate how severe spontaneous evolution of Dandy-Walker syndrome may be expressed and the problems and dilemmas which may appear related to its treatment.
Case report. A six-year-old boy was referred to the neurosurgeon because of the excessive growth of the skull in anteroposterior axis caused by a wide base occipital encephalocele. Although the psychological development was near the low limit of the IQ, the enormous head had not allowed verticalization of the child and further progress of his psychomotor development. The head was so heavy that could not be supported by the child's neck.
Surgical procedure. We performed a cranial skull reduction with primary cranioplasty assisted by a plastic surgeon and Pudentz shunt procedure.
Result. The follow-up period lasted two years. The child started to walk, hypotonia and Babinski signs disappeared, communication and his IQ improved. The esthetic results are quite acceptable allowing him better development.
Conclusion. The early recognition of anomalies such as Dandy-Walker syndrome with occipital encephalocele using ultrasound may suggest interruption of the pregnancy on time [6-9]. However, the right diagnostic procedure for detecting deformities of the newborn and infant's head at birth is MRI, and the adequate surgical treatment can prevent abnormal and excessive growth of the skull and disorders in the psychomotor development during child's growth. A multidisciplinary approach may prevent new disabled individuals in the society.

Keywords: Dandy-Walker syndrome, excessive macrocephaly, occipital encephalocele, surgical treatment

Correspondence to: Vladimir Mirchevski, University Clinic for Neurosurgery, Clinical Center "Mother Teresa" Skopje, Macedonia; E-mail: neurosurgery.skopje@yahoo.com

Апстракт

Вовед. Синдромот на Dandy-Walker подразбира конгенитална малформација на мозокот, која го зафаќа малиот мозок со делумна и со комплетна агенезија на вермис, зголемување на четвртата мозочна комора и околните ликворни простори, формирање циста во задната черепна јама, туркајќи го нагоре тенториумот [1,2]. Хидроцефалија или покачување на притисокот во ликворните простори, а можни се и други малформации како агенезија или хипоплазија на корпус калозум, окципитална енцефалоцела, малформација на срце, лицето, екстремитетите и прстите [3,4,5].
С симптомите, често настануваат рано кај новороденчето, и вклучуваат бавен моторен развој и прогресивно зголемување на черепот. Дијагнозата се

поставува со ултразвучен преглед, компјутеризирана томографија и магнетна резонанца [6-11].
Третманот на овој синдром е комплексен, и некогаш вклучува разни специјалности, како што се педијатар, детски неврохируг, физијатар, социолог и др. Третманот се состои од третман на пропратните проблем како хидроцефалијата [12-15]. Прогнозата на синдромот на Dandy-Walker е варијабилна, морбидитетот и морталитетот зависат од тежината на синдромот и придружните малформации [17].
Приказ на случај. Шестгодишно машко дете беше упатено кај неврохируг, поради прекумерен раст на черепот во антеро-постериорен правец, предизвикан од нелекувана окципитална енцефалоцела на широка база. И поред психички развој, со коефициент на интелегенција блиску до долната граница на нормалата, големата глава не дозволуваше вертикализација на детето и натамошен психомоторен развој. Главата тежеше премногу за да биде држена од детскиот врат.
Хируршки третман. Ние реализиравме редукција на черепот со примарна краниопластика, со помош на хирург специјалист за пластична и реконструктивна хирургија, и вградивме Pudentz цистоперитонеален шант.
Резултати. Периодот на следење изнесува две години. Детето почна да оди, исчезнаа хипотонијата и знаците на Бабински, комуникацијата се подобри како и коефициентот на интелигенција. Естетските резултати се прилично прифатливи овозможувајќи му подобар развој.
Заклучок. Раното препознавање на овие аномалии, како синдромот на Dandy-Walker, со окципитална енцефалоцела, употребувајќи ултразвучен преглед може да оди во прилог на навремен прекин на бременоста [6-9]. Вистинската дијагностичка процедура за дијагностицирање деформитети на главата на новороденото е магнетната резонанца, а адекватниот оперативен третман може да спречи ненормален и прекумерен раст на черепот и пореметување во психомоторниот развој за време на раст на детето. Мултидисциплинарниот приод може да спречи појава на нови хендикепирани лица во општеството.

Клучни зборови: синдромот на Dandy-Walker, макроцефалија, окципиталма енцефалоцела, оперативно лекување

Introduction

Dandy-Walker syndrome is a congenital brain malformation involving cerebellum with partial and complete agenesia of vermis, enlargement of the fourth ventricle and surrounding fluid spaces, cyst formation in posterior cranial fosse, enlargement of posterior fosse pushing tentorium upward [1,2]. Hydrocephalus or an increase in the pressure of the fluid spaces may also be present. Corpus calosum hypoplasia or agenesia, occipital encephalocele and malformation of the heart, face, limbs fingers and toes may also be seen [3-5]. Dandy-Walker malformation is estimated to affect 1 in 20,000 to 30,000 newborns [1,18,19]. Research suggests that Dandy-Walker malformation could be caused by environmental factors that affect early development before birth. For example, exposure of the fetus to teratogens may be involved in the development of this syndrome [1,19]. In some cases a gene mutation may be found [1,19,20].
The symptoms often occur in early infancy and include slow motor development and progressive enlargement of the skull. In older children, symptoms of increased intracranial pressure and signs of cerebellar dysfunction predominate. Breathing problems, occulomotor nerve disorders, or other lower cranial nerves may be present [12-16]. Antenatal and postnatal diagnostic is done by ultrasound and MRI [6-11].
The treatment of this malformation may be complex and sometimes include various experts such as pediatrician, pediatric neurosurgeon, physiatrist, psychologist, sociologist or others. The treatment consists of treating the associated problems such as hydrocephaly (neuroendoscopy, implanting shunt), and may include other forms of therapy such as physical, occupational, and specialized education [12-15].
The prognosis of Dandy-Walker syndrome is variable with some children having normal cognition and others never achieving normal intellectual development even when hydrocephalus is treated [17]. The morbidity and mortality depends on severity of the syndrome and associated malformations. The existence of multiple malformations may shorten the life span.
The **aim** of this paper is to present this very rare case of Dandy-Walker malformation with enormous posterior fosse cyst and macrocephaly and to demonstrate how severe spontaneous evolution may be expressed and the problems and dilemmas which may appear related to the treatment.

Case report

A six-year-old boy was referred to the neurosurgeon because of the excessive growth of the skull in anterior and posterior axis, or dolychocephaly. Although the psychological development was near the low limit of the IQ, the enormous head did not allow verticalization of the child and sustained further progress of his psychomotor development.
His cranial perimeter was 1046 mm and he presented with bilateral hypotonia and bilateral Babinski sign. The computerized tomography showed partial ossify-

cation of the parietal and upper and lower occipital part of the cyst while middle occipital part of the cyst was not covered with bone. The distance of anteroposterior axis of the head was 332 mm; there was no cerebellar vermis with voluminous posterior fosse cyst and there was moderate dilatation of supra-tentorial ventricles. The diagnosis of Dandy-Walker syndrome was confirmed by MRI. MR veinography was performed in order to see the disposition of lateral sinuses.
The lateral sinuses were pushed upward to the parietal region together with the tentorium. We had no other data because the child was coming from an orphanage and was abandoned by his parents.

Fig. 1. The head of our six-year-old child before treatment

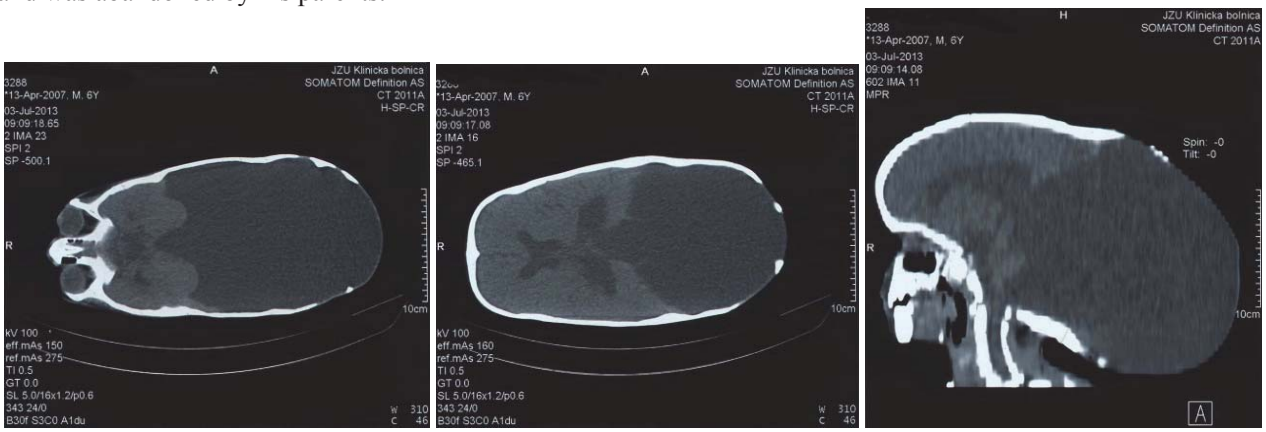

Fig. 2. Preoperative CT scan of the boy's head before treatment

Surgical procedure

The procedure was done under general endotracheal anesthesia with the child placed in a prone position with the head in Mayfield holder. The procedure was started with vertical median skin incision from the parietal to the lower occipital region. Supraperiosteal skin dissection was realized creating two skin flaps to the retroauricular region.The periostium was dissected from the dural tissue and the edge of bone defect followed by dissection of the periostium and dura from both sides of the parietal and lower part of the occipital bone to the lateral sinuses. Reducing the bone to 1 cm below the lateral sinuses we exposed the major part of the cyst and we opened it. Two large cores of ossification were left between periostium and dura in posterior parietal region right after lateral sinuses, one for each side for further cranial reconstruction. We observed a giant cyst covered with arachnoid. Excision of the free arachnoid was made and the cyst was opened. The forth ventricle and Silvius aqueduct were wide opened. Excision of the thick arachnoid free wall of the cyst was performed followed by diminishing the dura. Two large cores of ossification left between periostium and dura in posterior parietal region were rotated and used for reconstruction of the posterior wall of the vault; "Water-tide" closure of the dura was performed by 4-0 polypropylene suture. We proceeded with reduction of the excess skin and cranioplastic closure of the skin with interrupted Blair-Donatti 4-0 polypropylene sutures, without using epicranial drainage. Later a cysto-peritoneal Pudentz middle pressure shunt was inserted.

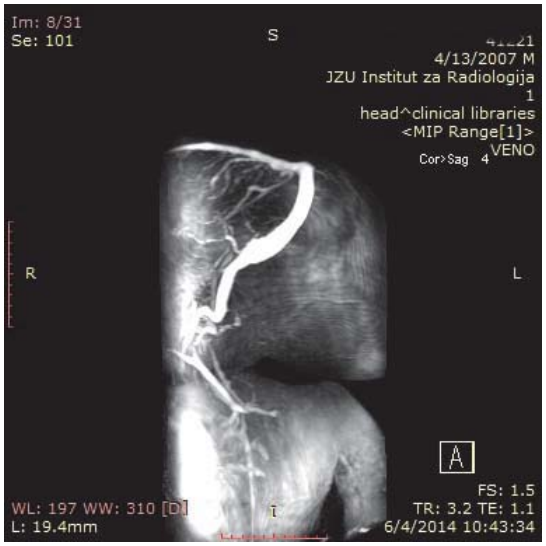

Fig. 3. Preoperative MR veinograhy before the treatment

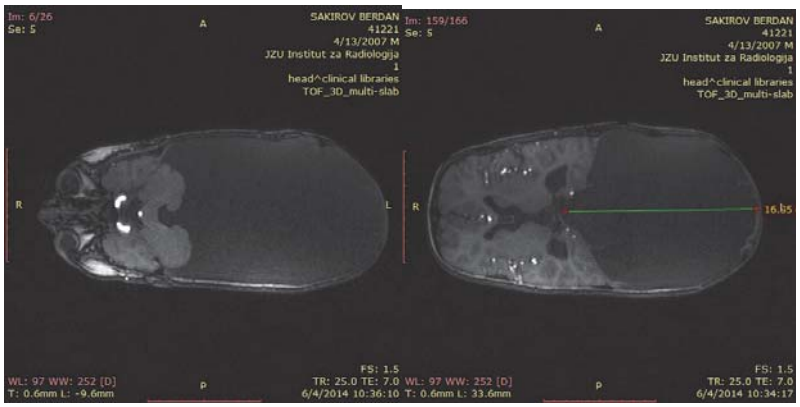

Fig. 4. Preoperative MRI before treatment

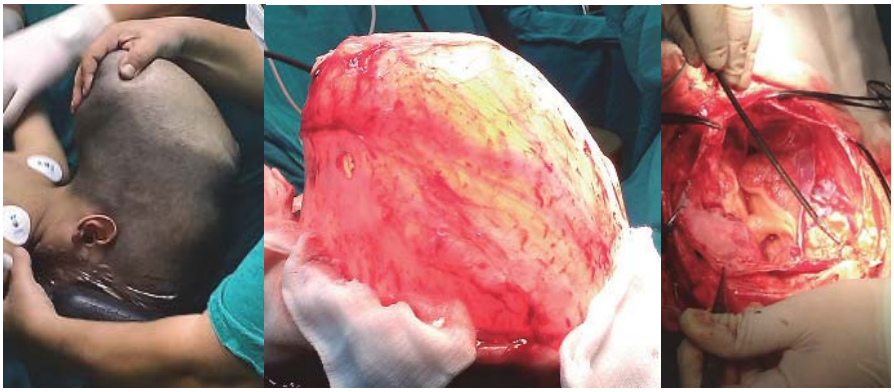

Fig. 5. Difficulties with positioning and surgery

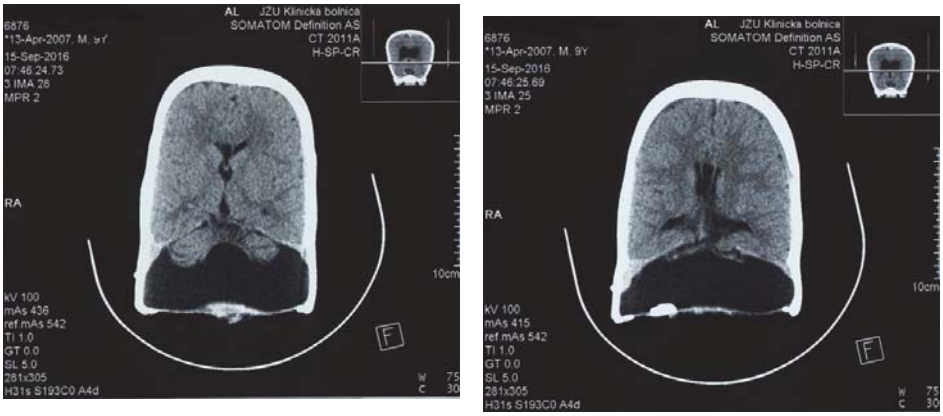

Fig. 6. Late post-operative CT-scan of our patient

Results

In the early postoperative period the child had nausea and vomited for 4 days. We achieved to verticalize the child on the 18th day after surgery helping him from the side. Three weeks after surgery the child was released from the hospital. Physiotherapy was applied in the parent institution. The follow-up period lasted two years. The child started to walk, hypotonia and Babinski signs disappeared, communication and his IQ improved. The esthetic results are quite acceptable allowing the child better development.

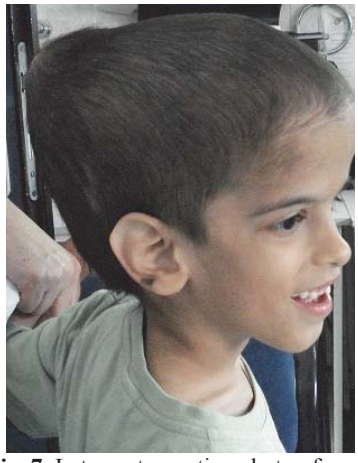

Fig. 7. Late postoperative photo of our patient

Discussion

Early prenatal diagnostic of Dandy-Walker syndrome is very important in order to interrupt the pregnancy on time. If the early diagnostic fails we are facing a baby with Dandy-Walker syndrome. Antenatal diagnostic has been improved in the Republic of Macedonia, but in this case it is obvious that failed.

The treatment of this malformation may be complex and sometimes includes various experts such as pediatriccian, pediatric neurosurgeon, physiatrist, psychologist, sociologist or others. The treatment consists of treating the associated problems such as hydrocephaly. A shunt procedure is to be inserted as soon as possible after establishing a diagnosis of Dandy-Walker syndrome to avoid excessive growth of the skull. Direct surgical approach may be realized if other local compressive problems exist including Silvius aqueduct narrowing. It is very rare to meet a case with Dandy-Walker syndrome with occipital encephalocele and excessive macrocephaly as ours. It is obvious that treatment at birth would have been the best option for this child.. But, this child was abandoned, with unsolved parental responsebility for a long period and hence he was referred to a neurosurgeon very late, at the age of 6.5 years. The major problem in this case was that the child had giant macrocephaly for more than 6 years. Facing the difficulties and the possible complications [21-23], the main question was whether to undertake any procedure and treatment or not. If we did not do anything in this case, then his further development would have been blocked because of a lack of ambulation, communication, etc… Thus, we took a risk and decided to diminish the head exciding the large part of the cyst, dura, bone and the skin, performing a primary cranioplasty in collaboration with a plastic surgeon and then inserting the Pudentz middle pressure shunt. Modulated shunt was to be taken into consideration, but we do not have such devices.

Conclusion

The early recognition of anomalies such as Dandy-Walker syndrome by using ultrasound may suggest interruption of the pregnancy on time. However, the right diagnostic procedure for detecting the deformities of the newborn and infant's head at birtht is MRI, and the adequate surgical treatment, which can prevent abnormal and excessive growth of the skull and disorders in the psychomotor development during child's growth. A multidisciplinary approach may prevent new disabled individuals in the society.

Conflict of interest statement. None declared.

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Case report

SURGICAL TREATMENT OF PATIENT WITH RUPTURED DISSECTION OF THE THORACIC AORTA – STANFORD A, DE BAKEY I – CASE REPORT OF THE PATIENT SURGICALLY TREATED AT UC OF STATE CARDIOSURGERY – SKOPJE

Kratok: Surgical treatment of patient with ruptured dissection of the thoracic aorta

ХИРУРШКИ ТРЕТМАН НА ПАЦИЕНТ СО РУПТУРИРАНА ДИСЕКЦИЈА НА ТОРАКАЛНА АОРТА - ПРИКАЗ НА СЛУЧАЈ НА ПАЦИЕНТ ОПЕРАТИВНО ТЕРТИРАН

Sashko Jovev[1], Aleksandar Kolev[1], Suzana Dameska[1], Nadica Mehmedovikj[1], Omer Dzemali[2], Sasha Kachar[3] and Mirjana Kachar[3]

[1]University Clinic of State Cardiosurgery, University ”Ss Cyril and Methodius”- Skopje, Republic of Macedonia, [2]University Clinic Triemli - Zurich, Germany, [3]Institute for Cardiovascular Diseases – University Clinical Center Serbia (falat drzavi, a negde I gradovi

Abstract

Introduction. A 59-year-old male patient with dissection of the thoracic aorta, DeBakey I, Stanford A is presented in this case study. We present his symptoms, his preoperative condition, diagnostic procedures, the surgical procedure and his postoperative treatment at the UC of State Cardiosurgery-Skopje.
Case report. The surgery was performed two days after establishment of the diagnosis and more than 3 days (72 hours) after the symptoms occured, due to absence of patient’s consent for the surgery. This resulted in more difficult preoperative condition of the patient, surgical procedure harder to perform, and reduced survival expectations. Preoperative risk of predicted mortality from the cardiovascular surgery calculated according to EUROSCORE was 28.6%.
Results. In this case study we also present classification, etiology, pathophysiology, and some statistics about the incidence of thoracic aorta dissection and survival rates emphasizing the increased mortality rate in delayed surgical interventions.

Keywords: thoracic aorta, dissection, rupture, surgical treatment

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Апстракт

Вовед. Во овој приказ на случај на пациент е претставен 59 годишен маж со дисекција на торакалната аорта, Станфорд А. Ги презентираме неговите симптоми, неговата предоперативна состојба, дијагностичките процедури, оперативната-хируршка процедура, како и неговиот постоперативен третман на Универзитетската клиника за државна кардиохирургија-Скопје.
Приказ на случај. Предоперативниот ризик за предвидената смртност од кардиохируршката интервенција според EUROSCORE скалата изнесуваше 28,6 проценти.
Резултати. Во овој приказ на случај ја презентираме и класификацијата, етиологијата, патофизиологијата, како и дел од статистиката за инциденца на дисекциите на торакалната аорта и стапката на преживување, нагласувајќи ја зголемената стапка на смртност при одложување на хируршката интервенција.

Клучни зборови: торакална аорта, дисекција, руптура, хируршки третман

Introduction

Definition

An aortic dissection is a very severe medical condition where the inner layer of the aorta (intimma) tears and then the blood surges through the tear between the inner and the middle layer separating (dissecting) them. The acute form of the dissection is often rapidly lethal while patients that survive the initial event usually develop chronic dissection with more variable symptoms.

Classification

Depending on the timing, the dissection can be acute, when the patient is admitted to the clinic within the first two weeks, or chronic when the patient comes to

Correspondence to: Sashko Jovev, University Clinic of State Cardiosurgery, Clinical Center “Mother Teresa” 1000 Skopje, R. Macedonia; E-mail: jovev99@yahoo.com

the clinic more than two months after the initial event. Subacute dissection is added recently to this classification to describe patients in the period between two weeks and two months from the initial event.
There are two classification systems most frequently used in the clinical practice, and they describe different types of dissection depending on the location, and the extent of the dissection-De Bakey, and Stanford classification.
In De Bakey classification there are four groups of aortic dissections depending on the location and the extent (Figure 1).

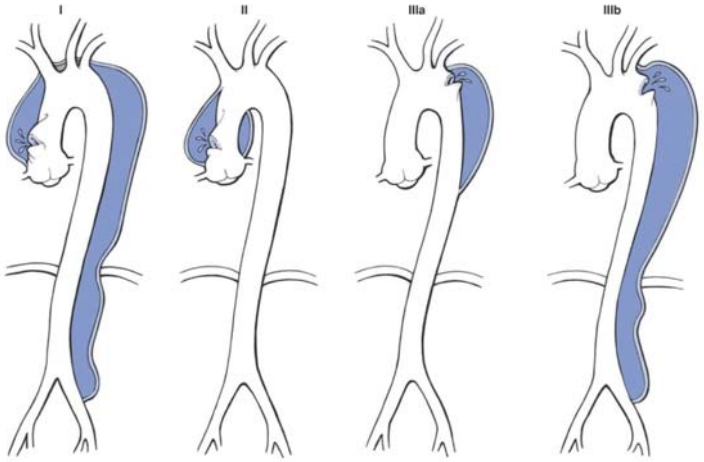

Fig. 1. Types of dissection of the thoracic aorta according to De Bakey

Stanford classification is more functional one, and it differs two types of dissection, type A-where all dissections that include the ascendant part of the aorta are classified, and type B when the ascendent part of the aorta is not included in the dissection.
The tear in the inner layer occurs in the ascendent part of the aorta in 70% of all dissections, 10% in the arch, and the rest is in the descendent part.
In Stanford A in 90% the tear occurs in the ascendent part of the aorta with distal propagation, and in 10% the tear is in the arch.
In Stanford B in 85% the tear is in the descendent part of the aorta, and in 15% in the arch.
Stanford A dissections are twice more often than Stanford B.

Epidemiology

Aortic dissection is the most frequently diagnosed lethal condition of the aorta. There is an estimated worldwide prevalence of 0.5-2.95 per 100.000 per year. In Macedonia it will be 10-30 cases per year. It is an estimated number, and the real number is probably quite larger due to autopsies that show that many of the dissections have fatal results without being diagnosed [1,2].

Etiology

Around 40% of patients with acute aortic dissection die. If not treated, Stanford A, 25% of the patients will die in the first 24 hours, 50% in the first week and 90% in the first month. Type 2 has 70% survival with medical therapy [5,6].
There is not a single factor that directly causes the dissection. Usually we speak about risk factors. The most common risk factor is hypertension. It weakens the media and gives the opportunity to other forces to result in dissection [7.8]. Other risk factors are shown in Table 1.

Table 1. Risk factors for Type A and B Thoracic Aortic Dissection

Hypertension
Connective tissue disorders:
Ehlers-Danlos Syndrome
Marfan disease
Turner Syndrome
Cystic medial disease of aorta
Aortitis
Iatrogenic
Atherosclerosis
Thoracic Aortic Aneurysm
Bicuspid Aortic Valve
Trauma
Pharmacologic
Coarctation of the aorta
Hypervolemia (pregnancy)
Congenital aortic stenosis
Polycystic kidney disease
Pheochromocytoma
Sheehan syndrome
Cushing syndrome

Clinical presentation - Symptoms

Clinical presentation of thoracic aorta dissection depends on the type of the aorta. Usually the symptoms begin with strong interscapular pain, followed by retrosternal pain, together with dyspnea, and later symptoms depending on the compromitation of the blood vessels exits from the aorta (neurological symptoms, anuria, cold extremities, lack of sensibility and motion). Type A may

rupture intrapericardially resulting in tamponade. Type B ruptures in the left pleural space. If the rupture doesn't occur, then false lumen usually progresses in saccular aneurysm. In patients with chronic dissections, 56% of the lethal results are due to a rupture of the saccular aneurysm [3.4].
Type A dissection may be presented with aortic regurgitation (due to the loss of the commissural function), myocardial infarction (because of the compression of the coronary ostia), cardiac tamponade, vena cava superior syndrome, neurological symptoms, shock.
Around 40% of the patients suffering from acute dissection of the thoracic aorta die. Mortality of the Stanford type A dissections if left untreated is 25% in the first 24 hours, 50% in the first week, and 90% in the first month after the initial event. Type B has 60-80% survival rate with medicamentous treatment.

Case report

Preoperative condition

A 59-year-old patient with symptoms of chest pain and pain in the right leg was admitted in the ICU at the University Cardiology Clinic-Skopje. The symptoms began on the night, one day before admittion, starting with chest pain and dyspnea, and afterwords the pain in the right leg started in the hip and later spreading to the foot with inability to move the leg.
The patient had history of sinus bradycardia and obstructive syndrome. He said he was receiving cardiac and pulmonary drug therapy, but without documentation on the condition and treatment (Tab. Aspirin, Tab. Enap, Tab. HHTZ, Tab. Aminophylline).
The patient is a heavy smoker, and has no food or drug allergies.
On admission to the Cardiology Clinic, the patient had high-pitched auscultatory sounds bilaterally. His blood pressure was 120/80 mmHg and heart rate 45.
His laboratory results were normal.
A cardiac surgeon was called for consultation and the patient underwent diagnostic procedures to assess his condition.

Echocardiography

The dimensions of the left ventricle were normal, with good systolic function. Kinetics of the basal third of the lower wall was reduced.
Valves: mitral valve had fibrosis and light mitral regurgitation.
Aortic valve had three leaflets, no stenosis and fibrosis on the leaflets.
Tricuspid valve – light regurgitation.
Aorta: Atheromatous wall. Dimensions of the aorta in the visualized part were within the reference range. The arch and the descending part could not be visualized.
No signs of PAH, and pericard without effusion.
Doppler of lower extremities showed pathologic signals on the right AFD and AP.
CT angiography showed dissection of the aorta beginning right after the exit from the heart, continuing through the ascending aorta and aortic arch where double lumen exists. Dissection continued through the whole thoracic aorta and abdominal aorta. Dissection of both iliacas is shown, the right in the upper part, and the whole left (Figure 2, 3, 4 and 5).

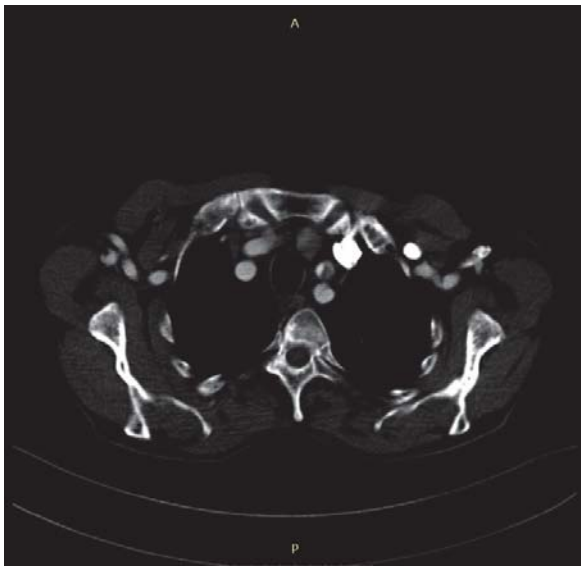

Fig. 2. Dissection of the left carotid artery and the left subclavia and brachiocephalic trunk without dissection

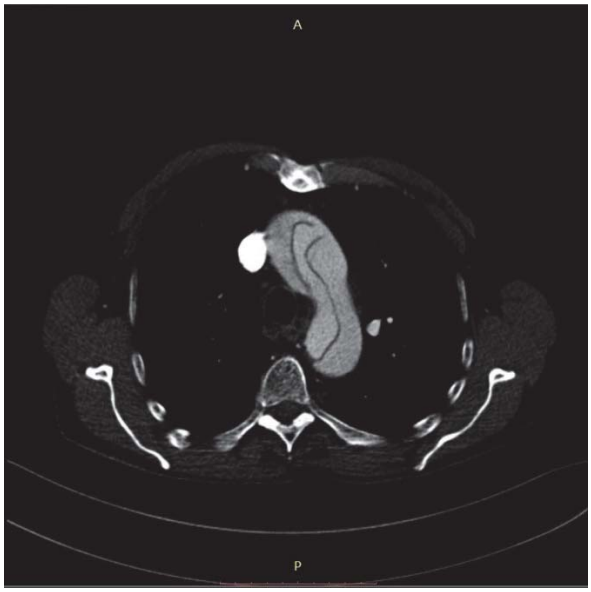

Fig. 3. Dissection of the aortic arch

With these investigations the patient was diagnosed with dissection of the aorta, Stanford A, De Bakey I, and our cardiosurgery team indicated an urgent surgery of the thoracic aorta.
The situation was explained to the patient, and the urgent need for surgery was emphasized, but still, he did not

want to sign the consent for the surgery. Thus, at that moment he did not undergo the surgery.

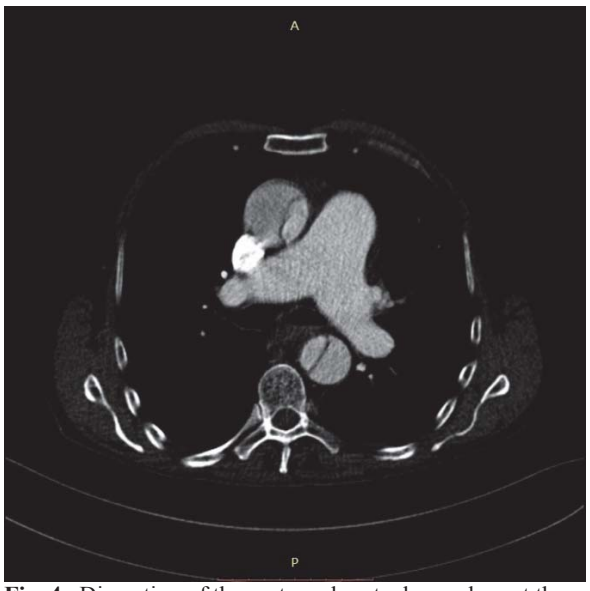

Fig. 4. Dissection of the aorta and aorta descendens at the level of the branching

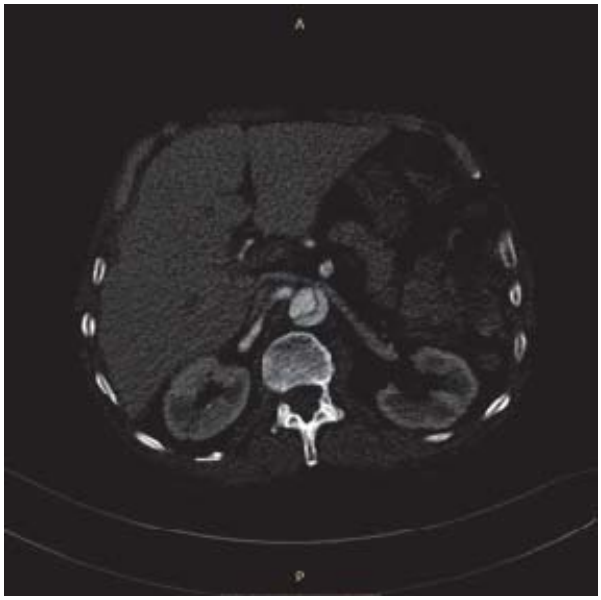

Fig. 5. Dissection of the abdominal aorta at the level of the branching of renal arteries of pulmonal arteries

He stayed at the Cardiology Clinic, where he was treated with analgesic and antihypertensive drugs.
Two days later the patient's condition worsened and he finally signed the consent for surgery, and he was transferred to UC for State Cardiosurgery.
He was admitted in an extremely bad general condition, tension of the left arm was 190/102 mmHg, and of the right arm 180/93 mmHg, with heart rate 96/min, with border blood gas values. He had obvious venous distention of the chest wall and his neck and cyanosis, as part of well developed vena cava superior syndrome.

Prior to the surgery his laboratory results were: WBC-13.7; RBC-4.12; HGB-140; Hct-0.417; Plt-62; Glucose-5.86; Urea-10.2; Creatinine-88; Total proteins-66; Albumins-39; Globulins-27; ALT-40; AST-63; LDH-364; Na-137; K-3.8; Cl-99; Ca-2.23; Mg-0.77; CRP-305.9; Fe-2.9; Lact-2.82. Heart enzymes were: CK-1817; CK-MB-49; Troponine-27.43. INR-1.0, D-dimers-24500.
Preoperative risk of cardiac surgical intervention as estimated mortality according to EUROSCORE calculation was 28.6%.

Operation

Resectio aortae ascendens, arcus aortae, pars proximalis aortae thoracalis, pars proximalis arteriae subclaviae sinister et pars proximalis a carotis communis sinister.
Reconstructio aortae ascendens cum Dacron graft No. 24. Reconstructio pars proximalis aortae thoracalis et arcus aortae cum Dacron graft No. 22. Sutura arteriae subclaviae. Reconstructio a. carotis communis sinister cum interpositionem Dacron grafti No. 8.
The patient with acute dissection of the aorta (type I De Bekey) (type A Stanford), and interpericardial rupture of the aorta, with chronic obstructive pulmonary disease, occlusion of the right iliac artery, ischemia of the right leg, without neurological disorder.
He was operated on under general endotracheal anesthesia. First we found and isolated the right axillary artery, and then we looped it. Then we gave 5000 IU of heparin and sutured 8 mm graft "end to side" on the artery, placing an arterial cannula through the graft (Figure 6).

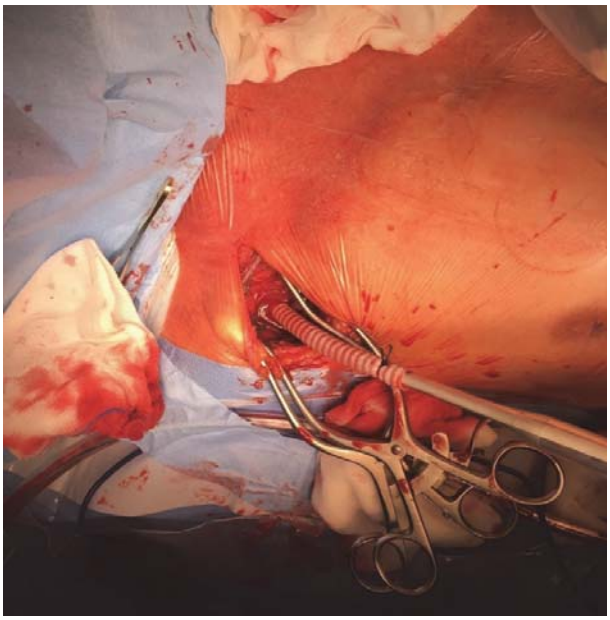

Fig. 6. Arterial cannula placed through the graft in the right axillary artery

Median sternotomy followed, then pericardiotomy, venous cannulation. Then we put the patient on the EKC/ECG machine. Then we clamped the aorta just beneath

the brachocephalic trunk, we started with antegrade perfusion through the axillary artery, we resected the aneurysm and gave cardioplegia direct into the coronary ostia. Then we cooled the patient to 18°C, started with total circulatory arrest, declamped the aorta, and we excised the whole diseased aorta (the arch and part of the descending aorta). Then we reimplanted the brachiocephalic trunk and the left carotid to the new arch. We put a new clamp on the prosthesis, made the proximal anastomosis, rewarmed the patient, and when the parameters including heart work were good, we stopped the machine. After that we did hemostasis and closed the patient in usual manner (Figure 7, 8 and 9).

Postoperative treatment

Postoperatively the patient was transferred and treated in the ICU at the UC of State Cardio surgery. After transferring the patient from the operating theater he was given adrenaline and noradrenaline support, which was reduced in the following days and fully stopped at the third postoperative day. The therapy included solutions, laxatives, cardio tonics, antihypertensive, antiulcerogenics, antiemetics, antibiotics and blood derivates.

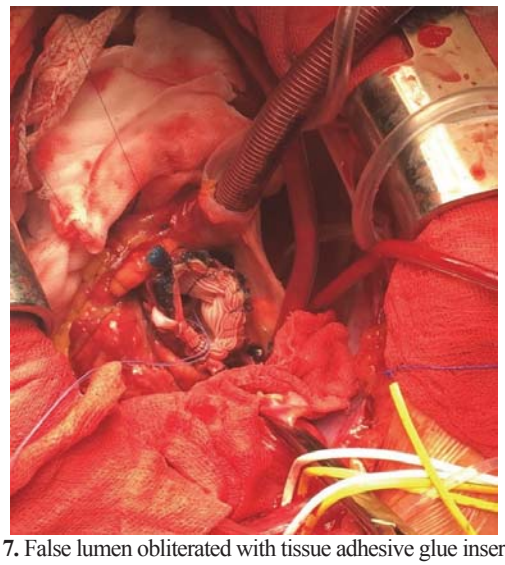

Fig. 7. False lumen obliterated with tissue adhesive glue inserted between the flap and the adventitia, and Dacron graft size 24 sutured afterwards

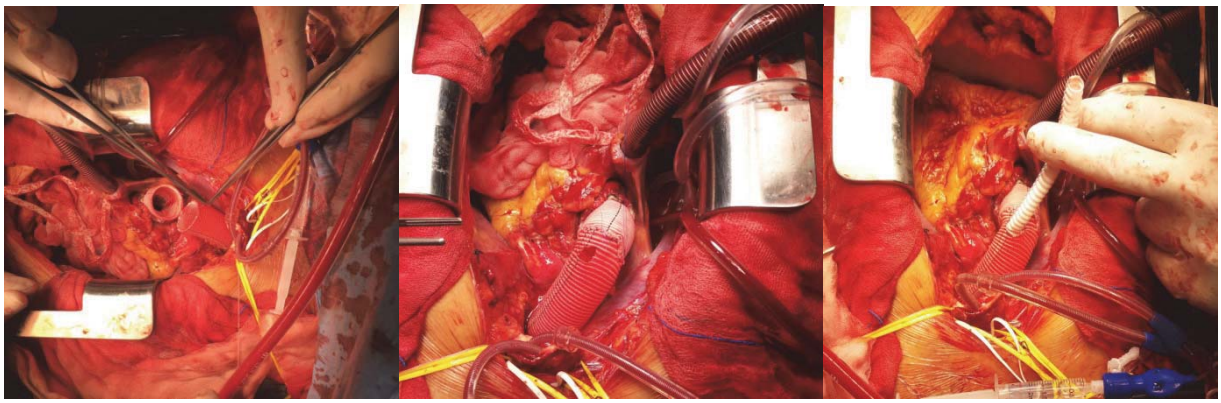

Fig. 8. Suturing the proximal to distal graft and forming a new arch with consequent sutured dacron graft 8 mm

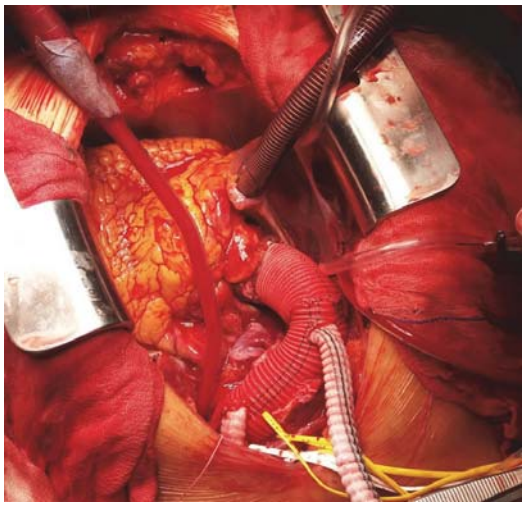

Fig. 9. Final view of the newly formed arch with dacron graft size 8 mm from the left carotid artery and truncus brachiocephalicus sutured on it

The patient was hemodinamically stable in regular sinus rhythm. Regarding postoperative respiratory condition, the patient was still with marginal levels of blood gases, because of the bad pulmonary condition preoperatively. He had normal hour portions of diuresis, with normal laboratory results. He was extubated on the second postoperative day, but still was respiratory limited, so in few times backed on the invasive ventilation. Drains were taken out on the sixth postoperative day, after the drainage stopped. On X-ray we saw athelectasis, and performed bronchial aspiration and bronchial lavage, which resulted in improvement of the patient condition. At the fourteenth postoperative day, the patient was in improved general condition and transferred to the cardiology ward.

Conflict of interest statement. None declared.

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ММП

Сѓпецијален ѓруд - Преѓораки

УПАТСТВО ЗА КЛИНИЧКА ПРАКСА ЗА ТЕРАПИЈА НА ПАЦИЕНТИ СО ДИЈАБЕТЕС И ХРОНИЧНА БУБРЕЖНА БОЛЕСТ ВО СТАДИУМ 3b ИЛИ ПОВЕЌЕ (eGFR <45 ml/min)

CLINICAL PRACTICE GUIDELINE ON MANAGEMENT OF PATIENTS WITH DIABETES AND CHRONIC KIDNEY DISEASE STAGE 3b OR HIGHER (eGFR<45 ml/min)

Henk Bilo[1], Luis Coentrao[2], Cecile Couchoud[3], Adrian Covic[4], Johan De Sutter[5], Christiane Drechsler[6], Luigi Gnudi[7], David Goldsmith[8], James Heaf[9], Olof Heimburger[10], Kitty J Jager[11], Hakan Nacak[12], Maria Jose Soler[13], Liesbeth Van Huffel[14], Charlie Tomson[15], Steven Van Laecke[16], Laurent Weekers[17], Andrzej Wiecek[18], Davide Bolignano[19], Maria Haller[20], Evi Nagler[16], Ionut Nistor[4], Sabine van der Veer[21], Jelka Masin-Spasovska[22], Gulsen Selim[22], Olivera Stojceva-Taneva[22], Goce Spasovski[22] and Wim Van Biesen[23]

[1]Consultant physician, Department of Internal Medicine, Isala Clinics, Zwollw, the Netherlands University Medical Center, Groningen, the Netherlands, [2]Consultant nephrologists, Nephrology and Infectious Diseases Research and Development Group, INEB-)13S), University of Porto, Portugal, [3]Epidemiologist, REIN registry, Agence de ka biomedecine, Saint-Denis La Plaine, France, [4]Consultant nephrologist, Clinic of Nephrology, C. I. Parhon University Hospital, Gr T. Popa, University of Medicine and Pharmacy, Iasi, Romania, [5]Consultant cardiologist, Maria Middelares Ziekenhuis, Ghent, Belgium, Consultant nephrologists, [6]Division of Nephrology, University of Wurzburg, Germany, Member of the ERBP Methods Support Team, [7]Consultant endocrinologist, Unit for Metabolic Medicine, Department of Diabetes and Endocrinology, Cardiovascular Division,, Guy`s and St. Thomas Hospital, King`s College London, London United Kingdom, [8]Consultant nephrologists, Renal and Transplantation Department, Guy`s Hospital, London, UK, [9]Consultant nephrologists, Department of Nephrology B, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark, [10]Consultant nephrologists, Division of Renal Medicine, Department of Clinical Science, Karolinska Institutet, Huddinge University Hospital, Stockholm, Sweden, [11]Epidemiologist, director of the ERA-EDTA registry, Department of Medical Informatics, Amsterdam Medical Center, Amsterdam, the Netherlands, [12]PhD-student, department of Clinical Epidemiology, University Medical Centre, Leiden, the Netherlands, [13]Consultant nephrologists, department of Nephrology, Hospital del Mar, Barcelona, Spain, Institut Hospital del Mar of Medical Research (IMIM), Barcelona, Spain, [14]Resident endocrinologist, Endocrinology Division, Ghent University Hospital, Ghent, Belgium, [15]Consultant nephrologist, Newcastle upon Tyne Foundation Trust, Newcastle upon Tyne, United Kingdom, [16]Consultant nephrologist, Renal division, Ghent University Hospital, Ghent, Belgium, [17]Consultant nephrologist, Service of Nephrology, Dialysis and Transplantation, Centre Hospitalier Universitaire, Liege, Belgium, [18]Consultant nephrologist, Department of Nephrology, Endocrinology, and Metabolic Diseases, Medical University of Silesia, Katowice, Poland, [19]Clinical researcher, Institute of Clinical Physiology, National Council of Research, Reggio Calabria, Italy, [20]Specialist registrar nephrology, KH Elisabethinen Linz, Linz, Austria, [16]Consultant nephrologist, Renal division, Ghent University Hospital, Ghent, Belgium, [4]Consultant nephrologist, Gr T. Popa, University of Medicine and Pharmacy, Iasi, Romania, [21]Implementation specialist, Centre for Health Informatics, University of Manchester, Manchester, United Kingdom, [22]Nephrologist, Skopje University Hospital, Macedonia, [23]Chair of the guideline development group, Chair of ERBP Consultant nephrologist, Renal Division, Ghent University Hospital, Ghent, Belgium

Апстракт

Преваленцијата на дијабетес мелитус во голема мера се зголемува и се смета за состојба која води до растечка загриженост во здравствените системи. Покрај кардиоваскуларните компликации, дијабетесот е асоциран и со хронична бубрежна болест (ХББ). ХББ кај пациентите со дијабетес може да е предизвикана од етаблирана дијабетичка нефропатија, но исто така може да е предизвикана и индиректно од дијабетесот, како на пр.: поради полиневропатска дисфункција на уровезиката, зголемена инциденција на рекурентни ури-

Кореѕпонденција и ретѕинѓ до: Гоце Спасовски, ЈЗУ Универзитетска клиника за нефрологија, "Водњанска" 17, 1000 Скопје, Р. Македонија; E-mail: spasovski.goce@gmail.com

нарни инфекции или макроваскуларна ангиопатија. Но, многу пациенти кои развиваат ХББ чија причина не е дијабетес, ќе развијат или можеби веќе имаат дијабетес мелитус. И на крајот, многу лекови кои се користат за терапија на ХББ, на пр.: кортикостероиди или калцинеурински инхибитори, може да предизвикаат дијабетес.
И покрај силната интеракција меѓу дијабетесот и ХББ, терапијата на пациентите со дијабетес и ХББ во стадиум 3b или повеке (eGFR<45 ml/min) останува и понатаму проблематична. Создадена е голема документација со упатства за терапија на пациенти со дијабетес чија цел е спречување или забавување на прогресијата кон ХББ, најчесто дефинирана како микро или макроалбуминурија. Но, ниту еден од овие документи специфично не ја обработува терапијата на пациентите со ХББ стадиум 3b или повеќе (eGFR<45 ml/min). Постои недостиг на добро дизајнирани, проспективни студии кај оваа популација, бидејќи многу студии ги исклучуваат или пациентите со дијабетес или со ХББ стадиум 3b или повеќе (eGFR<45 ml/min), или и двете. Ова ја ограничува заснованоста на докази во овие приоди. Заради тоа, советодавниот борд на ERBP донесе одлука дека има потреба од упатство за терапија на пациенти со дијабетес со ХББ стадиум 3b или повеќе за употреба во секојдневната клиничка пракса.

Клучни зборови: диабетес мелитус, ERBP, хронична бубрежна болест

Abstract

Diabetes mellitus is becoming increasingly prevalent and is considered a rapidly growing concern for healthcare systems. Besides the cardiovascular complications, diabetes mellitus is associated with chronic kidney disease (CKD). CKD in patients with diabetes can be caused by true diabetic nephropathy, but can also be caused indirectly by diabetes, e.g. due to polyneuropathic bladder dysfunction, increased incidence of relapsing urinary tract infections or macrovascular angiopathy. However, many patients who develop CKD due to a cause other than diabetes will develop or may already have diabetes mellitus. Finally, many drugs that are used for management of CKDs, e.g. corticosteroids or calcineurin inhibitors, can cause diabetes.
Despite the strong interplay between diabetes and CKD, the management of patients with diabetes and CKD stage 3b or higher (eGFR <45 mL/min) remains problematic. Many guidance-providing documents have been produced on the management of patients with diabetes to prevent or delay the progression to CKD, mostly defined as the presence of micro- and macro-albuminuria. However, none of these documents specifically deal with the management of patients with CKD stage 3b or higher (eGFR <45 mL/min). There is a paucity of well-designed, prospective studies in this population, as many studies exclude either patients with diabetes, or with CKD stage 3b or higher (eGFR <45 mL/min), or both. This limits the evidence base to these approaches. Thus, the advisory board of ERBP decided that a guideline on the management of patients with diabetes and CKD stage 3b or higher was needed for everyday clinical practice.

Key words: diabetes melitus, ERBP, chronic kidney disease

Вовед

Преваленцијата на дијабетес мелитус во голема мера се зголемува и се смета за состојба која води до растечка загриженост во здравствените системи. Покрај кардиоваскуларните компликации, дијабетесот е асоциран и со хронична бубрежна болест (ХББ). ХББ кај пациентите со дијабетес може да е предизвикана од етаблирана дијабетичка нефропатија, но исто така може да е предизикана и индиректно од дијабетесот, како на пр.: поради полиневропатска дисфункција на уровезиката, зголемена инциденција на рекурентни уринарни инфекции или макроваскуларна ангиопатија. Но, многу пациенти кои развиваат ХББ чија причина не е дијабетес, ќе развијат или можеби веќе имаат дијабетес мелитус. И на крајот, многу лекови кои се користат за терапија на ХББ, на пр.: кортикостероиди или калцинеурински инхибитори, може да предизвикаат дијабетес.
И покрај силната интеракција меѓу дијабетесот и ХББ, терапијата на пациентите со дијабетес и ХББ во стадиум 3b или повеке (eGFR<45 ml/min) останува и понатаму проблематична. Создадена е голема документација со упатства за терапија на пациенти со дијабетес чија цел е спречување или забавување на прогресијата кон ХББ, најчесто дефинирана како микро или макроалбуминурија. Но, ниту еден од овие документи специфично не ја обработува терапијата на пациентите со ХББ стадиум 3b или повеќе (eGFR<45 ml/min). Постои недостиг на добро дизајнирани, проспективни студии кај оваа популација, бидејќи многу студии ги исклучуваат или пациентите со дијабетес или со ХББ стадиум 3b или повеќе (eGFR<45 ml/min), или и двете. Ова ја ограничува заснованоста на докази во овие приоди.
Како дополнување на ова, а поради некои нови сознанија на ова поле, советот на ERBP донесе одлука дека е крајно време и има потреба од

упатство за терапија на пациенти со дијабетес и ХББ во стадиум 3b и повеќе (eGFR<45 ml/min):

1. Поради јасното препознавање на важноста од приоди за здравствена грижа засновани на докази за да се зголеми квалитетот, да се подобри безбедноста и да се етаблира јасна и транспарентна рамка за развој на услуги и здравствени мерки.
2. Поради напредокот на нови дијагностики и терапевтици во ова поле фрлајќи светло на потребата од валиден, доверлив и транспарентен процес на евалуација кој ќе биде поддршка за клучните одлуки. Дополнително на ригорозниот приод кон методологијата и евалуацијата, ние бевме енергични во целта да обезбедиме документ кој ќе се фокусира на исходите важни за пациентот и кој ќе биде од корист за клиничарите во секојдневната пракса.

Се надеваме дека со уживање ќе го читате ова упатство и дека ќе ви биде од корист во секојдневната грижа за пациентите со дијабетес и ХББ во стадиум 3b и повеќе.

Одрекување од одговорност: ова упатство е преведено со одобрение на ЕРБП, официјалното тело за упатства на ЕРА-ЕДТА. Но, ЕРБП превзема само целосна одговорност за оригиналното упатство во целост на англиски јазик како што е публикувано во Nephrol. Dial. Transplant.
http://ndt.oxfordjournals.org/content/30/suppl_2/ii1.full
http://european-renal-best-practice.org/

ГЛАВА 1. Теми поврзани со изборот на бубрежен заместителен модалитет кај пациенти со дијабетес и терминална бубрежна болест

Глава 1.1. Дали треба пациентите со дијабетес и ХББ во стадиум 5 да започнат со перитонеална дијализа или хемодијализа како прв модалитет?

Препорачуваме да се даде приоритет на општиот статус на пациентот и преференциите на пациентот при изборот на бубрежна заместителна терапија бидејќи не постојат докази за супериорност на било кој модалитет над друг кај пациентите со дијабетес и ХББ во стадиум 5 (1C).

Препорачуваме пациентите да бидат информирани без пристрасност за различните достапни терапевтски опции (1A).

Кај пациентите чиј избор за започнување ќе биде хемодијализа (ХД) сугерираме да се преферира *high flux* во однос на *low flux* секогаш кога е тоа можно (2C).

Сугерираме дијабетесот да нема влијание врз изборот меѓу ХД и хемодијафилтрација (ХДФ) (2B).

Совет за клиничка пракса

Доколку сите различни модалитети на бубрежна заместителна терапија можат да бидат достапни на пациентот "перитонеална дијализа (ПД), хемодијализа во центар за ХД, сателитска ХД, домашна ХД, ноќна дијализа, разни модалитети на трансплантација" овозможете неопходно слободен избор на модалитет.

Глава 1.2. Дали пациентите со дијабетес и стадиум 5 на ХББ треба да започнат со дијализа порано, т.е. пред појавата на симптоми, во однос на пациентите без дијабетес?

1.2.1. Препорачуваме започнување со дијализа кај пациенти со дијабетес врз основа на истите критериуми како и пациенти без дијабетес (1A).

Совет за клиничка пракса

- Да се разликуваат тегобите како резултат на долготраен дијабетес (полиневропатија, гастропареза наспроти гадење поради уремија итн.) од уремичните тегоби, може да биде тешко во клиничката пракса
- Кај пациенти чиј избор е ХД, мора да имате предвид и да дискутирате со пациентот за следните фактори за да се донесе одлука за оптималното време за креирање на васкуларниот пристап:

а) брзината на губењето на бубрежната функција;
б) проектирана веројатност дека ќе се добие функционален васкуларен пристап;
в) проектирано очекувано преживување.

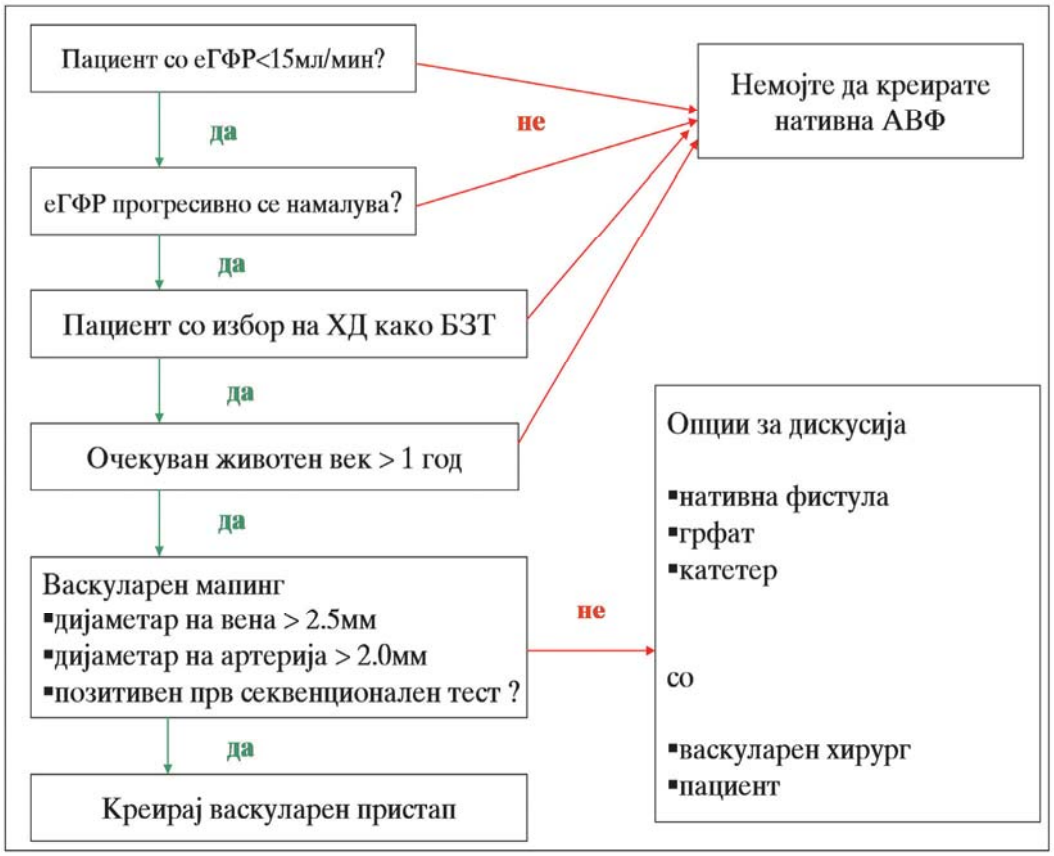
Глава 1.3. Кај пациентите со дијабетес и стадиум 5 на ХББ дали треба да се преферира како иницијален васкуларен пристап нативна фистула, графт или тунелизиран катетер?

1.3.1. Препорачуваме да се направат разумни напори за да се избегне креирање на тунелизиран катетер како примарен пристап кај пациентите со дијабетес кои започнуваат со ХД како бубрежна заместителна терапија (1C).
1.3.2. Препорачуваме сите предности, недостатоци и ризици на секој тип на пристап да се дискутираат со пациентот.

Совет за клиничка пракса

Кога се одлучува дали да се креира или не нативен васкуларен пристап, треба да се имаат во предвид следните ставови:

- Очекуваното преживување на пациентот;
- Очекуваниот квалитет на живот на пациентот;
- Веројатноста на успешност на креирање на



Сл. 2. Дијаграм на креирање на васкуларен пристап кај пациент со дијабетес

нативен пристап, според предикцијата заснована на резултатите од ехо и Доплер (слика 2).

Глава 1.4. Дали постои бенефит од бубрежна трансплантација кај пациенти со дијабетес и стадиум 5 на ХББ?

1.4.1. Препорачуваме да им се овозможи едуцирање за различните опции на трансплантација (Слика 3) и нивните очекувани исходи на пациентите со дијабетес ХББ во стадиум 4 или 5 кои се сметаат подобни за трансплантација (1D).

Искази само за пациенти со дијабетес тип 1 и ХББ во стадиум 5

1.4.2. Сугерираме бубрежна трансплантација од живо дарителство или симултана панкреас-бубрег трансплантација за да се подобри преживувањето на прифатливите пациенти (2C).

1.4.3. Не сугерираме трансплантација на бета-клетки по бубрежна трансплантација со цел да се подобри преживувањето (2C).

1.4.4. Сугерираме графт на панкреас по бубрежна транпслантација за да се подобри преживувањето (2C).

Искази само за пациенти со дијабетес тип 2 и ХББ во стадиум 5

1.4.5. Не сугерираме панкреасна или симултана панкрес-бубрег трансплантација (1D).

1.4.6. Препорачуваме дека дијабетесот сам по себе не треба да се смета за контраиндикација за бубрежна трансплантација кај пациенти кои инаку ги задоволуваат инклузионите и ексклузионите критериуми за трансплантација (1C).

Совет за клиничка пракса

- Успешна симултана панкреас-бубрег трансплантација го подобрува квалитетот на живот, невропатијата, гликемиската контрола и дијабетичната ретинопатија кај тип 1 дијабетес.
- Периоперативниот коморбидитет кај симултаната панкреас-бубрег трансплантација може да биде значаен.
- Упатуваме на ERBP-упатството за еваулација на донор и реципиент кај бубрежна трансплантација (60) и периоперативниот третман за проценка дали или не пациентот се смета подобен за трансплантација.

Сл. 3. Дијаграм на одлука за трансплантација кај пациенти со тип 1 дијабетес

ГЛАВА 2. Теми поврзани со гликемиска контрола кај пациенти со дијабетес и ХББ стадиум 3б или повеке (eGFR < 45 ml/min)

Глава 2.1.

А. Дали треба да ни биде цел намалување на HbA1c преку стриктна гликемиска контрола Кај пациенти со дијабетес и ХББ во стадиум 3b или повеке (eGFR < 45 ml/min)?

Б. Дали е агресивната терапевтска стратегија (во број на инјекции, контроли и следење) супериорна во однос на порелаксирана терапевтска стратегија кај пациенти со дијабетес и ХББ во стадиум 3b или повеке (eGFR<45 ml/min) кои се на инсулинска терапија?

Не препорачуваме стриктна гликемиска контрола доколку тоа води кон тешки хипогликемиски епизоди (1B).
Препорачуваме внимателни обиди да се засили гликемиската контрола со цел да се намали нивото на HbA1C кога вредностите му се >8,5% (69 mmol/mol) (1C).

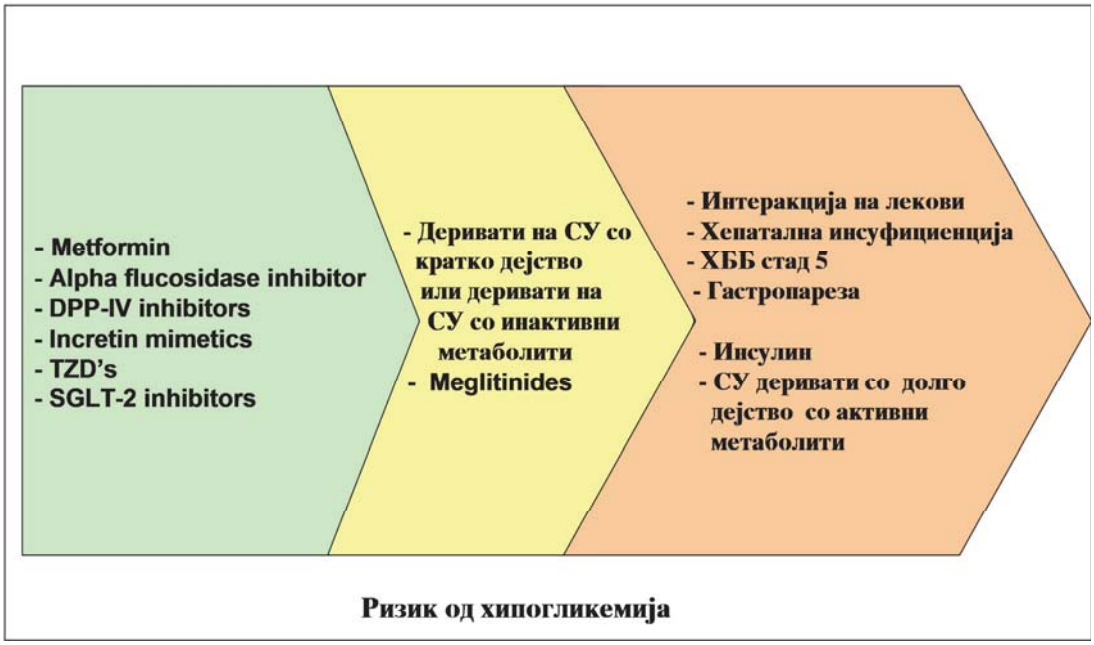
Сугерираме внимателни обиди да се засили гликемиската контрола со цел да се намали нивото на HbA1C според дијаграмот на Слика 4 во сите други состојби (1D).
Препорачуваме интензивно само-мониторирање само со цел да се избегнат хипогликемии кај пациент со висок ризик за хипогликемија (2D).

Совет за клиничка пракса

- Тежината на хипогликемиските епизоди се дефинира како "лесна" кога може да се третира од страна на самиот пациенти, и како "тешка" кога е потребна асистенција;
- Најважната грижа е да се избегнуваат епизоди на хипогликемија;
- Овластете ги пациентите со умерен и висок ризик од хипогликемија да прават редовни проверки на нивото на глукоза во крвта со помош на валидизирани апарати;
- Пациентите и состојбите со низок, умерен и висок ризик од хипогликемиски епизоди се наведени во слика 5.

Табела 6. Споредба на различни гликемиски маркери кај пациенти со дијабетес и ХББ стадиум 3б или повеке

Маркер	Предности	Недостатоци
HbA1c	- Маркер на долготрајна гликемиска концентрација - Одлична стандардизација на есеи на HbA1c - Универзално достапен систем за мерење на основната референца - Научно потврдена асоцијација со исходот од повеке студии - Во споредба со гликемија, помалку сензитивен за преаналитички варијабли, пониска во рамките на биолошка варијабилност, малку/без дневни варијации, малку/без влијание од акутен стрес и малку/без влијание од вообичаени лекови кои влијаат на гликозниот метаболизам - Одлична сепарација на HbA1c фракцијата од останатите хемоглобински соединенија и непостоење на мешање од карбамилиран хемоглобин поради технолошкиот напредок во мерењето на HbA1c.	- Лажно зголемени вредности при дефицит на железо, дефицит на витамин Б12, намалена еритропоеза, алкохолизам, хронична бубрежна слабост, намален pH на еритроцити, зголемен животен век на еритроцити, спленектомија, хипербилирубинемија, карбамилиран хемоглобин, употреба на големи дози на аспирин, хронична употреба на опијати. - Лажно намалени вредности по примање на еритропоетин, железо или витамин Б12; со ретикулоцитоза, хронична хепатална лезија, ингестија на аспирин, витамин Ц, витамин Е, одредени хемоглобинопатии, зголемен еритроцитен pH, намален животен век на еритроцити, спленомегалија, реуматоиден артритис, лекови од групата на антиретровируси, рибавирин и дапсон, хипертриглицеридемија. - Варијабилни промени се видени кај пациенти со HbF, хемоглобинопатија, метхемоглобин, генетски детерминанти
Гликолизиран албумин	- Мерка за пократок период на гликемиска контрола (2-3 недели) - Не е под влијание на пол, животен век на еритроцити, терапија со еритропоетин или серумска концентрација на албумин - Сигнификантна асоцијација со маркери на васкуларна оштета	- Вредноста може да биде под влијание на липемија, хипербилирубинемија, хемолиза, зголемена урична киселина, уремија, употреба на високи дози на аспирин, намалена серумска концентрација на протеини/нутритивен статус, возраст, албуминурија, цироза, тиреоидна дисфункција и пушење - Концентрација е обратнопропорционално под влијание на индекс на телесна маса, маса на телесни масти и висцерално масно ткиво - Разлика во референтни граници зависно од аплицираната метода - Ограничени податоци, собено за влијанието на неговото користење како таргет - Скап, одзема долго време, без широка употреба
Фруктозамин	- Корелира со просечните гликозни вредности во предходните 10-14 дена - Едноставна, автоматска анализа	- Контрадикторни резултати кои се однесуваат на корелацијата меѓу фруктозамин и средна концентрација на гликоза кај пациенти со ХББ стадиум 3б или повеке - Вредностите можат да бидат под влијание на нефротски синдром, тиреоидна дисфункција, примена на гликокортикоиди, хепатална цироза, иктерус. - Концентрацијата кај уремиски пациенти може да биде под влијание на бројни варијабли освен гликемијата, вклучувајки хипоалбуминемија, хиперурикемија. - Варијациите се повисоки во однос на HbA1c
1.5-anhydroglucitol	- Рефлектира дневни промени на гликозни вредности - Одржува метаболна инертност, стабилна состојба на вредностите во сите ткива, минимално е влијанието на условите при земање на примероци како време на земање на примерок, телесна тежина, возраст, пол и внес на храна	- Полоши перформанси за идентификација на случаи на недијагностициран дијабетес во споредба со останати гликемиски маркери - Подвлијание на традиционални Кинески билни лекови - Лимитираност при употреба кај пациенти со ренална тубуларна ацидоза или напредната бубрежна болест - Не се достапни за широка употреба, ограничени се податоците за негова секојдневна клиничка вредност
Континуирано гликемиско мерење	- Теоретски најидеален маркер на гликемиска контрола - Овозможува испитување на краткотрајни гликемиски промени во тек на дијализата	- Исцрпеност на сензорот, лимитирачки податоци



Сл. 5. Проценка на ризикот од хипогликемија

Глава 2.2. Дали постојат подобри алтернативи отколку HbA1c за проценка на гликемиската контрола кај пациенти со дијабетес и ХББ во стадиум 3b или повеќе (eGFR<45 ml/min/1.73m^2)?

2.2.1. Препорачуваме употреба на HbA1C како рутинска референца за проценка на долготрајна гликемиска контрола кај пациенти со ХББ во стадиум 3b или повеќе (eGFR<45 ml/min/1.73m^2) (1C).

Совет за клиничка пракса

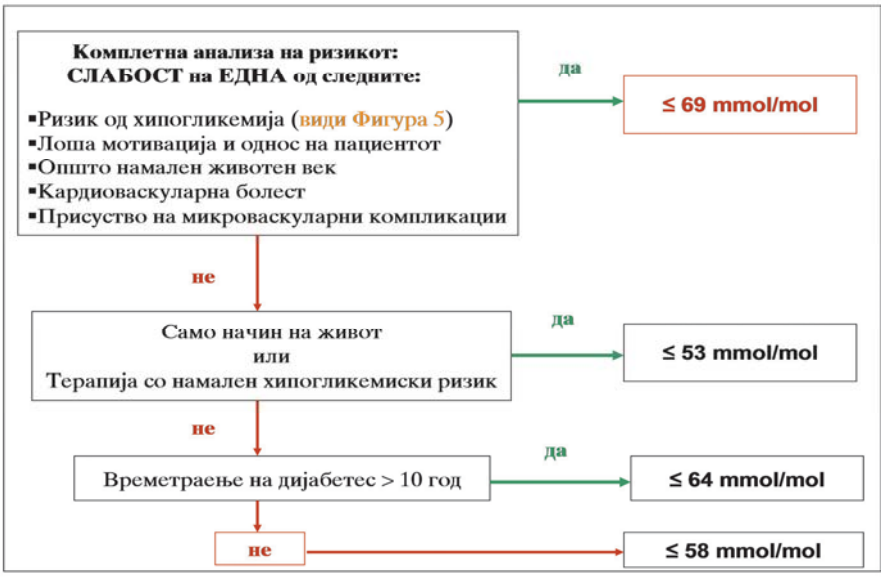
- Континуирано планирано одредување на глукоза може да се земе во обзир кај пациенти со висок-ризик кај кои е потребна многу строга контрола на гликемија.
- Асоцијацијата помеѓу HbA1C и долготрајната контрола на гликемијата може да се разликува кај пациенти со ХББ во стадиум 3б или повеќе (еГФР<45мл/мин), наспроти оние кои немаат ХББ, и тоа и во двата случаи како за апсолутната вредност така и за падот на асоцираната крива.
- Следните фактори се потенцијално асоцирани-поврзани со помала од очекуваната вредност на HbA1C:
- намалено преживување на црвените крвни клетки;
- зголемена формација на црвените крвни клетки (употреба на железо, RhuEpo).
- Следните фактори се потенцијално асоцирани-поврзани со поголема од очекуваната вредност на HbA1C:
- акумулација на уремични токсини.

Глава 2.3.

- *Дали е некоја орална терапија супериорна наспроти друга во однос на морталитет/компликации/гликемиска контролата кај пациенти со дијабетес тип 2 и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2)?*

- *Кај пациенти со дијабетес тип 2 иХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), дали е максималната орална терапија подобра во однос на започнување/додавање инсулин во порани стадиуми?*

2.3.1. Препорачуваме употреба на метформин во доза адаптирана спрема бубрежната функција како прва терапевтска линија кога промените на стилот на живеење се недоволни за постигнување на посакуваните вредности на HbA1C според вредностите дадени во слика 4 (1B).
2.3.2. Препорачуваме додавање на лек со низок ризик за појава на хипогликемија (слика 5, 6 и 7) како додатен-дополнителен лек (табела 7) кога подобрувањето на гликемиската контрола е соодветно (1B).
2.3.3. Препорачуваме привремено исклучување на метформин кај пациенти при: состојби на претечка (постоечка) дехидратација, инвестигации со употреба на контрасни средства, или во ситуации со зголемен ризик за акутно бубрежно оштетување-АБО (1C).



Сл. 4. Дијаграм на менаџирање со целни вредности на HbA1C кај пациенти со дијабетес и ХББ стадиум 3б или повеке (еГФР<45мл/мин)

Табела 7. Орални хипогликемиски лекови: механизам на дејство

Класа на лекови	Механизам на дејство	Примери
Biguanides	Намалува хепатална продукција на гликоза Зголемува инсулинска сензитивност Зголемува инсулин-зависна утилизација на гликоза во периферни ткива	Metformin
Sulfonylureas	Намалува гликозна интестинална апсорпција Стимулира инсулинска секреција од панкреас Ги затвара K-АТП каналите на плазма мембрана на β-клетките	Acetohexamide, chlorpropamide, glibenclamide, gliclazide, glyburide, glimeperide, glipizide, gliquidone
Meglitinides	Стимулира панкреасна инсулинска секреција преку затварање на K-АТП каналите на плазма мембрата на на β-клетките	Nateglinide, repaglinide
Alfa glucosidase inhibitors	Блокира дејство на -глукозидаза преку редукција на хидролиза на комплексни сахариди Реверзибилна инхибиција на панкреатичниот ензим -амилаза	Acarbose, miglitol
Glitazones	Намалува инсулинска резистентност Зголемува влез на гликозата во мускули и масно ткиво	Pioglitazone
DPP-IV inhibitors	Намалува хепатална гликозна продукција Го инхибира DPP-4, кој го инактивира ендогениот инкретин	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin,
Incretin mimetics	Овозможува гликоза зависна секреција на инсулин преку β клетките на панкреасот Супресија на глукагон скреција Бавно желудачно празнење	Eexenatide, liraglutide, lixisenatide
Amylin analogues	Регулира ниво на гликоза во зависност од внесот на храната Го контролира желудачното празнење и постпрандијалната секреција на глукагон Намалува внес на храна преку зголемување на ситост	Pramlinitide
SLT-2 inhibitors	Го блокира натриумглукоза транспортниот протеин од подтипот 2, со што се зголемува ренална елиминација на глукозата	Canagliflozin, dapagliflozin, empagliflozin

		ХББ -1	ХББ-2	ХББ -3	ХББ -4	ХББ -5 НХД	ХББ -5 ХД
	Metformin	без корекции		1.5g-850 мг/ден	500 мг/ден	внимателно/се чекаат податоци	
Sulfonylureas	Chlopropamide	без корекции		100-125 мг/ден	да се избегнува		
	Acetohexamide	да се избегнува					
	Tolazamide	да се избегнува					
	Tolbutamide	250mg, 1-3 пати/дневно				да се избегнува	
	Glipizide	без корекции					
	Glicazide	старт со ниски дози и титрирање на дозата секоја 1-4 недела					
	Glyburide	да се избегнува					
	Glimepiride	намалување на дозата за 1 мг/дневно				да се избегнува	
	Gliquidone	без корекции					
	Repaglinide	без корекции				ограничени искуства	
	Nateglinide	без корекции				Старт 60 мг/ден	да се избегнува
α-gluc inhibitors	Acarbose	без корекции			употреба на најмала доза и < 50 мг		
	Miglitol	ограничени искуства					
	Pioglitazone	без корекции					
DPP-IV inhibitors	Sitagliptin	без корекции		50мг/дневно	намали на 25 мг/дневно		
	Vildagliptin	без корекции		намали на 50мг/еднаш дневно			
	Saxagliptin	без корекции		намали на 2.5мг/еднаш дневно			
	Linagliptin	без корекции					
	Alogliptin	без корекции		намали на 12.5мг/еднаш дневно			
Incretin Mimetics	Exenatide	без корекции	5мцг/еднаш до два пати дневно		да се избегнува		
	Liraglutide	ограничени искуства					
	Lixisenatide	без корекции	внимателна употреба при ГФР 80-50 мл/мин			нема искуства	
	Pramlintide	ограничени искуства					
SGLT-2 inhibitors	Dapagliflozin	ограничени искуства					
	Canagliflozin	намалена ефикасност		внимателно следење		да се избегнува	
	Empagliflozin	ограничени искуства					

Сл. 6. Препорачани дози при ХББ

		Вкупен морталитет	Кардиоваскуларна случка	Ризик од хипогликемија	Пораст на телесна тежина	Промени во HbA1c	Адаптација на доза при напреднат стадиум на ХББ
Biguanides	Metformin						да
Sulfonylureas	Chlopropamide						се избегнува
	Acetohexamide						се избегнува
	Tolazamide						се избегнува
	Tolbutamide						се избегнува
	Glipizide						не
	Glicazide						да
	Glyburide						се избегнува
	Glimepiride						се избегнува
	Gliquidone						не
Meglitinides	Repaglinide						да
	Nateglinide						да
α-gluc inhibitors	Acarbose						не
	Miglitol						нема податоци
DPP-IV inhibitors	Sitagliptin						да
	Vildagliptin						да
	Saxagliptin						да
	Linagliptin						не
	Alogliptin						да
Incretin Mimetics	Exenatide						се избегнува
	Liraglutide						поверојатно не
	Lixisenatide						да
	Pramlintide						нема податоци
SGLT-2 inhibitors	Dapagliflozin						избегни;нема ефект
	Canagliflozin						избегни; нема ефект
	Empagliflozin						избегни; нема ефект

Сл 7. Влијание на различни класи на хипогликемиски лекови при различни исходи
Темно зелена означува-корисен ефект; црвено означува-негативен ефект; жолто-непостоење на испитувања или недостиг на податоци; боја на лосос-слаб негативен ефект; боја на аквамарина-неутрално слаб позитивен ефект; темно сино недостиг на ефект

Совет за клиничка пракса

- Имај го во предвид давањето на инструкции на пациентите преку примена на кредит-карт тип на флаери за кога привремено да се исклучи метформинот.
- Состојби кои се сметаат за слаби, умерени или со висок ризик за појава на хипогликемија се опишани во слика 5.
- Ризикот за хипогликемија од различни лекови е прикажан во слика 5 и 7.
- Кај пациенти со дијабетес тип 2 и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2) кои примаат метформин, одлуката да се продолжи да се прима лекот 48 часа пред и по администрација на контрасно средство треба да ја превземе ординирачкиот лекар, притоа избегнувајќи ја можноста од појава на контраст-индуцирана нефропатија (тип и количина на контраст, интравенска наспрам интра-артериска апликација на контрастот) и присуство на други (коегзистирачки) постоечки фактори кои може да предизвикаат нагло влошување на бубрежната функција (дехидратација, употреба на НСАИД, употреба на инхибитори на РААС) наспроти можните штети при прекинување на лекот (кои треба да се сметаат за мали, со оглед на краткиот период на неговата примена).
- Како реналните клиренси на различни лекови за намалување на гликемијата се разликуваат, формулација на нивно комбинирање во една таблета може да доведе до предозирање на една од составните делови (конституенти) кај пациенти со ХББ во стадиум 3б или повеќе.

Глава 3. Теми поврзани со терапија на кардиоваскуларниот ризик кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе

Глава 3.1. Кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2) или на дијализа и со коронарна артериска болест, дали треба да се преферира перкутана коронарна интервенција (ПКИ), коронарен артериски бајпас со графт (КАБГ) или конзервативна терапија?

3.1.1. Препорачуваме да не се прескокнува (пропушта) коронарна ангиографија со единствена цел да се спречи можноста од контраст-поврзаното оштетување на бубрежната функција кај пациенти со ХББ во стадиум 3б или повеќе (еГФР<45мл/мин), кај кои коронарната ангиографија е индицирана (1D).
3.1.2. Препорачуваме оптималниот медицински третман да се смета како претпочитан третман кај пациентите со ХББ во стадиум 3б-5 кои имаат стабилна КАБ, освен ако постојат големи површини на исхемија или значајни оштетувања на лева главна или проксимални ЛАД (1C).
3.1.3. Препорачуваме, примена на КАБГ како преферабилна метода во однос на ПКИ кај пациенти со мултисадовна или комплексна (SYNTAX score>22) КАБ, кога се донесува одлука во однос на коронарна реваскуларизација (1C).
3.1.4. Препорачуваме, примена на ист третман кај пациенти со ХББ во стадиум 3б или повеќе (еГФР<45мл/мин) кои имаат акутен коронарен инцидент и кај пациенти со ХББ во стадиум 3б или повеќе (еГФР<45мл/мин) кои немаат дијабетес или кај пациенти со дијабетес кои немаат ХББ стадиум 3б или повисок (еГФР<45мл/мин) (1D).

Совет за клиничка пракса

За пациенти со стабилна КАБ,

- Оптималниот медицински третман е најприфатлив, преферирaн третман.
- Кога постојат големи површини на исхемија или индикации за сигнификантни лева главна или проксимални ЛАД оштетувања, КАБГ е преферирaн третман.

За пациенти кај кои се присутни СТ-елевација миокарден инфаркт (СТЕМИ), најпрво се препорачува ПКИ пред фибринолиза доколку истата може да се изведена во препорачаните временски лимити.
За пациенти кај со нон-СТЕМИ (НСТЕМИ) КАБГ резултира со подобри исходи (во однос на смртност, МАСЕ) во однос на ПКИ каде се јавуваат лезии на главното васкуларно стебло и /или напредната мултисадовна болест.
Фармаколошкиот третман, вклучувајќи антитромботична терапија, има место во одредување на дозите на лековите адаптирани според бубрежната функција.

Глава 3.2. Кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2) или на дијализа и со кардијална индикација (срцева слабост, исхемична срцева болест, хипертензија) дали треба да се препишуваат инхибитори на РААС како кардиоваскуларна превенција?

3.2.1. Препорачуваме пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2 или кои се на дијализа) и со кардијална индикација (срцева слабост, исхемична срцева болест) да се третираат со АКЕ-и во максимално толерантни дози (1B).
3.2.2. Предлагаме дека нема доволно докази кои би оправдале примена на ангиотензин-рецептор блокатор (АРБ) кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2

или кои се на дијализа) и со кардијална индикација (срцева слабост, исхемична срцева болест), и кои имаат неподносливост на АКЕ-и (2В).
3.2.3. Препорачуваме да не се комбинираат различни класи на ренин-ангиотензин-блокатори (АКЕ-и, АРБ или директни ренин-инхибитори) (1А).

Совет за клиничка пракса
Нема доволно докази дали употребата на РААС инхибиторите треба или не треба да се стопира кај пациенти со ХБП која прогредира кон ХБП стадиум 5. За исклучување на РААС инхибитор, со цел да се одложи потребата од започнување со бубрежно заместителна терапија, би требало да се дискутира со пациентот.

Глава 3.3. Кај пациенти со дијабетес и ХБП во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2) или на дијализа, дали треба да се препишуваат бета блокатори за да се превенира ненадејна срцева смрт?

3.3.1. Предлагаме започнување со селективен бета-блокатор како примарна превенција кај пациенти со дијабетес и ХБП во стадиум 3б или повеќе, и да се продолжи со примена доколку истиот се толерира (2С).
3.3.2. Предлагаме, примена на липофилни повеќе отколку на хидрофилни бета-блокатори кај пациенти со дијабетес и ХБП во стадиум 3б или повеќе (еГФР<45мл/мин) (2С).

Глава 3.4. Кај пациенти со дијабетес и ХБП во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), или на дијализа, дали треба да целиме кон пониски вредности на крвниот притисок во однос на општата популација?

3.4.1. Предлагаме да не се поставуваат пониски целни вредности за крвниот притисок кај пациенти со дијабетес и ХБП во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), во однос на општата популација (2С).
3.4.2. Предлагаме кај пациенти со дијабетес и ХБП во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), кои немаат протеинурија, да се употребуваат сите анти-хипертензивни лекови поседнакво (2С).

Совет за клиничка пракса
- Крвниот притисок треба внимателно да се контролира до постигнување на целни вредности >140 ммХг за СКП, притоа мониторирајќи ја толерабилноста и избегнувајќи ги споредните ефекти.
- Пациенти со дијабетес и ХБП во стадиум 3б или повеќе, може да страдаат од аутономна дисфункција заради што се посклони за компликации асоцирани со појава на нагла хипотензија.
- Дијастолен крвен притисок кој е премногу низок може да ја доведе во опасност коронарната перфузија (крвоснабдување).

Глава 3.5. Кај пациенти со дијабетес и ХБП во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), или на дијализа, дали треба да се препишува терапија за намалување на липидите како примарна превенција?

3.5.1. Препорачуваме употреба на статини кај пациенти со дијабетес и ХБП во стадиум 3б и 4 (1В).
3.5.2. Предлагаме употреба на статини кај пациенти со дијабетес и ХБП во стадиум 5 (2С).
3.5.3. Препорачуваме да не се употребуваат статини кај пациенти со дијабетес и ХБП во стадиум 5Д (1А).
3.5.4. Не постои општо прифатен став од страна на работната групата за препораки во однос дали треба или не треба да се прекине со употреба на статини кај пациенти со дијабетес и ХБП во стадиум 5Д.
3.4.5. Предлагаме фибратите да ги заменат статините кај пациенти со дијабетес и ХБП во стадиум 3б, кои покажуваат нетолеранција кон статини (2В).

Совет за клиничка пракса
- Дозите на лековите кои ги намалуваат липидите во крвта (анти-липидемици) треба да се адаптираат според бубрежната функција (табела 8).
- Дозите дадени во табела 8 треба да се сметаат (да се прифатат како) за максимални дози кај пациенти со ХБП, поради тоа повторуваните мерења, одредувања на вредностите на липидите немаат дијагностичка или терапевтска вредност.
- За пациенти со ХБП во стадиум5 или ХБП во стадиум 5Д, изборот или мотивацијата на пациентот да зема друг лек со прифаќање на неговите споредни ефекти или намалениот очекуван бенефит (корист) треба да е во основа на водењето на пациентите.

Табела 8. Препорачани дози на статини кај пациенти со ХБП стадиум 3б или повеке (еГФР<45 мл/мин). *Адаптиран од Tonelli and Wanner Ann Intern Med 2014; 160: 182.*

Статини	Максимални дози при еГФР<45мл/мин
Lovastatin	Нема податоци
Fluvostatin	80 мг
Atorvastatin	20 мг
Rosuvastatin	10 мг
Simvastatin/ezetimibe	20/10 мг
Pravastatin	40 мг
Simvastatin	40 мг
Pitavastatin	2мг

Глава 3.6.

- *Кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), дали треба да препорачуваме интервенции насочени кон зголемена потрошувачка на енергија и физичка активност?*
- *Кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), дали треба да препора*чуваме интервенции насочени кон редуцирање на енергетскиот внос?

3.6.1. Предлагаме кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин)/ примена на додатни физички вежби најмалку три пати по половина до 1 час/неделно со цел да се намали масното ткиво и да се подобри квалитетот на живот (QoL) (2D).

3.6.2. Предлагаме дека не постои доказ за штета од промовирање на индувидуализиран режим на зголемена физичка активност (2C).

3.6.3. Препорачуваме супервизија од страна на дијабетолог за да се осигураме дека има само губиток на масно ткиво а малнутрицијата е избегната, кога се залагаме за губиток на телесна тежина кај пациенти со дијабет и со прекумерна тежина (1C).

Глава 3.7. Кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин/1.73м^2), дали треба да се препорачува антитромботична, независно од кардиоваскуларниот ризик?

3.7.1. Препорачуваме да не се применуваат гликопротеински IIb/IIIa инхибитори како стандардна терапија со цел да се намали смртноста, појавата на миокарден инфаркт, или потребата од коронарна реваскуларизација кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин) и акутни коронарни синдроми (АКС) или доколку постои висок ризик од коронарна артериска интервенција (1B).

3.7.2. Предлагаме да не се употребува thienopyridine или ticagrelor како стандардна терапија со цел да се намали смртноста, појавата на миокарден инфаркт, или потребата од коронарна реваскуларизација кај пациенти со дијабетес и ХББ во стадиум 3б или повеќе (еГФР<45мл/мин) и акутни коронарни синдроми (АКС) или доколку постои висок ризик од коронарна артериска интервенција, освен ако не постои дополнителен ризик фатор за крварење (2B).

3.7.3. Препорачуваме примена на аспирин како секундарна превенција, освен ако постои контраиндикација, споредни ефекти или интолеранција (1C).

3.7.4. Предлагаме примена на аспирин како примарна превенција само кај пациенти кои немаат дополнителни ризик фактори за обилно крварење (2C).

Совет за клиничка пракса

Предлагаме употреба на клопидогрел како алтернатива на аспирин кај пациенти со јасна интолеранција или контраиндикации за примена на аспирин.

Конфликт на интереси. Не е деклариран.

Литература

Bilo H, Coentrao L, Couchoud C, *et al*. Clinical practice guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant*. 2015; 30 Suppl 2:ii1-142.

УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:

1. **Изворни трудови**
2. **Соопштувања за клинички и лабораториски искуства**
3. **Прикази на случаи**
4. **Од практика за практика**
5. **Едукативни статии**
6. **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

1. ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) листата на Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

2. ПРИЛОЗИ

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).
Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

3. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени vo Index Medicus):
а) ***статија во списание*** (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор*.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.
б) заеднички автор
GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.
в) ***без автор*** **-** анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).
г) ***поглавје во книга или монографија***
Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

Адресата на Редакцијата
Даме Груев бр. 3
Градски sид блок II,
1000 Скопје,
Тел.: ++ 389 02 3162 577

Електронска адреса (Е-маил): mld@unet.com.mk

Известување за членовите на МЛД

Сите што сакаат и натаму да го добиваат списанието треба да ја имаат уплатено членаринатa за 2014 година во висина од 600 денари и за тоа да ја информираат стручната служба на Македонско лекарско друштво, писмено или преку телефон.

Детални информации можете да добиете на телефонот на Друштвото 02 3 162 557.

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД – 3162 557.