

NATIONAL UNIVERSITY OF PUBLIC SERVICE

Military Science Doctorate School

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**The correlation between depression and
cardiovascular diseases in the defense sector**

Doctorate (PhD) dissertation

THESIS BOOK

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1. DEFINITION OF THE SCIENTIFIC PROBLEM

Cardiovascular diseases (CVD) have become the leading mortality causes all over the world. According to the facts published by the Hungarian Statistics Office, 50.5% of mortal causes were those of the circulation system. The background of this illness is due to lifestyle (smoking, alcoholism, unsatisfactory dietary habits, lack of physical activity), together with psychosocial factors. 55% of the population dying of cardiovascular problems are females, 45% are males. This fact constitutes an important part of my research since the number of female soldiers has been constantly growing. It is the highest in our country, approximately 20%.

In 2004-2007, based on medical tests conducted on 3738 people, it was established that 13.3% of the Hungarian Defense Forces (HDF) personnel were undergoing medication treatment. The highest rate, 274 (7.3%) were diagnosed with circulatory illnesses which constitutes a bigger number than all other illnesses together. With the examination of all risk factors leading to the disease within the personnel of the HDF the first 5 were the following: familial hypertension (42%), smoking (30%), overweight (26.3%), familial diabetes (24.1%), and familial cancer (22.4%). Smoking, being overweight and the positive familial anamneses pose a higher degree of threat of heart and circulation diseases within the examined population.

Between 2009 and 2010, 206 volunteers took part in cardiovascular prevention testing, from 6 garrisons of the HDF. The average age of the participants was 32 years. They were mainly males (80%), 6% of them in the rank of higher officers. The risk factors of the CVD were examined, such as: overweight, smoking, high level of cholesterol and sugar, physical inactivity. Leaving out the protective influence of age, according to the highest level of risk factors, the following facts were observed: 5 persons were diagnosed as of high risk (2%), 33 persons as medium risk (16%), and 168 persons (82%) belonged to the low risk category. The persons who took part in the experiment were of young age, although the presence of CVD and the high risk factors, similarly to the civilian population, were quite high within the military personnel, too.

Depression, similarly to CVD can also be considered a general population disease. The prevalence of the major depression time is 5-17%. In the USA approximately 17 million people suffer from depression and the treatment costs are about 43 billion dollars yearly. CVD and

depression are the two main public health problems in the Western world and their prevention and adequate treatment is a basic task.

According to the tests conducted between 2005 and 2009 at the Military Hospital of the HDF, the rate of mental and behavioral problems within the personnel had been constantly growing. This number was 2.3% in 2005 and it grew to 4.77% in 2009.

There is a lot of proof that depression contributes to CVD and heart disease mortality. According to test results from 1937, the mortality rate in “involution melancholy” of CVD was 6.8% higher with females and 6% higher with males compared to the general population. The first scientific research was described by a Danish epidemiologist who proved that unipolar and bipolar depression sufferers die of heart disease more often compared to the general Danish population. The prognosis of cardio disease is worse with patients who suffer from coronary depression than of those who don't have depression. This correlation is also proved with patients who had microcardio attack, with unstable angina patients and with those who had bypass surgery and with those who had heart problems. In an earlier test 222 people were involved. They had heart attacks and also suffered from depression. They were monitored for 6 months. The results showed that mortality rate of depression sufferers was 3.5% higher.

Those who suffer from depression have 2 to 4 times higher chance to develop some type of CVD compared to the general population. Depression sufferers die 2 to 4 times more often after a cardio event.

According to the mission described in the Combined Arms Doctrine of the HDF “the mission of the health service in military operations is to preserve life force, protection of life and to minimize physical and mental damage.” Accordingly, from the point of view of health service, the protection of the fighting force is the preservation of the soldiers' health, keeping them in deployable condition in their maximal strength at the given time and place.” The soldiers' value as a human factor has grown, today's soldiers have stronger capacity than before, and an occasional repatriation, due to medical reasons, can risk the success of the mission.

The success of performing military tasks can depend upon the fact that serving soldiers are prepared and selected properly and are able to adapt to special circumstances. To reach this goal,

not only soldiers who serve in a mission have serious tasks but the military health services as well, who perform defense tasks, too.

2. DEFINITION OF RESEARCH AIMS AND HYPOTHESES

1. To prove through clinical tests that depression and CVD are closely related.
2. To prove through molecular biological changes that depression can be an independent CVD risk factor.
3. To establish biomarkers, with their help to monitor depression development as well as the therapy success.
4. To develop cheap, easily available lab tests which help diagnose and decide on therapy effectiveness at an earlier stage.
5. To monitor the already existing depression for the quickest redeployment.
6. To include the results into professional protocols both for domestic and international NATO STANAG levels.

I want to support my research aims with the analysis of the following hypotheses:

- a. The number of circulating endothelial progenitor stem cells (EPC) significantly reduced during the examination of the known risk factors of CVD (smoking, high blood pressure, physical inactivity). I suppose that during clinical examinations of depression I will measure similar differences and thus I can prove that depression can be an independent risk factor of CVD.
- b. I suppose that the platelet aggregation and the consequent ATP release change, compared to the starting value, will foretell the improvement in the symptoms of major depression on the 8th day of treatment, according to the objectivized point scale of Hamilton and Beck.

3. RESEARCH METHODS

- a. As the first step of my research I prepared a study and research plan which was followed by continuous and step by step execution.
- b. Data necessary for setting up the aims of research and hypotheses was collected by special literature and documentation studying.
- c. To acquire and analyze material from special libraries as well as to search for the latest data and articles on the subject has been continuous on the internet.
- d. I studied PhD dissertations that deal with military-related health issues, different researches, scientific articles, studies and papers.
- e. I worked with background literature materials with the method of analysis and synthesis.
- f. As a member of a research group, I used an experimental method of invasion to test my hypotheses and I proved my planned aims.
- g. The evaluation of the research data and the interpretation were done by mathematical methods, quantitatively and qualitatively.
- h. I used the method of abstraction and generalization to establish the conclusion.
- i. I processed and documented data collected from the observation of my own patients and I published this material on many domestic scientific forums.
- j. I systemized the results and finished my dissertation after processing documentation and clinical and theoretical material necessary for the achievement of the set aim.

4. BRIEF DESCRIPTION OF THE PERFORMED EXAMINATION IN CHAPTERS

In the introduction I introduced the scientific topic and I explained the reason why I chose the topic and its place in the system of the health care in the HDF. I will also introduce the aims of the research and the applied research methods.

In the main part the research topic is worked out in 6 chapters. In the 2nd chapter I analyze the actual health condition of the HDF personnel, with special emphasis on chronic stress and work-related stress. I introduce the actual psychosocial status of the personnel which is supported by epidemiological data and tests.

In the third chapter I introduce the notion of depression, its epidemiology and gravity. The symptoms of this disease are described here with its possible somatic complications. I briefly describe the available pharmaceutical and psychotherapy treatments. Depression is a general population disease of our times, its point-prevalence is 5%, its life-time prevalence can reach up to 20%. According to epidemiological tests this illness is present within the military population as well. It is especially high with those who serve in missions. Accordingly, the fight against this illness is a military interest, too. Besides psychological consequences, this illness has several somatic aspects, probably the most serious is the CVD.

In the 4th chapter I describe the main characteristics of CVD, the main groups involved and the question of prevention. In our country and generally in the developed world, CVD statistically is the leading mortality cause. In Hungary in 2009 almost 65000 people died of CVD which is a frighteningly high number. This number presents half of all mortality causes. In the recent years this number shows a declining tendency in the developed world thanks, partially, to primer prevention. Unfortunately in our country this decline has not been observed. Since in Hungary not only CVD but depression is also a general population disease, their prevention is a general health and social task. The majority of those who suffer from depression smoke, have unhealthy diets, physically inactive, overweight and drink alcohol. Besides, as I prove it later, depression is an independent risk factor of CVD. Accordingly, primer prevention of depression and the reduction of the existing symptoms, or the secondary prevention, will improve not only mood but will protect from dangerous somatic, potentially lethal complications.

In the 5th chapter I summarize etiological correlation between depression and CVD. The two illnesses are interconnected in many aspects, they often appear together. I will specifically mention the question of endothelial dysfunction and platelet aggregation, because both of them prove molecular level changes, thus the pathological mechanism of depression can be understood easier.

In the 6th chapter I discuss the importance of biomarkers and in a longer subchapter I introduce the possible biomarkers of depression. One of the main aims of my research was to find biomarkers that are easily available, cheap and can be widely applied, and bring closer the understanding of the correlation between depression and CVD, to diagnose easier and to start the proper therapy sooner.

In the 7th chapter I introduce the two clinical tests in which the correlation between depression and CVD are proved through molecular level changes. In the first part of the chapter I prove through the change in number of (EPC) that depression is an independent risk factor of CVD. The change in EPC number can give opportunity to monitor depression later. In the second part of the chapter, I examine the effectiveness of anti-depression treatment in the early stages by measuring the outcome of the ATP level during platelet aggregation.

In the last chapter, by summarizing the performed scientific work, I introduce my scientific results and I formulate professional recommendations. It contains the formulation of consequences and their application in the military.

5. SUMMARY OF CONSEQUENCES

Our results proved that with people suffering from major depression the number of endothelium progenitor cells (EPC) are present in a more limited number than with those who do not suffer from mood springs.

Since we excluded all existing CVD risk factors from the tests, we can suppose that the EPC number reduction due to depression, it is possible that depression can be an independent risk factor of CVD. As far as we know, this is the first scientific proof of this long-time existing factor.

The validity of test results is limited by several factors. Those who suffer from depression undergo pharmacological treatment, anti-depressants, and the effect of these psychotropic materials on EPC is not known. On the other hand, patients stay in hospitals, their physical activity is limited, and as we know, these factors influence the EPC number in a negative way. Consequently, it is possible that it is not the illness itself (depression) but the physical inactivity is the reason for the reduced number of the circulating EPC.

The results of the test show that the effectiveness of anti-depression therapy can be prognosticated after a few days from its start since with those patients whose depression is clinically proven later by test, we can experience an increase in the ATP release. One of our patients remained depressed during the thirty day period of tests and nothing changed in the condition of the ATP release compared to the starting value. Accordingly, we cannot say that these changes would only be the direct result of the applied medication (selective serotonin reuptake inhibitor (SSRI)) since in this case we would have experienced changes in the ATP release with the patient whose condition did not improve. It would be better to assume that the medication changed the ATP level and the level of the closely connected serotonin. From the examination of the ten patients we cannot derive statistical data but it can definitely be used to represent a certain tendency. After we have studied special literature we could be the first to prove, with the help of the molecular method that the later effectiveness anti-depression therapy can be prognosticated in the very early stages of its use.

With all the above-mentioned facts we could verify the assumption that there are changes in molecular level and these changes can be measured. We again proved that there is interdependence between body and soul. In psychiatric illnesses we can find the same molecular level changes that are present in somatic illnesses, but since the brain is the most sophisticated organ of our body, their detection takes a long time. We must seriously focus on these facts because they can be very important in the future. These factors also proved that blood tests should be performed often because it is easier to detect depression at an early stage.

6. NEW SCIENTIFIC RESULTS

1. As a member of a research group, with the help two clinical tests, through molecular biological changes I proved that there is close correlation between depression and CVD, and I was the first one to verify that depression is an independent risk factor of CVD.
2. I was the first one to establish that in the process of platelet aggregation the change in the quantity of outgoing ATP, the effectiveness of anti-depression therapy can be recognized on the eight day of taking the medication.
3. I was the first one to develop lab tests that help diagnose depression as well as the effectiveness of its treatment as soon as possible.
4. I developed two bio-markers which are cheap, unique, widely applicable, specific and sensitive enough to monitor depression and to indicate the effectiveness of anti-depression treatment at an early stage.

7. PRAGMATIC APPLICATION OF RESEARCH RESULTS AND RECOMMENDATIONS

a) EPC is a relatively constant marker which is characteristic of an individual and its number is strongly influenced by different risk factors. Any change can indicate suspicion for the appearance of the illness, so in our case EPC can be used to monitor depression. Before going on missions the actual number of stem cells could be established with any soldier and this process could be repeated during retesting. If we have any suspicion of depression indicated by clinical symptoms the change in the number of stem cells can effectively prove it. The same procedure can be applied for medical fitness tests. According to the existing parameters, the first depression episode does not indicate unsuitability for military service, but its recurrence does. The correctness of the diagnosis can be reinforced if during the first episode the EPC number was monitored from time to time. Thus it could help identify potential patients and establish proper therapy.

In case of retired (inactive) soldiers, the situation is more complicated, because they may already suffer from several diseases, have several risk factors that influence the number of stem cells, so in their case application is highly limited. On the other hand, younger soldiers demobilized at the age of 35-40 due to the military reform, the above-mentioned lab tests can be successfully performed.

I would like to mention the new generation of reserve personnel. They serve for a maximum of six weeks a year. In the interim time, they do not belong to the military healthcare system. The tests should be performed in this interim time, so as to have information about their actual psychological condition.

b) The extent of ATP change could also be built into the regular examinations. Depression is a general population disease, with the military personnel included. The right treatment at the right time would protect the soldiers from being found unsuitable for military service. A good example of this is that in the Norwegian military, a pilot who takes anti-depression medication is allowed to fly a plane. The indication of ATP number can help in cases where depression was diagnosed, the therapy started and its effectiveness could be established after a few days following a simple lab test. By this, the time needed for recovery can be minimized, so the soldier can qualify for service much earlier.

It may mean, for example that soldiers suffering from depression do not need to be repatriated from missions, and their treatment can be started there and then. This method can be used to examine patients in our department or out-patients because the time factor is an important part of therapy effectiveness in their case, too. This way, we can reduce the unwanted side effects, and the number days off work can also be significantly decreased.

In case of inactive (retired) personnel, this examination could be performed on a relatively small number of patients as they have several other diseases that strongly influence platelet aggregation. Regardless of this, in the earliest possible establishment of the effectiveness of the indicated therapy, the introduced marker can play a significant role.

As a summary we can state that both tests can be built into the protocol of military healthcare system. These tests are relatively cheap, easily applicable with one or two blood tests, they can be performed in any circumstances and they do not need complex laboratories. We must not

forget that both tests are unique in their nature. Our research group was the first to describe the correlation between depression and EPC changes. We were the first ones who verified the relationship between the change in ATP release and the effectiveness of anti-depression therapy. Both tests can be recognized internationally and thus can be built into the examination methods used in international military healthcare systems.

Depression is a general population disease which affects 20 % of people during their life this way or another. This is why we would like to draw international attention to our results, because they can be used not only in the military but can also be built into the protocols of diagnosis and treatment of depression.

PRESENTATION AND PUBLICATION

- Presentations:

1. Pszichofarmakológiai lehetőségek a stresszellátás során 2001, Főszakorvosi összevónás
2. Stressz-immunrendszer 2001, Katasztrófakongresszus, szatellit-szimpozium
3. Katonai alkalmasság a pszichiátriadiagnosztika és terápiájában 2003, MH KHK Jubileumi emlékülés
4. Depresszió epidemiológiája és komorbiditása 2005, Főszakorvosi összevónás
5. Hospitalizált pszichiátriabetegek komorbiditása 2005, MH KHK kongresszus, Balatonkenese
6. Hospitalizált pszichiátriabetegek komorbiditása 2006, Magyar Pszichiátriai Társaság kongresszusa, Budapest
7. Comorbidity and co-medication in a psychiatry ward 2006, Nemzetközi Pszichofarmakológiai kongresszus (CINP), Chicago (poszter)
8. A közelmúlt háborúinak pszichés következményei 2006, Katasztrófakongresszus, szatellit-szimpozium

9. Comorbidity and co-medication in psychiatry ward 2006, Tihany (poszter, I. hely)
10. Krízisállapotok differenciáldiagnózisa és ellátása 2006, Főszakorvosi összevónás
11. Antidepresszívumok 2007, Főszakorvosi összevónás
12. Kardiovaszkuláris betegségek és a depresszió 2008, Magyar Pszichofarmakológiai Társaság kongresszusa, Tihany
13. Endotélössejtek 2008, MH HEK kongresszusa
14. A depresszió farmakoterápiája 2008, Főszakorvosi összevónás
15. Az ATP felszabadulás és a trombocita aggregáció változásának vizsgálata depressziós epizód kezelés során 2010, Tihany (poszter)
16. A szorongásos és szomatikus betegségek közötti összefüggések 2011, Főszakorvosi összevónás
17. Az ATP felszabadulás és a trombocita aggregáció változásának vizsgálata depressziós epizód kezelés során 2011, Richter szimpózium
18. Pszichiátriai és kardiovaszkuláris betegségek összefüggései 2011, Főpszichológusi összevónás, Mályi
19. Biomarkerek a pszichiátriában 2011, Tihany
20. Az agresszió biológiai és patofiziológiai alapjai 2012; Főszakorvosi összevónás
21. A depresszió és a kardiovaszkuláris betegségek összefüggései 2013. Főszakorvosi összevónás

• Publications:

1. Péter László, Kovács Gábor: Comorbidity and co-medication in a psychiatry ward 2006 (The International Journal of Neuropsychopharmacology volume 9, supplement 1)
2. Péter László: Akut pszichiátriai esetek ellátása katasztrófa során 2007 (Honvédorvos 2007/3-4. szám, 181)

3. Döme P., Teleki Z., Rihmer Z., Péter L., Dobos J., Kenessey I., Tóvári J., Tímár J., Paku S., Kovács G., Döme B.: Circulating endothelial progenitor cells and depression: a possible novel link between heart and soul 2007 (Molecular Psychiatry, 2009 14 (5) 523-531)
4. PéterLászló, DömePéter, RihmerZoltán, KovácsGábor, FaludiGábor: Kardiovaszkulárisbetegségekésdepresszió. Azepidemiológiaiés a lehetségesetiológiai összefüggésekáttekintése 2008 (NeuropsychopharmacologiaHungarica X/2, 73-82)
5. DömePéter, PéterLászló: Csökkentkeringőendotél progenitor sejtszám: egylehetséges összefüggés a szívés a lélekközött 2008 (NeuropsychopharmacologiaHungarica X Suppl 2, 17)
6. PéterLászló, KovácsGábor, Schweitzer Katalin: Az ATP felszabadulásés a trombocita aggregációváltozásánakvizsgálatadepressziósepizódkezelésesorán 2010 (NeuropsychopharmacologiaHungarica XII/ Suppl 1, 35)
7. PéterLászló, UrbánNóra: A katonákkoránhalnak 2010 (HonvédségiSzemle 2010/4, 56-57)
8. PéterLászló: Az ATP felszabadulásés a trombocitaaggregációváltozásánakvizsgálatadepressziósepizódkezelésesorán 2010, Richter GedeonyógyszergyárkutatóésipályázataI. hely
9. PéterLászló: Azönpusztítóagresszióésdepressziókatonáknál 2011 (SzakmaiSzemle2011/1 szám 170-180)
10. PéterLászló: Szorongásosés szomatikus betegségek közötti összefüggések 2011 (Honvédorvos (62) 3-4. szám 128-134)
11. PéterLászló, KovácsGábor, Schweitzer Katalin: ATP felszabadulásés trombocitaaggregációváltozása, mint az antidepresszív kezelés hatásosságának predikciója? 2011 (NeuropsychopharmacologiaHungarica XIII/2. szám 87-91)
12. PéterLászló: Biomarkerek a pszichiátriában 2011 NeuropsychopharmacologiaHungarica XIII/Suppl 2, 40)

13. PéterLászló, UrbánNóra: Katonaiviselkedésinterkulturáliskörnyezetben 2011 (FelderítőSzemle X. évf., 1-2. szám 216-226)
14. LászlóPéter, NóraUrbán: The Psychological approach of suicide bombing: are there any specific psychological and personality characteristics of the motivation? Azöngyilkos terrorizmuspszichológiai megközelítése: avagy léteznek –e specifikus személyiséglélektani jellegzetességek a motiváció tekintetében 2013 (Hadtudományi Szemle online 6 évf. 3. szám)

PROFESSIONAL CURRICULUM VITAE

Personal data

- Marital status: married
- Nationality: Hungarian
- Age: 40 years

Education

- 1987-1991: Radnoti Miklós practice secondary school for the Eötvös Loránd University of Sciences
- 1991-1997: Semmelweis University of Medicine, General Medicine Department, General MD
- 1997-2002: Hajnal Imre University of Medical Science, Psychiatry Specialization Department, psychiatry MD
- 2003-2006: University of Western Hungary, Department of Economics, MD-economist
- 2003-2006: Hajnal Imre University of Medical Science: Department of Catastrophe MD specialization: special MD for the military and catastrophe defense

- 2008: PhD student at the Military Science PhD school of the ZrinyiMiklos National Defense University

Professional experience

- 1997- 1998: Military Hospital of the HDF: Radiology Department
- January 15,1998-October 14, 2006: Military Hospital of the HDF, assistant doctor at the Psychiatry Department
- October 15, 2006-June 30, 2007: RadoGyorgy Military Hospital, senior assistant MD at the Department of Psychiatry
- From July 1, 2007: State Medical Center, senior assistant MD at the Department of Psychiatry
- From November, 2011: senior assistant MD at the Psychiatry Department of the Military Hospital
- From April 1, 2013: Head MD of the Psychiatry Department at the Military Hospital

Language knowledge

- 1990: medium level “C” type exam in Russian
- 1997: medium level “C” type military language exam in English

IT knowledge, driving license

- 1990: “ B” type driving license
- User level knowledge of Word, Excel, Power point, Internet

Society membership

- Hungarian Psychiatry Society

- Hungarian Pharmacology Society
- Hungarian Society of Military and Catastrophe Medical Science
- Mentor-Mentee Research Program