”GEORGE EMIL PALADE” UNIVERSITY OF MEDICINE, PHARMACY, SCIENCE AND TECHNOLOGY OF TÂRGU MUREŞ

DOCTORAL SCHOOL OF MEDICINE

ABSTRACT OF PhD THESIS

Evaluation of Cardiovascular Risk in Elderly Hypertensive and Diabetic Patients: Impact of Drug Therapy and Phytotherapeutic Possibilities

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Introduction

Cardiovascular diseases and diabetes mellitus are major global public health issues today. The aging population, cognitive decline, and polypharmacy in the context of existing comorbidities represent real challenges for healthcare workers. Vitamin and mineral deficiencies, especially in the elderly population, are often undetected and improperly treated, which can negatively impact health status. An individualized, holistic approach to patients, considering psychosocial factors, lifestyle, dietary habits, the severity and complexity of comorbidities, pharmacological and non-pharmacological treatments, as well as the results of paraclinical examinations, could help to improve therapeutic strategies. Information obtained through appropriate questionnaires, specialized laboratory tests, and the calculation of derived parameters useful in assessing cardiovascular risk factors can offer significant benefits from the perspective of disease progression and prognosis.

General Objectives

In this work, we aimed to comprehensively investigate elderly hypertensive patients with and without type 2 diabetes mellitus, including the assessment of cardiovascular risk, cognitive function, and dietary habits, correlated with a wide range of laboratory analyses, including numerous specialized tests. Another objective was to study the differences between the two sexes regarding protective factors against atherosclerosis. We also examined some adverse effects of drug therapy in two groups of patients, hypertensive and diabetic, in the context of possible vitamin and mineral deficiencies.

General Methodology

The patients in the study are part of the cases hospitalized at the Cardiovascular Rehabilitation Clinic in Târgu Mureș, where they are monitored long-term both clinically and paraclinically. In our studies, we focused on selecting cases with grade II and III hypertension, most of whom have high and very high cardiovascular risk. We aimed for a comprehensive approach, involving clinical and paraclinical data, as well as information obtained through questionnaires. In the diabetic group, we formed two subgroups based on therapy (metformin or another antidiabetic treatment).

Most of the biochemical laboratory analyses were performed on the Konelab Prime 60i analyzer using the photocolorimetric method, except for zinc and hs-CRP measurements, which were processed on the Konelab 20Xti using the photocolorimetric and turbidimetric methods, respectively. Fibrinogen level was measured on the Thrombolyzer XR analyzer, ESR was read using the Kima Vacutest, and urine analysis was conducted using the LabUReader Plus (strip reader) and

UriSedMini (urine sediment reader) devices. Hormonal assays (TSH, FT4), as well as vitamin B12 and homocysteine, were measured on the Immulite One analyzer using the chemiluminescence method. A smaller number of samples were processed using the automated ELISA method for the measurement of vitamins D and B12. MDA and glutathione levels were measured using the HPLC method with Merck-Hitachi equipment.

To assess patients' cognitive status, we used three types of tests: MoCA, MMSE, and GPCOG, as well as the Beck questionnaire to identify potential depressive states that could influence cognitive function. For a detailed assessment of dietary habits, we used the validated Food Frequency Questionnaire from Harvard Medical School with some modifications. To evaluate psychosocial factors, we used a standardized questionnaire drafted by the European Society of Cardiology.

Statistical data processing was performed using IBM-SPSS version 22 and GraphPad InStat version 3. The threshold for statistical significance was set at $p<0.05$.

Results:

Study 1: Evaluation of Cardiovascular Risk in Hypertensive Patients with and without Diabetes Mellitus using Metabolic and Oxidative Stress Parameters

Study 1a: In this broader study, we evaluated BMI, smoking, metabolic, inflammatory, mineral, and hormonal parameters, as well as cardiovascular risk factors in a cohort of hypertensive patients, using direct results and derived indices. This allowed us to identify a group at-risk patients who require increased attention. In some patients, retinal investigation was also possible.

Study 1b: In this research, we monitored a series of special laboratory parameters in hypertensive patients with and without type 2 diabetes mellitus: the concentration of MDA, an indicator of lipid peroxidation, and the levels of glutathione and zinc. We observed an increased level of oxidative stress in the studied patient cohort and a different distribution of anti-atherogenic protective factors between the sexes. Besides HDL cholesterol, an anti-atherogenic protective factor showing higher values in women, we found statistically significant differences in the serum concentration of reduced glutathione, which proved to be a more important protective factor in men.

Study 2: Evaluation of the Impact of Psychosocial Factors and Eating Habits on the Homeostasis of Vitamins and Minerals and Cardiovascular Risk in Hypertensive Patients with or without Cognitive Dysfunction

Study 2a: In a larger case study, we evaluated the psychosocial and laboratory factors that can influence cardiovascular risk. Patients with a lower educational level had significantly higher BMI values than those with a higher educational level. It was found that obese individuals had higher values of uricemia and triglyceridemia than normo- or overweight patients.

Study 2b: In this study, we compared laboratory analyses and dietary questionnaire data in hypertensive patients with and without cognitive dysfunction. We found statistically significant differences in the mean values of BMI and daily intake of cholesterol and magnesium between the two subgroups. A negative correlation was observed between daily calorie intake and blood glucose values. The distribution of patients with and without cognitive dysfunction showed a significant difference between hypo/normocaloric and hypercaloric diet groups.

Study 3: Evaluation of the Side Effects of Metformin Treatment in Type 2 Diabetic Patients with or without Hypertension

In this research, we measured vitamin B12 and homocysteine levels in two stages in diabetic patients, with the first stage involving a larger cohort and a wider variety of paraclinical analyses. In both stages of the study, a negative correlation between homocysteine and vitamin B12 levels was observed. The level of oxidative stress was higher in diabetic patients compared to the control group. Most patients exhibited hyperhomocysteinemia, representing a risk for thrombosis. In patients treated with metformin, the average serum level of vitamin B12 was significantly lower compared to diabetics on other treatments, which could be related to the side effects of metformin use.

Study 4: Evaluation of the Side Effects of Statin Treatment in Hypertensive and Dyslipidemic Patients with or without Diabetes Mellitus

In this study, we evaluated the serum level of vitamin D in hypertensive patients (grade II and III) with dyslipidemia, comparing the values between those who are on statin treatment and those who do not use such medications. Approximately half of the patients in the study had type 2 diabetes mellitus as a comorbidity. The vast majority of patients had previously undetected hypovitaminosis D. There was no

statistically significant difference in the average serum vitamin D level between patients on statin therapy and those not receiving such treatment.

General Discussions

Our results are largely consistent with the literature regarding the high prevalence of obesity and type 2 diabetes mellitus in hypertensive patients. Many patients can be identified with multiple cardiovascular risk factors and deficiencies in certain vitamins or minerals, which could be detected if such analyses were more accessible to patients. Special laboratory analyses for investigating oxidative stress are more expensive and require modern equipment. In contrast, derived parameters such as non-HDL cholesterol or the calculation of indices based on standard biochemical results are readily available, do not require additional costs, and can help in assessing cardiovascular risk in elderly hypertensive patients.

General Conclusions

Many patients with arterial hypertension also have type 2 diabetes mellitus, obesity, and dyslipidemia as comorbidities. Most patients have a high degree of cardiovascular risk, with special laboratory analyses and the calculation of indices providing additional accuracy in this evaluation. Numerous patients have vitamin or mineral deficiencies; therefore, combining medicinal treatment with dietary supplements or phytotherapeutic preparations with antioxidant, hypotensive and hypoglycemic properties containing vitamins and minerals could be an appropriate approach in these cases.

As age advances, the number of medications used increases due to comorbidities associated with arterial hypertension, ”justifying” polypharmacy. The risks of adverse drug reactions are amplified by comorbidities, polypharmacy, inappropriate prescriptions and suboptimal monitoring of therapy. All these factors increase the vulnerability of elderly patients to pathogens and pharmacological agents. Severe adverse reactions in the elderly represent a constant challenge in their identification, treatment, and effective prevention.

Originality of the Study

In this research, we utilized a series of special analyses, which are not easily accessible to patients, providing essential complementary information for the evaluation of cardiovascular risk factors. Among these modern methods is the measurement of MDA using the HPLC method, which has an innovative character and was developed by our research team, and is currently undergoing improvement. Additionally, the measurement of reduced and oxidized glutathione using the HPLC method was

adapted by our research team on the existing equipment. The corroboration of laboratory analysis results with data obtained from dietary habit questionnaires, as well as the results of retinal investigations, also adds a touch of originality and complexity to our study.