Lipid Profiles and Framingham Risk Score in Patients with Coronary Artery Bypass Graft Surgery undergoing Cardiac Rehabilitation Program

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Coronary artery disease (CAD) is one of the major predictors of future cardiovascular events (CVEs). In addition, biomarkers such as high-sensitivity C-Reactive Protein (hsCRP), fibrinogen, homocysteine, and free fatty acid (FFA) correlate well with a future CVE. The Framingham Risk Score is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual. Cardiac rehabilitation is an instrument of medical management in cardiovascular diseases; beyond prevention, it can improve heart and muscle functioning in patients that were undergoing CABG, and cardiac and vascular adaptation. Over a 2-year period, 120 subjects were randomized and comprehensively evaluated. The mean age of the patients under study was 65.70 ± 9.91 years old. For the Framingham cardiovascular risk score, the mean value in the Phase I was 16.5, while the mean value in Phase III was 10.6. The difference registered after cardiac surgery and the value in 6 months after the onset of cardiac rehabilitation program was important and statistically significant, as $p < 0.05$. Fibrinogen showed significant phase-to-phase reductions of plasmatic values. Lipid profile values showed a statistically significant decrease. The renal filtration function evaluated by plasma creatinine showed statistically significant improvement and, in terms of absolute values, creatinine level was reduced in a range between 0.2-0.4 mg/dL. Also, it was recorded a significantly lower level of blood urea. By comparing the Phase I and Phase III results, we observed that the median 10-year Framingham cardiovascular risk score was approximately 6% lower ($p < 0.05$), reflecting the survival benefit gained by patients under the intensive cardiovascular recovery program.

Keywords: Framingham Risk Score, coronary-artery bypass graft, cardiac rehabilitation

The more important of the first models used frequently up to now in the research of cardiovascular risk factors impact on every people life is the Framingham system. The information included in the Framingham risk comprised the followings: age, gender, smoking status, systolic blood pressure, total and HDL cholesterol levels, the positive diagnosis of diabetes mellitus (DM) or the absence of diabetes, and the existence of hypertension (HT) under treatment or without medication. The total score revealed by the Framingham risk score allowed an estimation of a 10-year risk of developing coronary heart disease [1,2].

Cardiovascular disease (CVD) leads the world list of the etiology for disability and mortality. The Framingham study design remains a milestone in identifying the CVD risk factors. By using the Framingham Risk Functions (also called Framingham Risk Scores), many clinical trials showed that treating modifiable risk factors with evolution towards normal range of the values, the likelihood of developing CVD can be reduced. The Framingham investigators elaborated these functions through multivariate algorithms, where the dependent variable was the CVD, and, as for the explanatory variables, they considered the following independent variables: age, gender, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking behavior, and diabetes status. These items association enables to estimate the risk over a fixed time, as in ten years from now, of developing a cardiac or vascular condition (coronary heart disease, stroke, peripheral vascular disease, or heart failure). The Framingham study highlighted the multifactorial aspect of the cardiovascular risk and the time-correlation between the risk factors to induce the CVD onset, and the imperious need for drug treatment recommendations for high cholesterol or HT [3].

Sudden cardiac death (SCD) accounts for half of cardiovascular mortality, of which 50% of patients were not previously diagnosed with heart disease [4,5]. Coronary artery disease is the etiology of SCD in 80 % of cases, and thus, any risk factor for coronary artery disease (dyslipidemia, diabetes, hypertension, obesity, sedentary lifestyle, smoking, excessive alcohol consumption, family history, menopause and advanced age) can predispose to SCD.

Homocysteine, fibrinogen, lipoprotein(a), low density lipoprotein particle size and C-reactive protein are additional risk factors for the onset of CVD [6].

Hypercholesterolemia is an independent risk factor for ischemic heart disease [7]. Serum low-density lipoprotein (LDL) concentration has a direct positive correlation with the incidence of cardiovascular complications, mainly ischemic events, being set as the target for the lipid control. Different lipoproteins, as high-density lipoproteins (HDL) and triglycerides are responsible for the onset, development, and destabilization of the entire atherosclerotic process [8-10].

Prevention of cardiovascular conditions would be cost-effective, being given their leader position as a morbidity and mortality etiology [11]. Cardiac rehabilitation (CR) program comprehend medical evaluation and treatment, supervised exercises, education and counseling of patients. Primary, secondary, and tertiary cardiac prevention

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usefulness was referred in the guidelines for the management of cardiovascular (CV) diseases as necessary and safe, with great outcomes in postoperative care after CABG [12].

Repetitive physical effort plays an important role in CR program, with positive influence on cardiac and respiratory muscle training, and on functional capacity in patients undergoing CABG, as well as in oxidative stress, endothelial dysfunction and arterial stiffness [13,14]. The exercise training programs in CR have influenced the coronary risk factors, such as hypertension, arrhythmia, depression, and obesity [15,16]. Moreover, there was registered a 40% risk reduction in cardiac morbidity and mortality secondary to CR program implementation [17].

Experimental part

Material and methods

The purpose of this study was to determine whether lipid profiles and Framingham Risk Score would change in patients post CABG surgery, undergoing a cardiovascular recovery program. The levels were compared between the first phase developed during the first postoperative week, and the third phase carried out 6 months later.

This was a prospective study comprising 120 patients admitted in the Clinic of Cardiovascular Surgery of the Institute of Cardiovascular Disease, following the cardiovascular recovery program immediately, at 3 and at 6 months after the cardiac surgery in the Cardiovascular Rehabilitation Clinic of the Rehabilitation Hospital of Iasi. The inclusion criteria were: CABG patients (less than 1 week), aged 40-80 years old, BMI > 25 kg/m², and mixed dyslipidemia. The study was approved by the University Ethics Committee and all participants signed an informed consent.

In both phases, for every patient, it was performed a clinical examination, a set of hematological, biochemical, lipid, coagulation and inflammatory profile, and ECG and echocardiography (LVDd, LVSd, IVSd, PWd, LVM, LVMI, EF, and SF). Blood pressure, heart rate and effort capacity (METs) were monitored during the rehabilitation program.

Glucose (molecular formula: $C_6H_{12}O_6$) is a monosaccharide exists in nature only as D-isomer form.

Renal function was evaluated by serum urea, creatinine and uric acid level. Urea (CH_4N_2O) is an organic compound with a carbonyl (C=O) functional group linked to two $-NH_2$ groups. Creatinine (2-Amino-1-methyl-5H-imidazol-4-one), an important indicator of renal function, is byproduct of the muscle metabolism that is excreted unchanged.

Glomerular filtration rate (GFR) was calculated according to the most accurate formula of CKDEPI (Chronic Kidney Disease Epidemiology Collaboration) [18]:

$$eGFR = 141 \times \min(SCr/k,1)\alpha \times \max(\alpha Cr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if Female}]$$

(where SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1).

Uric acid (7,9-Dihydro-1H-purine-2,6,8(3H)-trione) – a diprotic aromatic acid – is a product of purine nucleotides metabolism, leading to gout and increased CV risk in case of high values.

Alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl transferase (GGT) were assessing the hepatic function. ALT catalyzes the reaction between L-alanine and α-ketoglutarate to form pyruvate and L-glutamate. AST interconverts aspartate and á-ketoglutarate to produce oxalo-acetate and glutamate. GGT, a key component in the gamma-glutamyl cycle, that transfers the glutamyl moiety to a variety of amino acids or peptides based on the reaction:

(5-L-glutamyl)-peptide + an amino acid peptide + 5-L-glutamyl amino acid

High–density lipoprotein (HDL) cholesterol, low–density lipoprotein (LDL) cholesterol, total cholesterol and triglycerides were assessing the lipid profile. HDL is the smallest and densest of lipoprotein particles and plays an anti-atherogenic role by removing the fat molecules from cells. The non–HDL cholesterol is considered to cause atheroma and it has been shown to be a better predictor of CV events than other lipid values [19]. LDL has a 10-fold larger diameter than normal cholesterol and represents a high cardiovascular risk by invading and oxidizing into the endothelium and promoting the atherosclerotic plaque. Cholesterol (=(3β)-cholest-5-en-3-ol), an organic molecule with 256 stereo-isomers biosynthesized by all animal cells, is a crucial component of cell membranes and a precursor for steroid hormones, vitamin D and bile acids. High triglycerides levels are associated with an increased risk of CV events. Triglycerides are esters derived from the combination of glycerol and three fatty acids (RCO_2H, $R'CO_2H$ and $R"CO_2H$), based on the formula:

$$HOCH_2CH(OH)CH_2OH + RCO_2H + R'CO_2H + R"CO_2H \rightarrow \rightarrow RCO_2CH_2CH(O_2CR')CH_2CO_2R" + 3H_2O$$

Serum fibrinogen (a large complex of 340 kDa plasma glycoprotein) level was used to determine the state of inflammation. Fibrinogen acts in the normal blood coagulation cascade and as a key regulator of inflammation in disease [20].

Ejection fraction (EF) and other cardiac parameters (LVDd, LVSd, IVSd, PWd, LVM, LVMI, and SF) were performed by cardiac echography.

Statistical Analysis

The database was compiled in Microsoft Office Excel 2010 version, and statistical analysis was performed in the IBM SPSS Statistics v.20, calculating the averages, frequencies, standard deviations, differences between the maximum and minimum values of the numerical parameters. The statistical significance of the difference between two frequencies was determined by the Chi-square test of independence. The *t* Student test was used to reveal the significance of the difference between two average values. The threshold values for p were considered < 0.05, providing a statistical significance level of the test. The regression equations and correlation coefficients were also calculated.

Results and discussions

The mean age of the patients under study was 65.70 ± 9.91 years old, of which male age was 65.26 ± 10.26, respectively 66.96 ± 8.89 for female patients. Approximately one third of these, 29 patients, were female and 81 were male. The median age was 65 years.

Most people were from urban areas (89%) and only 11% from rural areas. The smoking status was present in 58% of the cases and absent in 42% of the cases.

Electrocardiogram (ECG) changes showed that atrial fibrillation was relatively frequent in Phase I (66.33%), whereas 91% regained sinus rhythm in Phase III.

In the first stage, white blood cells (WBC) were high, probably indicating an inflammatory syndrome. Inflammation and postoperative hemorrhage could explain the low hemoglobin (Hb) and hematocrit (Ht) values, ameliorated six months later. An increase in the blood platelet counts was noticed.

Plasma glucose values decreased in the IIIrd Phase (table 1).

For biochemical samples (table 1), we obtained high statistical significance for all pairs of data that were compared, except for the serum *gamma-glutamyl transpeptidase* (GGT). According to the calculated means, a decrease of the values in Phase III was observed for all the studied variables. GGT did not undergo Phase III changes compared to Phase I.

The renal filtration function registered a statistical significant improvement, and both creatinine and blood urea were diminished.

Lipid profile values showed a statistically significant decrease, but with no change regarding the cardiovascular risk range (table 2).

Fibrinogen, supported by C-reactive protein (CRP) level changes, showed significant phase-to-phase reductions.

For bleeding times, there was statistical significance in all variables: $p < 0.001$. APTT decreased in Phase III, INR

Biochemical values	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
TGP 1	41.02	39.928	3.993	.000
TGP 3	26.50	14.749	1.475	
TGO 1	34.99	27.235	2.724	.000
TGO 3	25.03	18.449	1.845	
GGT 1	41.82	25.786	2.579	.955
GGT 3	41.55	48.110	4.811	
Glycaemia 1	139.55	58.081	5.808	.000
Glycaemia 3	121.28	46.451	4.645	
Urea 1	46.17	14.424	1.442	.000
Urea 3	42.13	12.139	1.214	
Creatinine 1	1.2972	.46679	.04668	.000
Creatinine 3	1.0924	.21551	.02155	

Table 1
BIOCHEMISTRY - COMPARATIVE DATA BETWEEN THE REHABILITATION PHASES

Biochemical tests	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
Chol 1	182.69	47.945	4.795	.003
Chol 3	170.31	50.619	5.062	
HDL 1	40.23	22.762	2.276	.000
HDL 3	50.04	26.586	2.659	
LDL 1	143.95	31.067	3.107	.000
LDL 3	122.06	29.619	2.962	
TG 1	146.63	55.629	5.563	.001
TG 3	131.62	56.238	5.624	

Table 2
LIPID MARKERS - COMPARATIVE DATA AFTER 6 MONTHS OF REHABILITATION

Bleeding Time	Mean	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
APTT 1	34.02	7.374	.741	.000
APTT 3	31.69	5.912	.594	
INR 1	1.2845	.65564	.06589	.000
INR 3	2.087	.6331	.0636	
TQ 1	17.29	6.873	.691	.000
TQ 3	13.82	4.012	.403	
CRP 1	3.88	3.179	.318	.000
CRP 3	1.725	2.6791	.2679	
Fibrinogen 1	640.79	175.120	17.512	.000
Fibrinogen 3	442.75	115.201	11.520	

Table 3
COAGULATION AND INFLAMMATION - COMPARATIVE DATA BETWEEN PHASE I AND III

increased in Phase III, and TQ decreased in Phase III (table 3).

For the echocardiographic parameters, we obtained statistical significance for the first 8 variables. These variables LVDd, LVSd, IVSd, PWd, LVM, and LVMI showed a reduced value in phase III (confirmed by the mean values) compared to first phase. EF and SF variables registered an increased value in Phase III, in concordance with symptomatology and effort capacity. The statistical significance confirmed that these changes were based on a factor that had a major influence upon the values in Phase III compared to Phase I.

Patients were grouped accordingly by the degree of physical exercise that they were able to achieve immediately after CABG. In the first recovery phase (one week after myocardial infarction), most patients were able to undergo only a minimal effort of one MET, less than 38% an exercise of two METs, and less than 10% an effort of 3 METs. No one did more than 3 METs. In the third phase of cardiovascular recovery, all patients have improved and even exceeded their poor physical condition by performing average efforts of 4-5 METs, with nearly 2/3 of patients reaching 5 METs.

The effects of the cardiac rehabilitation program in patients after cardiac surgery was seen in decreasing complications and improving QoL. Although there are specific recommendations after CABG surgery, there is a very low enrollment in the cardiac rehabilitation programs. In some countries, healthcare providers turned to home-based cardiac rehabilitation program instead of centre-based care [21].

The Framingham Risk Score (FRS) is a useful clinical tool enabling to assess the risk level of coronary artery disease and to identify the potential modifiable risk factors in vulnerable individuals. FRS is the most appropriate method of measuring a person's likelihood of developing long-term cardiovascular disease.

The FRS helps identify men and women at high risk in order to prevent future cardiovascular events. However, despite the applicability of this tool, it has no power in assessing key factors influenced by diet and metabolic change. Consequently, it is not known whether FRS is a good predictor of the metabolic disorders that underlie ischemic heart disease. In addition, it has been demonstrated that FRS overestimates the risk of coronary artery disease in Europeans and therefore recalibration is recommended for special populations [22].

Framingham's traditional risk factors such as age, hypertension, smoking, diabetes and cholesterol form the basis of the guidelines provided by Adult Treatment Panel III (ATP III). The FRS targets the predictive risk model for coronary artery disease. Abnormal values for lipid profile (non-HDL, LDL, total cholesterol, triglycerides), uric acid and renal function (creatinine, urea and GFR) present the best correlations with increased markers of subclinical atherosclerosis. That triggers the necessity to assess biochemical profile regularly in order to prevent CVD [23]. Cardiovascular risk is also related to family history, inflammation markers such as high sensitivity reactive C protein, and glycated hemoglobin in diabetics. These additional biomarkers are included in the Reynolds Risk Score, an alternative risk algorithm developed in 2007 for men and women. Both ATP-III and Reynolds scores received Class I recommendations from the American College of Cardiology and the American Heart Association, both scores being approved as part of the National Direction for the prevention of cardiovascular disease in Canada. However, to date, there has been no comparison between these two risk-rating systems in an independent prospective cohort. In addition, a Framingham prediction model for all cardiovascular disease has recently been developed, but this model has not yet been validated on an external population [24].

In our prospective study on hospitalized patients undergoing CABG, by comparing the Phase I and Phase III results, we observed that the median 10-year Framingham cardiovascular risk score was approximately 6% lower ($p < 0.05$), reflecting the survival benefit gained by patients

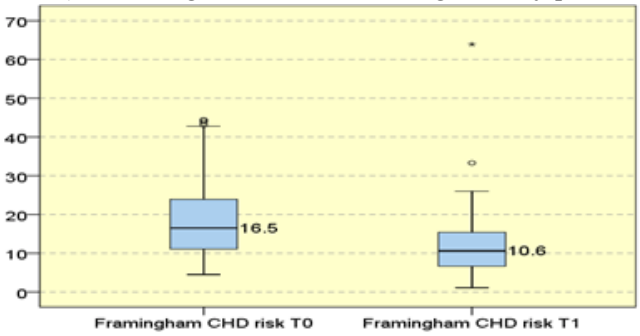

Fig. 1. Box-plot Diagram – Patients distribution on the Framingham CHD score in Phase I and III of cardiac rehabilitation after CABG

under the intensive cardiovascular recovery program (fig. 1).

The results obtained by calculating cardiovascular risk scores revealed important and useful correlations between several risk factors (myocardial infarction, atrial fibrillation, hypertension, sex, obesity, diabetes). This is one of the few studies that have attempted to investigate the possible association between lipid profiles and Framingham Risk Score.

We compared our results with those obtained from the Framingham Heart Study in April 2002, which identified major cardiovascular risk factors: hypertension (HTA), hypercholesterolemia, smoking, obesity, diabetes, sedentary, and other lipid fractions (HDL cholesterol, LDL-cholesterol, triglycerides), peculiarities related to gender and age group.

Numerous prospective studies following the FRAMINGHAM trial confirmed the major impact of these risk factors on the development of cardiovascular disease and acute myocardial infarction [25].

Conclusions

The decrease of plasmatic glucose in the IIIrd Phase proved that the better the carbohydrate metabolism profile is, the lower the cardiovascular risk will be.

In the cardiovascular rehabilitation program, the cycloergometer testing has an important place, both immediately after myocardial infarction and in the first stage of rehabilitation, followed by physical endurance training, which is recognized for increasing physical exercise capacity, walking distance and improving the quality of life.

Due to the fact that the Framingham Risk Score provides an indication of the possible benefits of prevention, it may also be useful for the patient and clinicians to choose earlier the lifestyle changes and preventive medical treatment.

After a thorough research into major international databases, this study is probably the first to attempt to evaluate the relationship between cardiovascular risk scores and aortic-coronary post-bypass cardiovascular recovery outcomes. In our study, by computing Framingham Risk Score we have been able to translate clinical practice data into statistically significant results,

comparing the results from the first phase of the recovery to the final phase.

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