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Low ALT blood levels are associated with lower baseline fitness amongst participants of a cardiac rehabilitation program

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ABSTRACT

Background/Objective: Objective assessment tools for patients' frailty are lacking. Such tools would have been highly valuable for assessment of candidates for cardiac rehabilitation programs. Low ALT (Alanine aminotransferase) values were recently shown to be a promising parameter for objective, quantitative frailly assessment.
Methods: This was a retrospective study of patients participating in a cardiac rehabilitation program.
Results: Patients with lower ALT activity levels at the initiation of rehabilitation program had lower estimated METs values (6.86 vs. 7.73; $p < 0.001$), shorter stress test duration (06:41 vs. 07:44 min; $p < 0.001$), higher resting heart rate (72 ± 13 vs. 70 ± 13 BPM; $p = 0.01$) and lower heart rate reserve (49 ± 24 vs. 54 ± 24; $p < 0.001$). Multivariate linear modeling demonstrated that ALT values were Independent determinants of baseline exercise capacity (expressed in METs).
Conclusion: Lower ALT values, measured prior to the initiation of cardiac rehabilitation programs may indicate frailty of patients and be indicative for poor rehabilitation outcomes. Further, prospective studies should assess the potential correlation between ALT values and rehabilitation efficiency. We aimed to assess the potential correlation between the baseline ALT values and the baseline exercise capacity, as expressed in METs (Metabolic equivalent of tasks). 3806 patients were included in our study.

Background

Exercise-based cardiac rehabilitation is well established for achieving better clinical outcomes among patients after AMI (Acute myocardial infarction) and CHF (Congestive heart failure).[1–3] System-based approach to referral of appropriate patients to rehabilitation programs is advocated,[4] i.e. appropriate patient selection, could potentially increase the yield of such rehabilitation programs.

Frailty assessment is an important step in such patients' selection process: it is known that patients who are deemed frail, experience worse outcomes after cardiac surgery.[5,6] Nevertheless, frail elderlies suffering from CVD (Cardiovascular disease) may benefit more from patient-centered, multi-disciplinary programs of cardiac rehabilitation.[7] Therefore, frailty assessment tools, preferably objective and simplified, should be sought.[8]

Low ALT (alanine aminotransferase) activity levels in the peripheral blood have been shown to be associated with lower total-body muscle mass, increased frailty and risk of mortality in elderlies[9] and increased risk of all-cause mortality in both healthy, middle-aged people[10,11] and patients suffering from stable IHD (Ischemic heart disease).[12] No previous study addressed the potential value of low ALT as a potential predictor for cardiovascular fitness.

In the current study we tried to assess whether low ALT blood activity, as a biomarker for increased frailty, is associated with lower baseline fitness of post-AMI and post-cardiac surgery patients going through a cardiac rehabilitation program.

Patients and methods

Study population

This was a retrospective study in a population of post-AMI and post-cardiac surgery patients participating in a comprehensive

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cardiac rehabilitation program in a tertiary hospital. Patients with ALT >40 IU (assumed to have some sort of hepatitis) were excluded as were patients with diagnosis of liver dysfunction or cirrhosis. We further excluded subjects unable to exercise due to cognitive impairment, severe neurological or orthopedic limitations and severe comorbidities with life expectancy <3 months duration.

Clinical information and laboratory assessment

All the subjects underwent blood testing including ALT activity routinely during their hospital stay. In case of multiple tests, we selected the latest lab test for the current analysis. Activity of ALT was assessed using a standardized Beckman Coulter® test. Quantitative determination of ALT levels was used by applying kinetic UV tests. In order to assure maximal catalytic activity of the ALT from the blood drawn, all test tubes were routinely supplemented with activated pyridoxal phosphate (P-5-P), serving as an essential co-factor for ALT catalytic activity.

Outcomes and definitions

The primary study endpoint was exercise capacity as assessed by graded exercise stress test and expressed in metabolic equivalents of task (METs) estimated according to widely used American collage of Sport Medicine (ACSM) formula.[13] All study subjects underwent a symptom limited stress test within a month prior to cardiac rehabilitation start. Stress tests were supervised by senior cardiologists using the Bruce (69%) or modified Bruce (31%) protocols without withholding cardiac medications. Appropriate stress test protocol was selected by experienced physicians based on patients' daily activity and reported physical activity. Stress test was limited by symptoms, target heart rate achieved or the appearance of significant ST changes, arrhythmia or other guideline test termination indications.

Statistical analysis

The study population was divided into two groups based on the ALT levels obtained during the baseline visit of the rehabilitation program. We used a cutoff value of 17 IU/l for defining a group of Low-normal ALT activity, relying on the relevant literature.[10–12] We compared the lower ALT group (ALT < 17 IU/l) to the ALT ≥ 17 IU/l group. Blood hemoglobin concentration and Creatinine concentration (needed for eGFR [estimation of Glomerular Filtration Rate] were also recorded).

Comparison of categorical variables was performed with chi-square analysis, and comparison of continuous variables was performed with the Student's t-test for variables with normal distribution and by the Mann-Whitney test for those that violated the normality assumption.

In order to establish independent predictors of low-normal ALT value, we performed multivariate logistic regression modeling introducing the following covariates: age, gender, Body Mass Index (BMI), diagnosis of diabetes, hypertension, active smoking, dyslipidemia, Chronic Obstructive Pulmonary Disease (COPD), cardiomyopathy, current atrial fibrillation or flutter, past stroke, Left-Ventricular Ejection Fraction (LVEF) < 50%, prior Myocardial Infarct (MI) or past cardiac valve or coronary bypass surgery (CABG).

In order to assess the independent association of low ALT values and reduced exercise capacity, as assessed by symptom limited exercise stress, we explored the adjusted linear association of METS as a continuous covariate with pretest ALT values.

Covariates which were found to have statistically significant correlation with Mets' results in the univariate analysis (necessitating level of significance (p) lower than 0.01) were included in the above described multivariate analysis. Thus, multivariate linear model was further adjusted for age, gender, LVEF % (as continuous covariate), hemoglobin level (g/dL) and prior diagnosis of COPD or heart failure.

All statistical tests were two-sided, and a p value of less than 0.05 was considered to indicate statistical significance. Analyses were carried out with the use of SPSS software, version 22 (IBM Inc.) and SAS, version 9.3.

Results

Baseline characteristics were available for 3806 patients (Table 1). Amongst patients with lower ALT activity at initiation of the rehabilitation program there was a larger proportion of female gender, Diabetes Mellitus, COPD and arterial hypertension. Baseline systolic function, measured as LVEF was not significantly different between participants with low-normal and normal ALT activity and

Table 1
Baseline characteristics of the whole study cohort.

P value	ALT ≥17 IU	ALT <17 IU	N
	2470	1336	
Patients demographics			
NS	61	64	Age (years, mean)
P < 0.001	474 (19.2%)	402 (30.1%)	Female [n (%)]
0.06	27.2 ± 4	27.8 ± 4	BMI (±SD)
Background diagnosis			
P < 0.05	667 (27%)	422 (31.6%)	Diabetes Mellitus [n (%)]
P < 0.001	1833 (74.2%)	900 (67.4%)	IHD
P < 0.001	1803 (73%)	935 (70%)	Past MI
P = 0.001	73 (3.0%)	70 (5.2%)	COPD
P < 0.05	1233 (49.9%)	727 (54.4%)	Hypertension
P = 0.052	311 (12.6%)	199 (14.9%)	CHF
P = 0.324	1325 (53.6%)	694 (51.9%)	Dyslipidemia
P = 0.091	74 (3.0%)	54 (4.0%)	PVD
P = 1	208 (8.4%)	113 (8.5%)	Active Smoking
P = 0.709	48.3%	47.7%	LVEF < 50%
0.44	198 (8%)	94 (7%)	Valve surgery
NS	17.8%	16.5%	I NYHA
	5.3%	5.9%	II
	3.2%	5.2%	IIIA
	0.9%	1.2%	IIIB
	0.2%	0.1%	IV
Laboratory values			
0.14	69	70	eGFR ml/min/1.73 m^2
NS	13.1	13.56	Hb (gr/dL)
Medications			
P = 0.309	78.5%	76%	ARB or ACE-I
P = 0.548	70.3%	69.5%	Beta Blockers
0.011	85%	88%	Statins
0.13	82%	86%	Platelet inhibitors
P = 0.303	5.7%	6.4%	Digitalis
Stress test parameters			
<0.001	7.73	6.86	METS value
<0.001	07:44	06:41	Test duration (min:sec)
0.01	70 ± 13	72 ± 13	Resting heart rate (BPM)
0.01	124 ± 19	126 ± 24	Resting SBP (mmHg)
<0.001	54 ± 24	49 ± 24	Heart rate reserve (BPM)
0.44	161 ± 27	164 ± 94	Max SBP (mmHg)

COPD, Chronic Obstructive Pulmonary Disease; IHD, Ischemic Heart Disease; CHF, Congestive Heart Failure; NS, Non-Significant; PVD, Peripheral Vascular Disease; NYHA, New York Heart Association functional status; ACE-I, Angiotensin Converting Enzyme Inhibitors; ARB, Angiotensin Receptor blockers; LVEF, Left Ventricle Ejection Fraction; BPM, Beats Per Minute; SBP, Systolic Blood Pressure.

Table 2
Patient characteristics found to be independent predictors for lower ALT activity.

P value	95%CI		OR	Covariate
	Upper	Lower		
<0.001	2.20	1.60	1.87	Female gender
0.04	1.39	1.01	1.19	Diabetes mellitus
<0.001	1.58	1.12	1.33	Past CABG
0.15	1.30	0.96	1.12	Hypertension
0.02	0.97	0.72	0.83	Dyslipidemia
0.68	1.35	0.82	1.05	Smoker
0.22	1.42	0.92	1.15	Past Valve surgery
0.11	1.06	0.59	0.79	Cardiomyopathy
0.00	2.41	1.21	1.70	COPD
0.70	1.17	0.79	0.96	Atrial Fibrillation or flutter
0.03	1.61	1.02	1.29	Past CVA
0.04	1.75	1.02	1.33	LVEF <50%
0.076	1.00	0.94	0.97	BMI
0.01	1.92	1.08	1.44	Blood Creatinine concentration (per 1 mg/dL increment)
0.04	0.99	0.57	0.75	Past MI
<0.001	1.03	1.01	1.02	Age (per year increment)

Table 3
A multivariate linear model for independent determinants of baseline exercise capacity (expressed in METs).

p value	Coefficient	Covariate
<0.001	0.024	ALT (IU/dl)[a]
<0.001	−0.117	Age[a]
<0.001	1.86	Heart failure diagnosis
<0.001	0.204	Hemoglobin g/dL[a]
<0.001	0.024	LVEF %[a]
<0.001	1.202	COPD diagnosis

[a] Introduced as continuous variables.

consequently, NYHA (New York Heart Association) functional status, was also not significantly different between these two groups. Essential medications used for the treatment of heart disease were also similar in both study groups.

Patients with lower ALT activity levels at the initiation of rehabilitation program had lower estimated METs values (6.86 vs. 7.73; $p < 0.001$), shorter stress test duration (06:41 vs. 07:44 min; $p < 0.001$), higher resting heart rate (72 ± 13 vs. 70 ± 13 BPM; $p = 0.01$) and lower heart rate reserve (49 ± 24 vs. 54 ± 24; $p < 0.001$) (Table 1).

Within our study population, patient characteristics that were found to be independently predictable of lower ALT blood activity were: age (OR = 1.02; 95%CI 1.01–1.03; P < 0.001); female gender (OR = 1.87; 95%CI 1.60–2.20; P < 0.001), and increased blood creatinine concentration (OR = 1.44; 95%CI 1.08–1.92; P = 0.01) (Table 2).

Correlation of lower ALT values with reduced exercise capacity

Multivariate linear modeling demonstrated that ALT values were Independent determinants of baseline exercise capacity (expressed in METs) (Table 3). With relation to a cutoff value of 17 IU/L, found to be significant in previous studies,[10,12] we found that low ALT activity, as a categorical parameter (below or above 17IU/L) was also significantly associated with low baseline exercise capacity. Additional significant predictors were age, hemoglobin, lower LVEF, diagnosis of COPD or heart failure.

Discussion

The aim of this study was to examine the association of low ALT, an independent marker of frailty, with the baseline exercise capacity of participants of a cardiac rehabilitation program. In this cohort, low ALT activity was associated with unfavorable baseline physical parameters in comparison with the general study population. These finding correlate well with previous studies that showed the association between low ALT activity and worse clinical outcomes, in variable patients' populations.[9–12] In our cohort, low ALT activity was associated with lower estimated METs values, higher resting heart rate and shorter stress test duration. We showed, in a multi-variate model, that low ALT serves as an independent predictor for low baseline exercise capacity, independent from other physiologic variables that share this prognostic value by themselves (including blood hemoglobin concentration and left-ventricular heart failure parameters). These findings raise the possibility that such patient populations might have lower rehabilitation potential, although further research is needed. The recognition of the frail patient itself and the markers of frailty before the initiation of cardiac rehabilitation program are imperative due to the need for better prognostication and for viewing the anticipated rehabilitation results. In light of our findings, it might be reasonable to suggest that ALT may be used, among other criteria, to identify a specific sub-population of frail patients requiring cardiac rehabilitation. The implication may be that these patients will require a specialized rehabilitation programs that will be suitable for their unique needs. This study did not address the question regarding the potential changes in ALT levels post-exercise. It is plausible to assume, that measurements of ALT levels would reflect exercise programs' impact on frailty and muscle mass. Such measurements, however, should not be made in close relation to intense exercise, after which increased ALT levels could potentially be associated with rhabdomyolysis.

Limitations

This was a retrospective study, and therefore, causality could not be inferred and the results are associated with statistically significant correlations only. Also, no conclusions can be drawn regarding rehabilitation programs differing from the standard cardiac protocols employed (e.g. anaerobic exercise).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jesf.2017.11.002.

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