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

Michael Kogan a,1, Robert Klempfner b,1, Dor Lotan a, Yishay Wasserstrum a, Ilan Goldenberg b, Gad Segal a,*

a Department of Internal Medicine “T”, Chaim Sheba Medical Center, Tel-Hashomer, Israel
b Leviev Heart Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel

Article info
Article history:
Received 3 March 2017
Received in revised form
4 November 2017
Accepted 10 November 2017
Available online 29 November 2017

Keywords:
ALT (alanine aminotransferase)
Cardiac rehabilitation
METS (metabolic equivalent of tasks)
Frailty
Fitness
Ergometry

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.

© 2017 The Society of Chinese Scholars on Exercise Physiology and Fitness. Published by Elsevier
(Singapore) Pte Ltd. This is an open access article under the CC BY-NC-ND license (http://
creativecommons.org/licenses/by-nc-nd/4.0/).

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,1 i.e. appropriate patient se-
lection, could potentially increase the yield of such rehabilitation
programs.

Frailty assessment is an important step in such patients’ selec-
tion 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, prefer-
ably objective and simplified, should be sought.8

Low ALT (alanine aminotransferase) activity levels in the pe-
ripheral blood have been shown to be associated with lower total-
body muscle mass, increased frailty and risk of mortality in el-
derlies9 and increased risk of all-cause mortality in both healthy,
middle-aged people10,11 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 pa-
tients 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
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 College of Sport Medicine (ACSM) formula. 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. 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 |
|---------------------------------|---------------------------------|---------------------------------|---|
| Patients demographics | | | 2470 |
| NS | 61 | 64 | Age (years, mean) |
| P < 0.001 | 474 (19.2%) | 402 (30.1%) | Female [n (%)] |
| 0.06 | 272 ± 4 | 27.8 ± 4 | BMI (≥SD) |
| Background diagnosis | | | 1336 |
| 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 (8.3%) | 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 m² |
| NS | 13.1 | 13.56 | Hb (g/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 | 128 ± 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 Ventricular Ejection Fraction; BPM, Beats Per Minute; SBP, Systolic Blood Pressure.
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 findings correlate well with previous studies that showed the association between low ALT activity and worse clinical outcomes, in variable patients' populations. 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.

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, 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 findings correlate well with previous studies that showed the association between low ALT activity and worse clinical outcomes, in variable patients' populations. 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

---

**Table 2**

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

| P value | 95%CI Upper | 95%CI Lower | OR | Covariate |
|---------|-------------|-------------|----|-----------|
| <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 | Blood Creatinine concentration (per 1 mg/dL increment) |
| 0.01    | 1.92        | 1.08        | 1.44 | Past MI |
| 0.04    | 0.99        | 0.57        | 0.75 | Past CABG |
| <0.001  | 1.03        | 1.01        | 1.02 | Age (per year increment) |

* Introduced as continuous variables.

**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)* |
| <0.001  | 0.117       | Age*       |
| <0.001  | 1.86        | Heart failure diagnosis |
| <0.001  | 0.204       | Hemoglobin g/dL* |
| <0.001  | 0.024       | LVEF %     |
| <0.001  | 1.202       | COPD diagnosis |

* Introduced as continuous variables.
References

1. Anderson L, Taylor RS. Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews. Cochrane database Syst Rev [Internet]; 2014 Jan [cited 2015 Jan 28];12:CD011273. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25503364.

2. Jelinek MV, Thompson DR, Ski C, Bunker S, Vale MJ. 40 years of cardiac rehabilitation and secondary prevention in post-cardiac ischaemic patients. Are we still in the wilderness? Int J Cardiol [Internet]; 2015 Jan 20 [cited 2015 Oct 19];179:e153-e159. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25464436.

3. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. Cochrane database Syst Rev [Internet]; 2014 Jan [cited 2015 Nov 21];4:CD003331. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24771460.

4. Keteyian SJ, Squires RW, Ades PA, Thomas RJ. Incorporating patients with chronic heart failure into outpatient cardiac rehabilitation: practical recommendations for exercise and self-care counseling—a clinical review. J Cardiopulm Rehabil Prev [Internet]. Jan [cited 2015 Dec 17];34(4):223–232. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24892309.

5. Sepehri A, Beggs T, Hassan A, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. J Thorac Cardiovasc Surg [Internet]; 2014 Dec [cited 2015 Dec 17];148(6):3110–3117. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25199621.

6. Thalji NM, Suri RM, Greason KL, Schaff HV. Risk assessment methods for cardiac surgery and intervention. Nat Rev Cardiol [Internet]; 2014 Dec [cited 2015 Dec 17];11(12):704–714. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25245332.

7. Aflalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol [Internet]; 2014 Mar 4 [cited 2015 Dec 17];63(8):747–762. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4571179&tool=pmcentrez&rendertype=abstract.

8. Mohler MJ, Fain MJ, Wertheimer AM, Najafi B, Nikolich-Zugich J. The Frailty syndrome: clinical measurements and basic underpinnings in humans and animals. Exp Gerontol [Internet]; 2014 Jun [cited 2015 Dec 17];54:6–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24503059.

9. Elinav E, Ackerman Z, Maaravi Y, Ben-Dov IZ, Ein-Mor E, Stessman J. Low alanine aminotransferase activity in older people is associated with greater long-term mortality. J Am Geriatr Soc. 2006 Nov;54(11):1719–1724.

10. Ramaty E, Maor E, Peltz-Sinvani N, et al. Low ALT blood levels predict long-term all-cause mortality among adults. A historical prospective cohort study. Eur J Intern Med [Internet]; 2014 Dec [cited 2015 Jun 5];25(10):919–921. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25468741.

11. Ramati E, Israel A, Kessler Tal, et al. [Low ALT activity amongst patients hospitalized in internal medicine wards is a widespread phenomenon associated with low vitamin B6 levels in their blood]. Harefuah [Internet]; 2015 Feb [cited 2015 Jun 5];154(2):89–93, 137. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25856859.

12. Peltz-Sinvani N, Klempfner R, Ramaty E, Sela BA, Goldenberg I, Segal G. Low ALT levels independently associated with 22-year all-cause mortality among coronary heart disease patients. J Gen Intern Med [Internet]; 2015 Aug 6 [cited 2015 Dec 15]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26245731.

13. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc [Internet]; 1998 Jun [cited 2016 Mar 6];30(6):975–991. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9624961.

https://doi.org/10.1016/j.jesf.2017.11.002.