# Ferritin and body mass index predict cardiac dysfunction in female adolescents with anorexia of the restrictive type

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**Background and aim** Decreased left ventricular mass index in anorexia nervosa is amply reported. The aim of this study is to identify non-burdensome predictors of reduced left ventricular mass/height$^{2.7}$ (cLVM) in a cohort of adolescent restrictive anorexic girls.

**Methods** This is a retrospective study of all anorexic girls of the restrictive type referred to our tertiary eating disorder unit between September 2002 and December 2012, for somatic assessment of weight loss. All subjects fulfilled DMS-IV criteria, without a family history of cardiac or cardiovascular diseases.

**Results** In all, 283 restrictive anorexic girls (age: 14.63 ± 1.65 y; body mass index: 15.72 ± 1.81 kg/m$^2$) were included. Ferritin and body mass index were independent, statistically significant predictors of the corrected left ventricular mass ($P < 0.05$).

**Conclusion** Decreased cLVM is very common in anorexia nervosa of the restrictive type. Two factors predicted decreased cLVM in our population: ferritin and BMI.

**Keywords** *Anorexia nervosa – adolescent girls – restrictive type – corrected left ventricular mass index – ferritin – body mass index.*

## INTRODUCTION

A recent meta-analysis of anorexia nervosa (AN) demonstrated a mortality of 5.1 deaths per 1000 person-years[1]. About one third of the mortality in this disorder is cardiac-related. Cardiac injury in AN may involve the myocardium, conduction system, vascular wall or pericardium[2]. Signs of cardiovascular compromise are sinus bradycardia, hypotension, arrhythmias, repolarization abnormalities, cardiac failure, silent pericardial effusions and sudden death[3-7]. Significant improvement after refeeding with weight recovery has been seen in functional and structural abnormalities[8]. Recently many studies focused on QT interval prolongation, changes in cardiac diameter (reduced left ventricular mass index) and myocardial mass using electrocardiography and echocardiography (2-D and tissue Doppler)[9,10]. In some patients with AN, small myocardial scars are missed with ultrasound and cardiac magnetic resonance (CMR) is now considered the "gold standard" for detection of transmural and subendocardial fibrosis[11,12]. The present retrospective study evaluated in a large group of anorexic adolescent girls of the restrictive type, various clinical, biochemical and cardiac variables to select significant predictors of the reduction of corrected left ventricular mass index (LVM/height$^{2.7}$)[2,13]. The final purpose was to design a model for the calculation of the corrected left ventricular mass (cLVM) based on non-burdensome predictors, in order to select patients with a poor outcome and therefore in need of close follow-up.

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## METHODS

### Patients

We included all anorexic girls of the restrictive type referred to our eating disorder unit from September 2002 to December 2012 for somatic assessment of weight loss. All fulfilled the DMS-IV criteria (Diagnostic and Statistical Manual of Mental disorders, 4th edition DMS-IV, 1994)[14]. The study was conducted according to the GCP guidelines and approved by the hospital's ethics committee with a written consent from patients and parents. We excluded girls with a family history of any cardiac or systemic disease involving the cardiovascular system. 284 adolescent girls (age: 9.9-17.9 y) (mean age: 14.63 y) and mean body mass index (BMI) of 15.72 kg/m² were retained. Somatic assessment in the acute stage of the disease was performed by the same paediatric nutritionist. This included personal history, clinical examination, biometry and calculation of body mass index (weight/height²; kg/m²) using curves and centiles reported by Rolland-Cachera[15] in 1991.

### Laboratory analysis

An admission protocol included measurement of complete blood count, serum urea nitrogen, creatinine, sodium, potassium, chloride, cholesterol, thyroid hormones, insulin-growth factor-1 (IGF-1), serum iron, ferritin, zinc, AST and ALT.

### Cardiovascular examination

All patients were examined by the same paediatric cardiologist and had a two-dimensional Doppler echocardiography (Vivid 7 GE, Horten, Norway) and a 12-lead electrocardiogram. QT and QTc intervals were manually measured in lead II and corrected for heart rate using Bazett's formula ($QTc = QT\sqrt{RR}$)[16]. QTc dispersion of the QTc intervals was defined as the difference between the maximum and minimum interval. In each subject the voltage of the T wave in V4 and the R wave in V6 was measured. Based on the M-mode measurements in the long axis, left ventricular mass was estimated with the standard Devereux formula as recommended by the American Society of Echocardiography[17,18]. To account for linear growth and body mass, the left ventricular mass index was corrected in each patient using the formula of de Simone (LVM corrected = left ventricular mass/height$^{2.7}$(cLVM) [13]. Automated blood pressure measurements (Criticon dynamap pro-100) were obtained on the right upper arm in supine position, after 5 minutes of rest and repeated 3 times with a 3-minute interval). The average systolic and diastolic blood pressure was calculated and registered. Cuffs were adjusted for age and body size. Two cuffs were used: the Ultra Check Blood Pressure Cuff model U 1826 small Adult Range 18-26 cm for girls ≤ 10 years and the Dura Cuff Adult Johnson & Johnson Medical Inc. 22-23 cm for older girls[19].

### Statistical analysis

Variables were described as mean ± standard deviation. The distribution of the reduction of corrected left ventricular mass index was tested for the normality assumption by the Kolmogorov-Smirnov test (interval $P > 0.2$). The independent associations between different clinical, biochemical and cardiac variables and the left ventricular mass index were studied using a multiple linear regression analysis (table 1). For the different models, $R^2$ was calculated in order to assess the proportion of variance explained. Variables were kept in the model depending on the statistical contribution and on considerations with respect to whether their assessment was more or less burdening (table 2). Data were analysed with the SPSS statistical software for Windows 20.0 (SPSS Inc.).

**Table 1** Results from multiple linear regression model predicting the LVM/ height2.7 (cLVM)

| | Unstandardized coefficients | Standard error | *P*-value |
|---|---|---|---|
| Constant | 9.613 | 3.045 | 0.002 |
| Ferritin (ng/ml) | – 0.008 | 0.004 | 0.056 |
| BMI (kg/m²) | 1.151 | 0.183 | < 0.001 |

**Table 2** Model summary

| Model | R | $R^2$ | Adjusted $R^2$ | Standard error of the estimate |
|---|---|---|---|---|
| 1 | 0.422[a] | 0.178 | 0.173 | 5.242 |

[a] Predictors: (constant), BMI, ferritin.

## RESULTS

Ferritin and body mass index (BMI) appear to be two independent predictors of cLVM (figure 1). They were kept in the final model (table 1): ferritin ($P = 0.056$) and BMI ($P < 0.001$). With the aid of the regression coefficients given in table 2 we can predict LVM/height$^{2.7}$. For example, the expected LVM/height$^{2.7}$ in a girl with anorexia nervosa with a ferritin level of 220 ng/ml and a BMI of 13.5 kg/m² provides the following result: LVM/height$^{2.7}$: $9.613 - (0.008 \times 220) + (1.151 \times 13.5) = 23.3$ 9 g/m$^{2.7}$ . In a simple linear regression analysis, ferritin could only explain 6.2% of the variance of LVM/height$^{2.7}$ (figure 1). In the multiple regression analysis, including ferritin and BMI (cfr. above) we were able to explain up to 17.3% of the variance of LVM/height$^{2.7}$ (cfr. adjusted $R^2$ in table 2). Compared to BMI, weight loss yielded a less pronounced increase of the variance explained ($R^2$ increase from 6.2% to 10.1%).

## DISCUSSION

Out of numerous clinical, biochemical and cardiac variables we have designed a very simple model based on two non-burdensome (non-invasive, inexpensive for patient and society) predictors, for the predictions of the corrected left ventricular mass (cLVM)[12]. The two predictors are the BMI and serum ferritin level. Numerous plausible parameters were analysed. They included insulin growth factor-1 (IGF-1), total cholesterol, liver enzymes (ATL and AST), prealbumin, QTc dispersion and, in a small dataset, adiponectin (n = 87). Percentage weight loss is an anamnestic conception and therefore subjective, while BMI is a calculated formula derived from two objective parameters, namely body weight and height. Moreover, percentage weight loss contributed less to the explanation of the variance of LVM/height$^{2.7}$. Addition or replacement of other variables in the model such as cholesterol, QTc dispersion and prealbumin was not informative because of the vast amount of missing values for these variables in our data set. As for the addition of adiponectins, a very expensive marker, a limited dataset of 87 patients was analysed. An $R^2$ value of 25.7% was obtained in this limited dataset, but in our opinion the reliability of this finding is rather limited (adiponectin $P$-value = 0.767). Hence we finally choose a very simple model, with two objective measurements in our AN group. The first predictor is BMI. Several studies reports an association with the body mass index (BMI) and decreased ventricular dimensions. Kastner et al. compared 173 adolescents with 40 controls (age 12-17 y) and observed significantly lower left ventricular end-diastolic and end-systolic dimensions than in the control

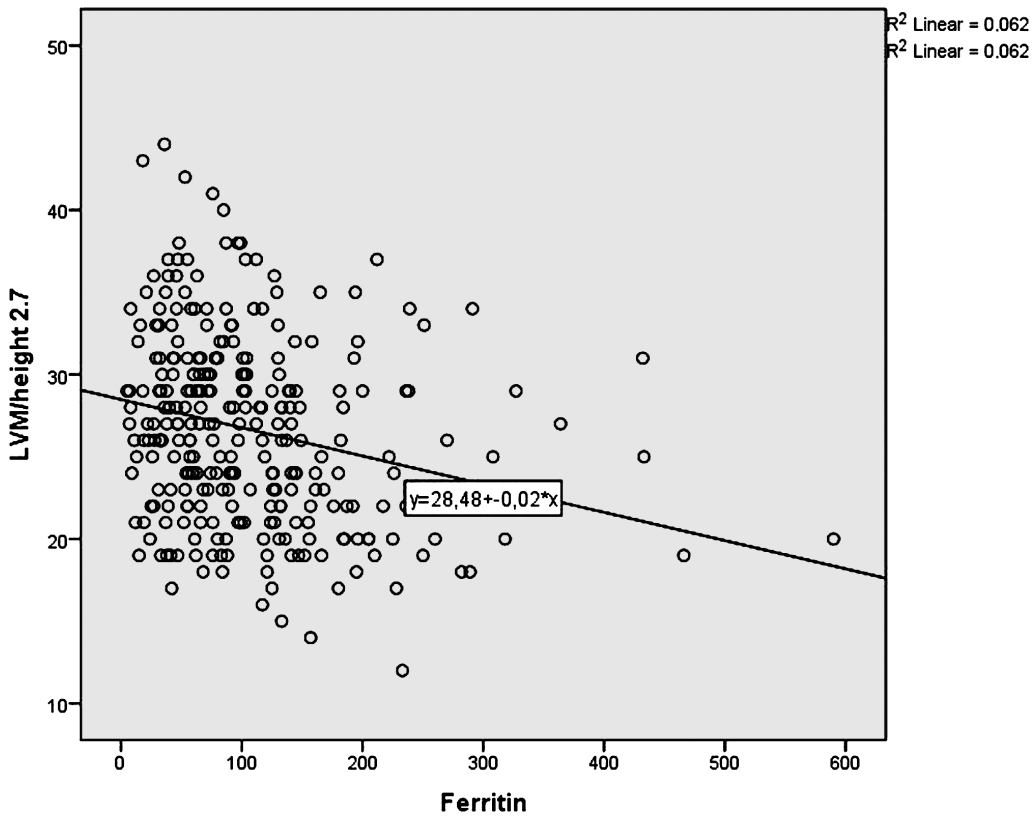


**Fig. 1** Scatter plot relation between ferritin and LVM/height$^{2.7}$ with a single linear regression.

group[20]. Olivares et al. demonstrated that left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular mass and cardiac index were decreased in patients with AN[21]. Swenne et al. report that atrophy of the heart can be caused by starvation with systolic dysfunction in the most severe cases[22]. Romano et al. showed also decreased left ventricular mass and some degree of systolic dysfunction[23]. Galetta et al. demonstrated in two studies that decreased left ventricular chamber mass was found in anorexic women compared with a control group of thin women with a normal BMI. They found also a positive correlation between the decrease in cardiac mass and the prolongation of the QT interval in AN patients[24,25]. An explanation can be found in autopsy results reporting myocytolysis, fat and mononuclear infiltration and collagen deposition in the myocardium of these patients. Myocardial atrophy is then the substrate for conduction and repolarization abnormalities and gives a predisposition to ventricular arrhythmias and sudden death[26]. Recently Oflaz et al. reported myocardial damage in AN patients by cardiac magnetic resonance[12]. Because small myocardial scars are overlooked by nuclear scintigraphy and segmental wall abnormalities cannot be detected by echocardiography and because previous examination of hearts post mortem from humans who died from starvation demonstrated myocardial fibrosis, the latter was clinically relevant as a predictor of morbidity and sudden death[11,27,28]. According to Oflaz et al. cardiac MRI is an expensive but necessary investigation to discover myocardial fibrosis in the more severe cases of AN, probably those with the lowest LVM/height$^{2.7}$[12]. Innovative is the use of ferritin in our model. The explanation of increased ferritin as a marker of heart muscle wasting, can be found in previous observations: serum ferritin concentrations indicate starvation and muscle catabolism with release of iron from muscle myoglobin. It has been proposed that the contraction of circulating blood volumes induces destruction of the red blood cells, iron release and, subsequently, an increase in ferritin synthesis[29,30,31]. In 2012 Papillard-Marichal observed in 26 anorexic adolescents higher hepcidin concentrations than in a control group. There was no evidence in their paper of iron overload or inflammation in the anorexic patient group. The investigators suggested that nutritional stress induced by malnourishment of the hepatocyte may stimulate both L-ferritin and hepcidin. Both parameters dropped on refeeding[32].

## CONCLUSION

In our study two simple predictors for LVM/height$^{2.7}$ are selected: body mass index (BMI) and serum ferritin. We suggest that, for an anorexic adolescent female population with the restrictive type with an age range from 10 to 18 years and a BMI range from 12 to 19 kg/m$^2$, cLVM can be estimated on the basis of two simple parameters. The two most important and practical reasons for the use of our simple model are, first, the simplicity of use by any medical and nursing staff to select those anorexic adolescents who need hospitalization and monitoring for their own cardiovascular safety, and, secondly, an important economical profit for our society because we can select those anorexic adolescent girls who need a more intensive somatic approach and closer cardiac follow-up to diminish late onset cardiac complications. Further research is needed to use this formula in a clinical setting where one cannot rely on daily intensive cardiac monitoring of all hospitalized adolescent females with severe anorexia.

**CONFLICT OF INTEREST:** none declared.

## REFERENCES


1. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. *Arch Gen Psychiatry* 2011; **68**: 724-31.
2. de Simone G, Scalfi L, Galderisi M, Celentano A, Di Biase G, Tammaro P, Garofalo M, Mureddu GF, de Divitiis O, Contaldo F. Cardiac abnormalities in young women with anorexia nervosa. *Br Heart J* 1994; **71**: 287-92.
3. Docx MKF, Gewillig M, Simons A, Vandenberghe P, Weyler J, Ramet J, Mertens L. Pericardial effusions in adolescent girls with anorexia nervosa: clinical course and risk factors. *Eat Disord* 2010; **18**: 218-25.
4. Cooke RA, Chambers JB, Singh R, Todd GJ, Smeeton NC, Treasure J, Treasure T. QT interval in anorexia nervosa. *Br Heart J* 1994; **72**: 69-73.
5. Goldberg SJ, Comerci GD, Feldman L. Cardiac output and regional myocardial contraction in anorexia nervosa. *J Adolesc Health Care* 1988; **9**: 15-31.
6. Neumärker KJ. Mortality and sudden death in anorexia nervosa. *Int J Eat Disord* 1997; **21**: 205-12.
7. Isner JM, Roberts WC, Heysmsfield B, Yager J. Anorexia nervosa and sudden death. *Ann Intern Med* 1985; **102**: 49-52.
8. Mont L, Castro J, Herreros B, Paré C, Azqueta M, Magriña J, Puig J, Toro J, Brugada J. Reversibility of cardiac abnormalities in adolescents with anorexia nervosa after weight recovery. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 808-13.
9. Gottdiener JS, Gross HA, Henry WL, Borer JS, Ebert MH. Effects of self-induced starvation on cardiac size and function in anorexia nervosa. *Circulation* 1978; **58**: 431-3.
10. Moodie DS, Salcedo E. Cardiac function in adolescents and young adults with anorexia nervosa. *J Adolesc Health Care* 1983; **4**: 9-14.

11. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, van Rossum AC, Shaw LJ, Yucel EK. Clinical indications for cardiovascular magnetic resonance (CRM): Consensus Panel report. *J Cardiovasc Magn Reson* 2004; **6**: 727-65.
12. Oflaz S, Yucel B, Oz F, Sahin D, Ozturk N, Yaci O, Polat N, Gurdal A, Cizgici AY, Dursun M, Oflaz H. Assessment of myocardial damage by cardiac MRI in patients with anorexia nervosa. *Int J Eat Disord* 2013; **46**: 862-6.
13. De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992; **20**: 1251-60.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition, Washington DC, 1994.
15. Rolland-Cachera MF, Cole TJ, Sempé M, Tichet J, Rossignol C, Charraud A. Body Mass Index variations: centiles from birth to 87 years. *Eur J Clin Nutr* 1991; **45**: 13-21.
16. Bazett HC. An analysis of the time relations of echocardiograms. *Heart* 1920; **7**: 353-70.
17. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977; **55**: 613-8.
18. Sahn DJ, De Maria A, Kisslo J, Weyman A. The committee on M mode standardization of the American Society Echocardiography. Results of a survey of echocardiographic measurements. *Circulation* 1978; **58**: 1072-83.
19. Arafat M, Mattoo TK. Measurements of blood pressure in children: recommendations and perceptions on cuff selection. *Pediatrics* 1999; **104**: e30.
20. Kastner S, Salbach-Andrae H, Renneberg B, Pfeiffer E, Lehmkuhl U, Schmitz L. Echocardiographic findings in adolescents with anorexia nervosa at beginning of treatment and after weight recovery. *Eur Child Adolesc Psychiatry* 2012; **21**: 15-21.
21. Olivares JL, Vazquez M, Fleta J, Morena LA, Pérez-González JM, Bueno M. Cardiac findings in adolescents with anorexia nervosa at diagnosis and after weight restoration. *Eur J Pediatr* 2005; **164**: 383-6.
22. Swenne I, Larsson PT. Heart risk associated with weight loss in anorexia nervosa and eating disorders: risk factors for QTc interval prolongation and dispersion. *Acta Paediatr* 1999; **88**: 304-9.
23. Romano C, Chinali M, Pasanisi F, Greco R, Celentano A, Rocco A, Palmieri V, Signorini A, Contaldo F, de Simone G. Reduced hemodynamic load and cardiac hypotrophy in patients with anorexia nervosa. *Am J Clin Nutr* 2003; **77**: 308-12.
24. Galetta F, Franzoni F, Cupisti A, Morelli E, Santoro G, Pentimone F. Early detection of cardiac dysfunction in patients with tissue Doppler imaging. *Int J Cardiol* 2005; **101**: 33-7.
25. Galetta F, Franzoni F, Cupisti A, Belliti D, Prattichizzo F, Rolla M. QT interval dispersion in young women with anorexia nervosa. *J Pediatr* 2002; **140**: 456-60.
26. Nazarian S, Bluemke DA, Lardo AC, Zviman MM, Watkins SP, Dickfeld TL, Meininger GR, Roguin A, Calkins H, Tomaselli GF, Weiss RG, Berger RD, Lima JA, Halperin HR. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. *Circulation* 2005; **112**: 2821-5.
27. Abel RM, Grimes JB, Alonso D, Alonso M, Gay WA Jr. Adverse hemodynamic and ultrastructural change in dog hearts subjected to protein-calorie malnutrition. *Am Heart J* 1979; **97**: 733-44.
28. Assomull RG, Prasas SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA, Pennell DJ. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 2006; **48**: 1977-85.
29. Kennedy A, Kohn M, Lammi A, Clarke S. Iron status and haematological changes in adolescent female in patients with anorexia nervosa. *J Paediatr Child Health* 2004; **40**: 430-2.
30. Nova E, Lopez-Vidriero I, Varela P, Casas J, Marcos A. Indicators of nutritional status in restricting-type anorexia nervosa patients: a 1-year follow-up study. *Clin Nutr* 2004; **23**: 1353-9.
31. Van Binsbergen CJ, Odink J, Van den Berg H, Koppeschaar H, Coelingh Bennink HJ. Nutritional status in anorexia nervosa: clinical chemistry, vitamins, iron and zinc. *Eur J Clin Nutr* 1988; **42**: 929-37.
32. Papillard-Marechal S, Sznaijder M, Hurtado-Nedelec M, Alibay Y, Martin-Schmitt C, Dehoux M, Westerman M, Beaumont C, Chevalier B, Puy H, Stheneur C. Iron metabolism in patients with anorexia nervosa: elevated serum hepcidin concentrations in absence of inflammation. *Am J Clin Nutr* 2012; **95**: 548-54.