Malnutrition in Community-Dwelling Anorexia Nervosa Patients: Alterations of Physical and Laboratory Features

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Abstracts: *Background and aims*: Malnutrition in Anorexia Nervosa may determine many abnormalities and consequences for both physical and psychological points. Their early detection and management may improve the prognosis.

This study aims at identifying clinical predictors of disease highlight possible correlations between signs-symptoms and degree of malnutrition.

Methods: The authors present a retrospective study of 302 Anorexia Nervosa outpatients aged 23.2 ± 9.4 years ($\bar{X}$ ± SD) observed at arrival in Eating Disorder Unit.

Results: 302 patients were examined, (BMI 14.7 ± 1.9 kg/m^2). We observed a significant reduction of measured basal metabolic rate (less 19.3 ± 15.3%) in almost all patients, and almost one patient over four have some clinical complications such as bradycardia, hypotension, anemia, hypoglycemia, showing a high correlation with malnutrition degree.

Conclusions: Determining malnutrition degree is relevant to identify and to treat Anorexia Nervosa patients as well as to contract setting of care with patients and parents for reducing delayed treatment.

Keywords: Anorexia nervosa, malnutrition, clinical alteration, physical and laboratory features.

1. INTRODUCTION

Anorexia Nervosa (AN) is a serious, potentially life-threatening illness characterized by severe malnutrition, with abnormally low body weight (BMI <17.5 kg/m^2 or body weight at least 15% below the expected value), with an intense fear of weight gain and an undue emphasis on weight and shape in self-evaluation [1-3].

Amenorrhea (i.e. loss of three consecutive menstrual cycles) is currently required for the diagnosis of AN, but often is hidden by contraceptive drugs. AN can cause significant clinical complications in every organ system, particularly relevant in adolescents in the growing and developing body with slowing in linear growth, impaired bone mineral accretion, structural and functional damage of the brain [4-7].

Early detection and management of an eating disorder may prevent the physical and psychological consequences of malnutrition such as obsessive-compulsive disorder, anxiety, depression and social isolation. All of these as well other perpetuating factors allow the progression of the disease to a later stage [8-11].

Most studies suggest that a short duration of symptoms before treatment results in a favorable outcome. A propos, it should be recalled that the today full recovery rate of AN is no higher than 40-50% [12-18].

Unfortunately, the diagnosis of AN can be elusive. More than one-half of all cases go undetected for a long period of time. This is in contrast to most patients with loss of weight for other medical conditions (i.e. hyperthyroidism, malignancy, etc) who express concern over their weight loss, patients with AN are actively pursuing an abnormally low body weight, usually hide their illness and deny their symptoms, hampering the collection of their medical history [19].

A further important barrier to help-getting AN patients is likely poor identification and knowledge about the disease by medical doctors particularly in primary care by general practitioners who should be the gatekeepers to specialist care [20, 21].

The present investigation aims at identifying malnutrition signs and clinical predictors of the disease which can be collected at every point of entry into the health care system. More specifically, focusing on the outpatient setting which will give detailed description of clinical features checking by physical and laboratory examinations of outpatients affected by AN and highlight possible correlations between signs-

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symptoms and the degree of malnutrition measured by BMI.

2. PATIENTS AND METHODS

2.1. Patients

The clinical records of 302 females aged 23.2 ± 9.4 years affected by AN as diagnosed by Diagnostic and Statistical Manual of Mental Disorders Fourth Edition criteria were reviewed [22].

Eligible to the study were the patients seeking care at the outpatient clinic for eating disorders of the Niguarda Hospital in Milan (Italy) from January 2007 to May 2010.

All patients initially received a clinical diagnosis by a medical doctor specialized in clinical nutrition with expertise in assessment of patients with eating disorders.

Male patients were excluded from analyses because of their small number.

2.2. Measurements

2.2.1. Anthropometry

Nutritional evaluation by antrhopometry was performed by a registered dietitian.

Body weight was recorded to the nearest 100 g using a standard physician's weighing scale with barefoot patients wearing only underwear. Height was determined to the nearest 0.5 cm on a standard stadiometer.

2.3. Basal Metabolic Rate

Basal metabolic rate: resting gas exchange was measured by open circuit, indirect calorimetry (Sensor Medics) for 30 minutes. Before each measurement, the system was recalibrated using a reference gas mixture of 95% O_2 and 5% CO_2.

A complete medical history was taken to determine illness durations, menstruation, evaluation of primary clinical variables such as heart rate, systolic and diastolic blood pressure.

2.4. Blood Samples

Blood samples were usually taken by an antecubital vein puncture. Blood-plasma-serum values were determined by the hospital laboratory according to published methods.

2.5. Data Analysis

The mean values, standards deviations, frequencies, regression statistics with their associated probability levels were obtained by the corresponding "procedures" of SAS ver. 9.1. The linear model was applied for regression.

3. RESULTS

Three hundred two patients were eligible for the study. Mean BMI was 14.7 ± 1.9 kg/m^2 (range 9.7-17.5 kg/m^2) and the mean age 23.2 ± 9.4 years.

The treatment statistic of 302 patients prior to their evaluation to our outpatient unit was:

the 39% had no previous treatment at all, the 33% had mono-disciplinary outpatient treatment, the 22% had been treated in inpatient units, for the 6% no data of previous treatment was available.

A summary of patient's anamnestic demographic and clinical characteristics is reported in Table **1**.

The arrival to our outpatient unit happened more than four years after the estimated outset of the illness; 271 patients were amenorrhoic, 9 were prepuberal and 22 were on estroprogestin therapy.

We observed a clinically significant reduction of measured metabolic basal rate (-19.3 ± 15.3%).

Table **2** shows the mean values and Standard Deviation of haematological parameter and biochemical values of 302 AN patients. Sexual hormonal values are referred to the 271 amenorrhoic patients.

Table **3** shows the percentages of abnormal (– abnormally low or high compared to the standard or usual normal clinical values –) values of the vital signs and biochemical values of whole population (302 patients), of 97 patients with BMI > 16 kg/m^2 - mean BMI 16.8 ±0.2 kg/m^2 -(subgroup 1) and of 205 pts with BMI ≤ 16 kg/m^2 – mean BMI 13.7 ± 1.6 kg/m^2 – (subgroup 2).

Both sets of values, vital signs and laboratory values are significantly more altered in AN with more severe malnutrition (subgroup 2), than in subgroup 1 pts where many values, but not all, are in normal range.

Table 1: Anamnestic, Demographic and Clinical Data of 302 Anorexia Nervosa Patients[a]

	Mean	S.D.	Range
Number of patients	**302**		
Age at reported onset of Anorexia Nervosa	18.2	6.7	(8 - 40.1)
Duration of disease (months)	56.5	72.2	(3 – 357)
Age (years) of admission	23.2	9.4	(8.3 – 48)
Body Mass Index (Kg/m²)	14.7	1.9	(9.7 - 17.5)
Body weight (Kg)	38.5	6.9	(19.2 - 56.8)
Height (cm)	161.3	8.5	(123.5 – 188)
Heart rate (beats/min)	63.8	12.3	(33 – 112)
Systolic blood pressure (mmHg)	96.0	12.9	(70 – 160)
Diastolic blood pressure (mmHg)	58.6	10.7	(40 – 90)
Amenorrhea (No.)	271		
Prepuberal (No.)	9		
Estimated resting metabolic rate (Kcal/24h)	1218.9	104.0	(867 – 1655)
Measured resting metabolic rate (Kcal/24h)	982.2	194.1	(526 – 1798)
% Difference versus estimated basal metabolic rate according to Harris Benedict formula	-19.3	15.3	(-47 – 98)

[a]Values are means ± SDs, ranges in parenthesis.

Table 2: Haematological Parameters and Biochemical Values in 302 AN Patients[a]

	Mean	S.D.
Red blood cells (4-5.3 10^{12}/L)[b]	4.3	0.5
Hemoglobin (12-16 g/dL)	13.1	1.4
Hematocrit (37 - 46%)	38.4	4.8
White blood cells (4-10 10^9/L)	5.3	1.8
Mean red cells volume (82-97 fl)	91.3	6.7
Platelets (140-440 10^9/L)	238.2	75.6
Lymphocytes (1.5-5 10^9/L)	2.8	0.7
Glucose (70-110 mg/dL)	75.7	13.8
Insulin (2-20 µU/mL)	5.8	7
Creatinine (0.5-1.1 mg/dL)	0.7	0.2
Aspartate aminotransferases (0-40 U/L)	31.6	49.3
Alanine aminotransferases (3-45 U/L)	37.1	60.5
γ-Glutamyl transferase (2-35 U/L)	21.6	19.7
Uric acid (1.5-5.7 mg/dL)	3.6	1.1
Amylase (28-100 U/L)	95.3	44.2
Total plasma cholesterol (<190 mg/dL)	180.4	44
Plasma HDL-cholesterol (>42 mg/dL)	70.6	18.3
Plasma triglycerides (<180 mg/dL)	85.3	40.2
Tri-iodothyronine (1.8-4.5 pg/mL)	2.5	1.9
Tetra-iodothyronine (9.2-17 pg/mL)	11.5	4.3
Thyroid-stimulating hormone (0.3-4.2 µU/mL)	2.1	1

(Table 2). Continued.

	Mean	S.D.
Total proteins (6.4-8.3 g/dL)	7.4	0.8
Transferrin (200-374 mg/dL)	237.6	60.7
Albumin (3.5-5.3 mg/dL)	4.9	0.5
Sodium (132-143 mmol/L)	140.4	3.4
Potassium (3.4-5.2 mmol/L)	4.3	0.5
Chloride (96-107 mmol/L)	101.7	5
Bicarbonate (22-30 mmol/L)	28.1	3.9
Calcium (8.5-10.5 mg/dL)	9.5	0.6
Phosphorus (3-4.5 mg/dL)	3.9	0.7
Magnesium (1.5-2.0 mEq/L)	1.7	0.2
Iron (50-150 µg/dL)	88.4	33
Ferritin (13-150 ng/mL)	95.2	105
Prolactin (3.4-24.1 ng/mL)[c]	14.7	17.4
Follicle-stimulating hormone (1.7-21.5 UI/L)[c]	6.3	15.9
Luteinizing hormone (1-95.6 UI/L)[c]	3.4	7.5
Estradiol (24-411 pg/mL)[c]	42.4	83.9
Progesterone (0.3-4.2 ng/mL)[c]	0.9	2.5

[a]Values as means ± SDs.
[b]Reference range shown in brackets.
[c]Sexual hormone values are referred to 271 amenorrhoic pts.

In Table **4** we show the prevalence of clinical features: almost one patient over four have some clinical complications. Vital signs of the 302 participants are as follows: 29.1% had hearts rate below normal (< 60 beats per minute), 9.3% has heart rates of less than 50 beats per minute and 2% had heart rates less than 40 beats per minute; 24.5% had systolic blood pressure less than 90 mmHg and 13.5% diastolic blood pressure less than 50 mmHg.

Hyperamylasemia was found in 36 percent of patients and may be considered as a consequence of vomit in purging subtype of AN patients; both frequency and type of vomiting seem to be correlated to salivary gland enlargement and hyperamylasemia [23].

Correlations of vital signs, basal metabolic rate and laboratory results with BMI, are shown in Table **5** which reports the R-squared value (i.e. amount of variance explained by BMI) and the probability level for the hypothesis of no linear correlation .

We found a highly significant correlation between the degree of malnutrition, as indicated by level of BMI, and blood pressure, anemia, level of triiodothryronine, transferrin and some indicators of liver function.

The most consistent correlation was found between measured resting metabolic rate and level of BMI.

Other authors described medical findings in AN patients, but our results represent, as far as we know, the largest case study on clinical findings in outpatients with AN [24, 25].

4. DISCUSSION

As AN patients often do not make their eating disorder and low body weight the subject of discussion, the physician is forced to rely on physical examination, metabolic and laboratory parameters as diagnostic hints.

In our study of 302 women with AN living in the community were found with a high prevalence of clinical findings, which are to be considered as effects of starvation of the body and should be regarded to guide physical aspects of care [26], because early intervention might be expected to exert positive effect, as indeed this was evident in many studies [14, 17].

All clinical evaluations used in this study, except for measured basal metabolic rate, particularly used during treatment to establish the amount of caloric intake to avoid refeeding syndrome [27], may be easily used at every point of entry into the health care system even by general practitioners and they may be useful to the physician to elicit the patient's physical concerns and to patient being treated.

Table 3: Percentage of Abnormal Vital Signs and Laboratory Values in all 302 Patients and in 2 Different BMI Subgroups[a]

Subgroups	Whole population		1 [b]		2[c]	
BMI (Mean ± DS)	**14.7 ± 1.9**		**16.8 ± 0.2**		**13.7 ± 1.6**	
Number of patients	**302**		**97**		**205**	
	Low[d]	**High[e]**	**Low**	**High**	**Low**	**High**
Heart rate (beats/min)	29	0.3	15	1	29	0
Blood pressure						
Systolic (mm/Hg)	24	0	15	1	29	0
Diastolic (mm/Hg)	13	0	2	0	19	0
White blood cells (10^9/L)	23	3	16	2	27	3
Red blood cells (10^12/L)	25	2	12	3	32	1
Hemoglobin (g/dL)	17	0	10	0	21	0
Hematocrit (%)	28	1	20	0	31	2
Mean red cells volume (fl)	6	14	9	11	4	16
Platelets (10^9/L)	5	2	1	1	6	3
Lymphocytes (10^9/L)	26	0	18	1	29	0
Glucose (mg/dL)	25	1	18	0	29	1
Insulin (µU/mL)	13	5	13	6	14	4
Total plasma cholesterol (mg/dL)	0	36	0	34	0	37
Plasma HDL-cholesterol (mg/dL)	0	0	0	0	0	0
Plasma triglycerides (mg/dL)	0	3	0	2	0	4
Aspartate aminotransferases (U/L)	0	14	0	6	0	17
Alanine aminotransferases (U/L)	0	17	0	6	0	22
γ-Glutamyl transferase (U/L)	0	16	0	5	0	21
Uric acid (mg/dL)	1	4	0	3	1	5
Total proteins (g/dL)	8	10	2	13	11	8
Creatinine (mg/dL)	0	0	2	0	11	0
Albumin (mg/dL)	1	20	0	20	2	20
Iron (µg/dL)	11	5	11	7	10	3
Transferrin (mg/dL)	25	1	12	2	31	1
Calcium (mg/dL)	3	2	0	1	4	2
Phosphorus (mg/dL)	8	16	5	16	9	16
Magnesium (mEq/L)	9	8	13	4	8	10
Sodium (mmol/L)	2	14	0	12	3	15
Potassium (mmol/L)	5	2	2	3	6	2
Chloride (mmol/L)	8	7	1	4	11	8
Amylase (U/L)	1	36	1	27	0	41
Bicarbonate (mmol/L)	2	17	2	7	2	22
Prolactin(ng/mL)[f]	1	10	2	4	0	12
Follicle-stimulating hormone (UI/L)[f]	26	2	11	3	33	1
Luteinizing hormone (UI/L)[f]	51	0	30	0	61	0
Estradiol (pg/mL)[f]	55	1	33	1	65	1
Progesterone (ng/mL)[f]	12	2	4	2	15	1
Tri-iodothyronine (pg/mL)	20	1	6	0	26	1
Tetra-iodothyronine (pg/mL)	10	1	6	0	12	1
Thyroid-stimulating hormone (µU/mL)	1	4	0	1	1	5

[a]Results of vital signs and laboratory values are expressed as percentage of patients. Percentage rounded to the first integer digit.
[b]Subgroup 1 = BMI above 16 kg/m^2 AN patients.
[c]Subgroup 2 = BMI below or equal 16 kg/m^2 AN patients.
[d]Low = Low compared to normal values.
[e]High = High compared to normal values.
[f]Sexual hormone values are referred to 271 amenorrhoic pts.

Table 4: Medical Complications in 302 Patients with Anorexia Nervosa

	Frequency[a]	Percentage[b]
Bradycardia		
Pulse < 60 min	88	29
Pulse < 50 min	33	9.3
Pulse < 40 min	5	1.7
Hypotension		
Systolic blood pressure (<90 mm/Hg) [c]	75	24.5
Diastolic blood pressure (<50 mm/Hg)	40	13.5
Anemia (Red blood cells <4 10^12/L)	75	25
Hypoglicemia (<70 mg/dL)	75	25
Hypotrasferrinemia (<200 mg/dL)	75	25
Leukocytopenia (White blood cells <4 10^9/L)	69	23
Liver function		
Aspartate aminotransferases (>40 U/L)	42	14
Alanine aminotransferases (>45 U/L)	51	17
γ-Glutamyl transferase (>35 U/L)	48	16
Hyperamilasemia (>100 UL)	108	36
Low measured respect to estimated resting metabolic rate	294	97.5

[a]Frequency equal numbers of patients.
[b]Percentage rounded to the first integer digit.
[c]Reference values in parenthesis.

Table 5: Regression of Medical Findings with BMI

Response variable	R Square	P Value
Heart Rate	0.001	0.8
Systolic Blood Pressure	0.09	0.0001
Diastolic Blood Pressure	0.10	0.0001
Measured resting metabolic rate	0.32	0.0001
Red blood cells	0.11	0.0004
Hematocrit	0.03	0.04
White blood cells	0.06	0.09
Lymphocytes	0.02	0.04
Tri-iodothyronine	0.02	0.002
Transferrin	0.11	0.001
Glucose	0.01	0.07
Aspartate aminotransferasi	0.04	0.01
Alanine aminotransferasi	0.07	0.001
γ-glutamyltrasferasi	0.15	0.0009

Treatment should be given by health care providers who have expertise in managing patients with eating disorders; management should be multidisciplinary and is best accomplished by a team consisting of medical, nutritional, nursing and mental health disciplines.

Contract setting of care is important for patients with AN, and the possibility to present the clinical findings to patients and parents prove to be very useful to determine the level of treatment (outpatient – inpatient) and the need for hospitalization, particularly for primary

care physician, but also for multidisciplinary team of Eating Disorders Unit [1, 2, 3].

In these 302 AN patients we proposed an extended outpatient treatment with a multidisciplinary treatment to the subgroup 1 (which presented a mild degree of malnutrition). In subgroup 2, having more an evident degree of malnutrition, we proposed an inpatients treatment with intensive day hospital therapy to 56 patients and a day and night treatment for 1-2 months and then a day hospital therapy to 149 inpatients, following our specific protocol of care [27, 28].

A limitation of our study was that the patients were recruited in outpatient ambulatory of Eating Disorders Unit; nevertheless these findings suggest that a clinical evaluations of all women with AN is fundamental and should proceed in correlation with psychological evaluation and treatment.

Clinical evaluations prove also essential to reduce and/or avoid delayed treatment, that so far have been frequently described, as also recently it was showed in a French multicenter study about AN patients treated in intensive care unit which report admission from home for 53% of patients and a crude mortality about 10% [29, 30].

CONFLICT OF INTEREST

The authors have no conflict of interest.

STATEMENT OF AUTHORSHIP

The authors' responsibility were as follows:

Maria Gabriella Gentile, MD, organized and supervised clinical evaluation and treatment, organized and reviewed data analysis and literature research, wrote the manuscript.

Giulia Maria Manna, MD, supervised the evaluation of subjects with anorexia nervosa and reviewed data analysis.

Laura Iaccarino, MD, collected clinical data of subjects.

Luisa Cometto, RD, collected anthropometric data and diet habits of subjects.

Nicoletta Mariani, RD, collected anthropometric data and diet habits of subjects.

Chiara Lessa, RD, collected anthropometric data and diet habits of subjects.

All authors read and approved the final manuscript.

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