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ORIGINAL ARTICLE

Excessive laboratory monitoring to prevent adolescent's refeeding syndrome: opportunities for enhancement

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Abstract

Purpose Anorexia nervosa (AN) is a complex medical condition affecting mainly adolescents and young adults. To monitor and prevent refeeding syndrome, current guidelines recommend daily laboratory testing in the first week of hospitalization and 2–3 times/week for the following 3 weeks. The aims of this study were to determine the proportion of abnormal results of the blood tests done during the first week of nutritional rehabilitation in adolescents with AN, the proportion of test having led to supplementation and the cost of all these tests.

Method A retrospective chart review of admissions for eating disorders between May 2014 and May 2015 in a tertiary Pediatric University Hospital center was performed. Patients were included if they were younger than 18 years, admitted for protocol-based refeeding and met criteria for AN (DSM 5).

Results Among the 99 hospitalizations included in the study, the mean age was 14.6 years (± 1.7), with a female predominance (97%). The mean admission BMI was 15.3 ± 2 kg/m^2 (*Z*-score − 2.6 ± 1.4). The mean length of hospitalization was 40.3 days ± 21.8. Of the 1289 laboratory tests performed, only 1.5% revealed abnormal values and 0.85% led to supplementation. No critical value was identified. The total cost for the tests performed was 148,926.80 CAD$, 1504$/admitted patient, instead of 3890$/admitted patient had we followed the recommendations.

Conclusion More precise criteria should be developed regarding the frequency of laboratory tests needed to monitor and prevent refeeding syndrome. At present, the recommendations could lead to unnecessary testing and expenses.

Level of evidence Level IV: Dramatic results in uncontrolled trials.

Keywords Refeeding syndrome · Anorexia nervosa · Electrolytes · Eating disorder

Introduction

Anorexia nervosa (AN) is a complex medical condition affecting mainly adolescents and young adults. According to a National Survey of Anorexia Nervosa in the United States, the lifetime prevalence among adolescents is 0.3% [1]. AN is a severe pathology in both the short and the long term, leading to potential high morbidity and mortality rates [2–6]. Mortality among patients seems to be decreasing as a result of more specialized care, with multidisciplinary collaboration, and a better knowledge of the physiological and psychological effects of starvation and nutritional rehabilitation [6–9].

The definition of refeeding syndrome is still being debated. It is defined either by biochemical changes or clinical manifestations and can potentially lead to fatal complications in a patient after prolonged fasting [10, 11]. To date the pathophysiology of RFS is still incompletely understood. During refeeding, glucose concentration and insulin secretion rise, leading to an increased sodium and water retention and extracellular volume expansion. Insulin drives phosphorus and potassium from the serum into the cells with life-threatening complications such as spasm or cardiac arrhythmias. Additionally, the hypophosphatemia also affects the phosphate-dependent ATP production resulting in possible rhabdomyolysis and muscle weakness [11].

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The incidence of refeeding syndrome remains unknown. A systematic review of 17 studies, including 1039 patients between 10 and 20 years with AN, established a relative incidence of 14% (0–38%) of hypophosphatemia [12], although this may be underestimated because some patients were supplemented with oral phosphate in the presence of declining but normal serum phosphorus levels. In adults, the incidence seems to be higher with 33.3% of hypophosphatemia in Brown's study [13]. Known risk factors for the refeeding syndrome include rapid weight loss, weight less than 70% of ideal body weight, low baseline levels of P, K+, or Mg, and low nutritional intake in the previous 5 to 10 days [10, 14–17].

For many years, the safest refeeding practices in severely malnourished patients with AN had focused on an approach with a low calorie start point, with slow and gradual increases [18]. The recent literature, mainly observational studies including more than 2600 patients, supports more aggressive inpatient nutritional rehabilitation for anorexia nervosa [19–24]. A review of 27 studies reports no increased risk of complications with more aggressive refeeding practices in patients with mild-to-moderate malnutrition, but reports improved weight gain and shorter length of hospitalization [20–23, 25]. The severity of the malnutrition remains the main determinant and risk factor for developing refeeding syndrome.

Professional organizations (British, American, Australian and French) have clinical guidelines to help physicians monitoring and preventing refeeding syndrome. Current guidelines recommend daily laboratory testing during the first week of refeeding in hospital and 2–3 times/week for the following 3 weeks [17, 18, 26, 27]. Laboratory testing includes phosphate, magnesium, potassium and liver function. These recommendations derive primarily from retrospective and observational studies in adults.

Within our Adolescent Eating Disorder program in a Pediatric University Hospital, we have noticed that we perform numerous tests to monitor refeeding syndrome, but the impact on management is not significant. This led us to question the value of excessive laboratory testing and the impact on outcome. In this study, we aim (1) to evaluate the incidence and risk factors of refeeding syndrome defined as abnormal laboratory tests in adolescents with anorexia nervosa; (2) to determine the proportion of pertinent abnormal values, including phosphate, magnesium and potassium levels in patients admitted for refeeding; (3) to determine the number of supplementations required; (4) to estimate the total cost associated with the key refeeding laboratory testing.

Methods

We conducted a retrospective chart review of patients admitted to the Adolescent Inpatient Unit for an eating disorder between May 2014 and May 2015. The Hospital is a tertiary pediatric University referral center that admits approximately 100 adolescents/year with an eating disorder. Patients are hospitalized because they are medically unstable or because out-patient treatment fails. It has an established inpatient refeeding protocol and offers a multidisciplinary approach for management of patients with eating disorders. Patients in this study are limited to oral feeding divided into four meals with structured meal plan, including supervised meals, with the assistance of a dietitian. Laboratory tests are requested routinely upon admission and during hospitalization according to the physician's clinical judgment.

The current in-hospital protocol includes an initial caloric intake of 1800 kcal/day for patients between 12 and 13 years of age, 2000 kcal/day for patients 14–15 years of age and 2200 kcal/day for patients 17–18 years of age. This amount has to be reached within 5 days of admission. The aimed weight gain is 1 kg/week. When weight gain is sub-optimal, below 700 g/week or not increasing for 2 days, caloric intake can be increased by 200 kcal/day. Meals are monitored and supervised individually on a one-to-one basis and within a group after a few days. Patients with purging behaviors are monitored up to 2 h after meals. We do not add phosphorus systematically to the diet. It is added only if the tests show a decrease in the phosphorus level.

Data were collected from Chartmaxx, an electronic chart by one author (RG) to ensure accuracy and consistency. Patients were included in the study if they were younger than 18 years, admitted for protocol-based refeeding, and met criteria for AN whether restrictive or purging sub-type (DSM5). For patients with multiple admissions, each admission was analyzed separately. Patients with bulimia nervosa or patients who presented with a pre-existing comorbidity causing electrolyte abnormalities were excluded.

We collected baseline data including age, gender, weight, height, menarchal status, amenorrhea, length of illness and number of hospitalizations. Vital signs were also collected to determine blood pressure and heart rate upon admission and the lowest measure during the hospitalization. BMI (maximum, minimum and admission), its *Z*-score and percentile were calculated using the admission height (anthrocalcwho.xls).

The main laboratory tests used to monitor refeeding syndrome are phosphate, magnesium and potassium levels. Within our eating disorder program, there is no routine

supplementation of electrolytes. All laboratory test results during the first week were collected. The values were defined as normal, low or high according to our laboratory definition of normal range. The normal range levels were defined as: phosphate between 1.02 and 1.79 mmol/L, magnesium, between 0.7 and 1 mmol/L and potassium between 3.5 and 5.1 mmol/L. Critical values predisposing for refeeding syndrome are as follows: Mg < 0.45 mmol/L, P < 0.4 mmol/L, K < 2.8 mmol/L. In the most malnourished, glucose monitoring was performed several times a day on the first day, before and 2 h after meal and then according to the patient status.

Since there is no consensual definition of the RFS, we defined non-serious RFS as any situation where the tests showed abnormal values (phosphorus; magnesium or potassium), and serious RFS in case of critical values (Mg < 0.45 mmol/L, P < 0.4 mmol/L, K < 2.8 mmol/L).

The cost per test is a fixed rate in Canadian dollar determined by the laboratories of the hospital. There is a basic rate for any blood sample of 44.40$CAD and a fixed cost for each analysis requested. No cost was applied for glucose monitoring.

Patient characteristics are presented as descriptive statistics, using percentages. Continuous variables are expressed by mean ± standard deviation and were analyzed using a Student's *t* test. Ethical approval from the Hospital Research Ethics Board was obtained.

Results

Population

During the study period, 99 inpatient admissions met the inclusion criteria with the majority being restricting subtype of anorexia nervosa ($n = 78$) ($n = 10$ purging/laxative, $n = 7$ purging, $n = 4$ laxative). Patient characteristics are described in Tables 1 and 2. Mean BMI was 15.3 ± 2 kg/m^2 (− 2.6 ± 1.4 *Z*-score or 6 ± 9 percentile). The mean median BMI was 78% ± 2%. Six patients had a percent median BMI under 70%.

During the renutrition period, we had no case of serious refeeding syndrome, in particular no clinical sign of severe edema, major hypoglycemia, hypotension/hypertension or tachycardia.

Laboratory tests

For the 99 admissions in our study, 1289 laboratory tests were performed to detect refeeding syndrome, an average of 13 per admission. Only 1.61% of the tests showed abnormal values (phosphorus, $n = 16$; magnesium, $n = 2$; potassium, $n = 2$) (Fig. 1) named non-serious RFS. There were no critical values (Mg < 0.45 mmol/L, P < 0.4 mmol/L, K < 2.8 mmol/L). The mean lowest level of glucose was 4.4 ± 0.7 mmol/l. Two patients had a result below 3 during the first 5 days.

Of all the laboratory tests performed, 0.85% led to supplementation (phosphorus, $n = 8$; magnesium, $n = 2$; potassium, $n = 1$). For every 64 laboratory tests performed, only one had an abnormal value. For every 117 laboratory tests, one led to supplementation. Levels of sodium, potassium and chloride were included with every phosphorus testing.

Patients with abnormal values and those who required supplementation had similar age, BMI, percent mean BMI, weight loss speed, length of illness and number of hospitalizations compared to patients with normal values. No risk factors were found. Table 3 provides more detailed

Table 1 Patient characteristics

	N = 99
Demographics	
Age (years)	14.6 ± 1.7
Gender (% female)	97
Clinical data	
Premenarchal[a] (%)	27
Restricting intake (%)	78
Purging behavior (%)	21
Number of hospitalizations	1.9 ± 1.2
Length of hospitalization (days)	40.3 ± 21.8
Length of illness (months)	14.5 ± 9.1
Median start point (Kcal)	2100 ± 188
Vitals	
Minimum HR (bpm)	45 ± 9
Minimum SBP (mmHg)	77 ± 10
Minimum DBP (mmHg)	42 ± 8

Table 2 Patients characteristics

Weight and BMI (mean ± SD)			
Admission weight (kg)	40.3 ± 7.9	Z-score	− 1.8 ± 1.2
BMI (kg/m^2)	15.3 ± 2		− 2.6 ± 1.4
% m BMI	78 ± 2		
Maximum weight (kg)	53.9 ± 12.2	Z-score	0.4 ± 0.9
Maximum BMI (kg/m^2)	20.4 ± 3.5		0.1 ± 1
Minimum weight (kg)	39.5 ± 7.9	Z-score	− 1.9 ± 1.2
Minimum BMI (kg/m^2)	15 ± 2.1		− 2.8 ± 1.5
Duration between BMI max and min (months)		12.2 ± 8.5	

Data presented in mean ± standard deviation, unless otherwise specified

BMI body mass index; *SD* standard deviation, *%mBMI* percentage median BMI

[a]13 data not available

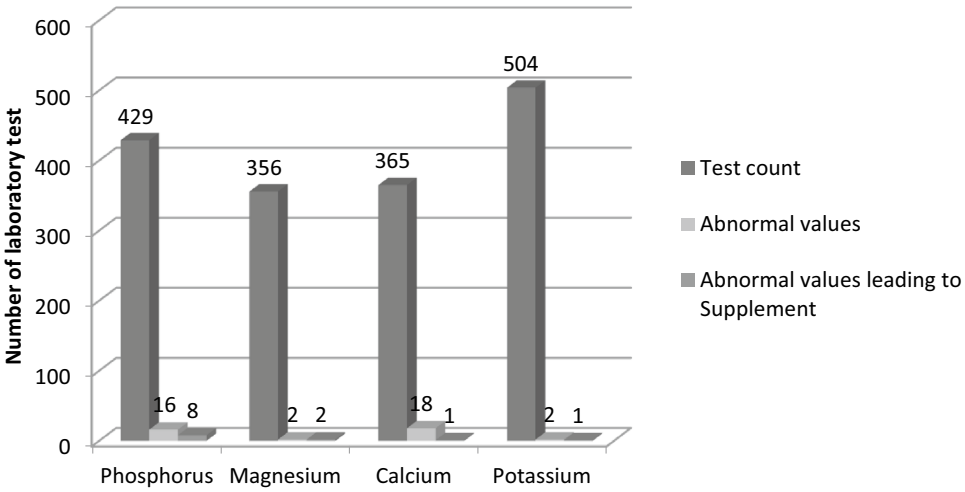

Fig. 1 Number of laboratory tests performed in hospitalized AN patients. This figure illustrates the number of laboratory test performed for 4 electrolytes (phosphorus, magnesium, calcium and potassium) to monitor refeeding syndrome. In dark grey we have the total count of test per electrolyte, in light grey the abnormal values and in mild grey the abnormal values having led to supplementation

Table 3 Description of patients with abnormal values

	Case 1	Case 2
Abnormal potassium ($n=2$)	# 54	# 83
	16-year-old female	16-year-old female
	BMI admission 15.7 (−2.39)	BMI admission 17.4 (−1.55)
	Length of illness 17 months	Length of illness 22 months
	# of hospitalizations 4	# of hospitalizations 1
	Purging behavior +	Purging behavior +
Abnormal magnesium ($n=2$)	# 4	# 25
	17-year-old female	15-year-old female
	BMI admission 18.9 (−0.78)	BMI admission 16 (−2.01)
	Length of illness 23 months	Length of illness 7 months
	# of hospitalizations 1	# of hospitalizations 1
	Purging behavior +	Purging behavior −
	Associated HypoPh	Associated HypoPh
Abnormal phosphate ($n=16$)	Mean age: 14.8 years	
	Mean BMI on admission 15	
	Length of illness 16 months	
	Number of hospitalizations: 2.8	

information concerning the characteristics of patients with abnormal laboratory values.

Figure 2 identifies the laboratory abnormalities according to the anorexia nervosa sub-types. As can be observed, 64% of the total abnormal values and 72% of supplementations were found in patients with restrictive sub-type of anorexia nervosa.

Table 4 describes the cost of each laboratory test, in addition to the total cost. The total cost for the key refeeding laboratory tests performed in our study was 148,926.8$, an average of 1504$/admitted patient. Patients with abnormal laboratory values had on average 3 more tests than patients with normal values (K: 5 vs 8.5, Ph 4 vs 6.5, Mg 4.5 vs 7.5).

Comparing two subgroups (admission percentage median BMI < 70% vs admission percentage median BMI > 70%), we found no significant difference in the number of abnormal values.

Discussion

This study uniquely examined the value of laboratory testing in monitoring the refeeding syndrome and the impact on outcome in adolescents hospitalized for AN.

In our study we had no documented serious case of refeeding syndrome, only slight decrease of electrolytes level with no critical laboratory value identified. Within our well-established multidisciplinary eating disorder program, we monitor closely our patients admitted for severe malnutrition. Patients with percentage median BMI below

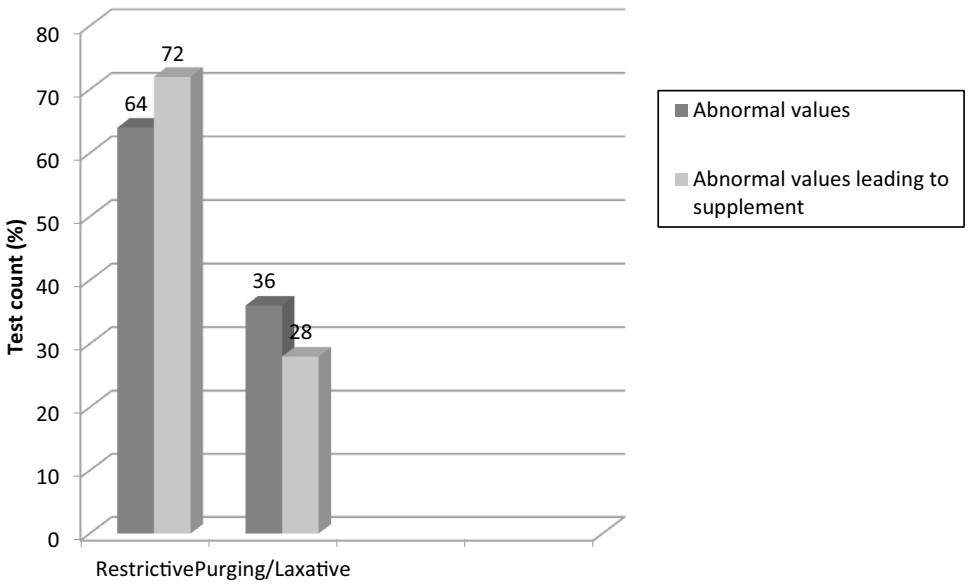

Fig. 2 Number of abnormal values by sub-types of AN. This figure illustrates the number of test count according to the different sub-types of anorexia nervosa. In dark grey we have the number of abnormal electrolyte test count (%), and in light grey we have the abnormal values having led to supplementation. The percentages are relative to the sub-type concerned, restrictive and purging/laxative, respectively

Table 4 Laboratory cost

Lab test	Test count	Cost per test $	Total cost $
Chem-7	504	288.4	145,353.6
Phosphorus	429	3.12	1338.5
Magnesium	356	3.55	1263.8
Calcium	365	2.66	970.9
Total			148,926.8

70% or bradycardia are under close surveillance. In some rare instances (heart rate below 30/min), monitoring is undertaken in the intensive care unit while refeeding is in progress.

The clinical practice guidelines state that electrolytes should be monitored once a day during the first week of hospitalization and then about 2–3 times per week in the second week until normalization of the blood work [17, 18, 27, 28]. Refeeding laboratory abnormalities were relatively low in our population, representing 1.61%. Of all the laboratory testing, only 0.85% led to oral supplementation. Like others, the use of a high-calorie diet has not led to a significant number of complications [20–22, 25, 29].

Hypophosphatemia is the most frequent refeeding laboratory abnormality observed. We identified 1.61% of hypophosphatemia, which is lower than what is described in the literature. In their review of 17 studies, nearly all retrospective, including 1039 adolescents with Anorexia Nervosa, O'Connor et al. found an average incidence of 14% of refeeding hypophosphatemia, the risk being greater in patients more severely malnourished [12]. Phosphate is a predominantly intracellular electrolyte that depletes during prolonged fasting. With re-feeding, insulin secretion causes the phosphate to enter the cell in order to produce ATP, which contributes to lowering the reserves. This leads to defects in phosphorylation, defects in myocardial and diaphragmatic contractility associated with respiratory insufficiency. According to several studies, hypophosphatemia is correlated with the severity of malnutrition. In a study based on adult patients with anorexia nervosa hospitalized for various reasons ($N = 10,197$ patients), the incidence of severe hypophosphatemia reached 43%. Malnutrition has been observed as the most important risk factor [30, 31]. This non-correlation in post-refeeding serum phosphate and total energy intake challenges our physiological understanding of refeeding syndrome in malnourished patients [12]. Refeeding syndrome is driven by insulin, and insulin secretion is directly proportional to glucose consumption, and therefore you would expect the greater energy intake to cause the greatest reduction in post-refeeding serum phosphate.

A retrospective study by Ridout et al. between 2010 and 2014 analyzed 196 adolescent patient encounters and found 3960 laboratory tests, an average of 20 tests per patient encounter. This represents 35% more laboratory tests compared to our study. Of these, 1.9% were abnormal, 0.28% required supplementation and 0.05% were critical values [32]. The number of key laboratory tests performed in our study was less than what is recommended and less than what is performed in Ridout study with only 1289 laboratory tests performed for 99 patient admissions or 13 lab tests/admission. Despite our low number of tests, we did not observe any complication or change in clinical management. However, our population seemed to be at greater risk of complications because presenting with a younger age on average and lower BMI upon admission compared to Ridout's population. In our study, the

length of illness in months, was shorter in duration (14 vs 23 months), which could be an indicator of lower severity of illness. Our results can be partially explained by the fact that most of our inpatients were mildly to moderately malnourished, the average BMI within our cohort was 15.3 upon admission, with the lowest value at 11.6. Also, we work with adolescents, who do not have a very long history of undernutrition leading to deficiencies. Our results are therefore not generalizable to adults.

An important cause of hypomagnesaemia is phosphate depletion, which is associated with increase in urinary excretion of magnesium. In our study, we chose to determine whether patients with hypomagnesemia also presented with hypophosphatemia. This was the case for both patients who presented with low levels of magnesium. The purpose behind this association would be to suggest dosing phosphate on its own without necessarily testing for the magnesium. If greater risk factors are present and only if phosphate levels are low would there be a reason to check the serum magnesium level. This can save unnecessary laboratory testing and with correction of the hypophosphatemia, the magnesium levels would normalize.

The total cost associated with our laboratory monitoring for refeeding syndrome was 148,926.8$CAD, or 1504$/admission. This is very significant considering the little impact it had on clinical management and outcome. If we had followed the current recommendations [17, 18, 26, 28], the total cost associated with the laboratory monitoring would have been 385,000$CAD at its minimum, 2.5 times higher than what we obtained in our population. This amount only includes the basic electrolytes (Chem (Na, K, Cl), phosphate, magnesium and calcium) and can be even higher if we include the liver function tests and other recommended laboratory testing. In fact, Leitner et al. conducted a retrospective chart review to consider empiric phosphate supplementation routinely in order to avoid refeeding hypophosphatemia [31]. Administering empiric phosphate supplementation with close clinical surveillance could be more cost-effective than daily laboratory testing in preventing refeeding syndrome.

Our study involved a relatively large number of patients in a tertiary pediatric hospital center that has expertise in the treatment of patients with Eating Disorder. In our protocol, apart from the admission assessment, repeated laboratory tests are at the discretion of the pediatrician. Doing a retrospective study ensures that practitioners are not biased by knowing that their attitude will be assessed. On the other hand, the retrospective nature of the study is a limitation, with data collection that is different from one patient to another. This said, each patient is subject to laboratory tests according to the clinical judgment of the physician. It may therefore be that we miss certain abnormal values by absence of tests done, for instance.

In our study population, no case of clinical refeeding syndrome was observed and only 1.6% of hypophosphatemia found. Although we performed a lower number of laboratory tests than currently recommended without any consequence on outcome or management, we believe there is potential for improvement in those numbers. In light of the results obtained, we believe the current recommended frequency of laboratory testing remains very conservative and this results in a significant cost to the healthcare system. The number of laboratory tests could eventually be determined based on the severity of malnutrition and admission values. For instance, patients with mild-to-moderate malnutrition can have 2–3 blood work/week in the first 10 days of admission and then once/week for the next 2 weeks. Tests could be done more frequently if abnormal or if severe malnutrition is identified. Routine phosphate supplementation for patients severely malnourished with close clinical surveillance could be an alternative approach that is more cost-effective than excessive laboratory testing.

Compliance with ethical standards

Conflict of interest There was no internal or external funding provided for this research project, and no conflict of interest of any author.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the Sainte-Justine's Hospital Research Ethics Board.

Informed consent Informed consent was obtained from all individual participants included in the study.

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