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Article

Association of Hepatic and Renal Injury in A Retrospective Cohort of Hospitalized Adolescents with Anorexia

Coline Mejean[1], Julie Berbis[2], Cyprien Fabre[2], Rachel Reynaud[3], Sarah Castets[3], Gilbert Simonin[3], Michel Tsimaratos[4] and Alexandre Fabre[1,5].

[1]Department of Multidisciplinary Pediatrics, Department of Pediatric Gastroenterology & Nutrition, AP-HM, Marseille, France
[2] Aix Marseille University, EA 3279 CEReSS, School of Medicine - La Timone Medical Campus, Health Service Research and Quality of Life Center, AP-HM, Marseille, France
[3]Department of Multidisciplinary Pediatrics, Pediatric Endocrinoly unit, AP-HM, Marseille, France
[4]Department of Multidisciplinary Pediatrics, Pediatric Nephrology unit, AP-HM, Marseille, France
[5] Aix Marseille University, INSERM, MMG, Marseille, France
* Correspondence: FABRE, Timone Hospital, Department of Pediatric Gastroenterology & Nutrition, 15th Floor, 13385 Marseille, Cedex 05, France (e-mail: alexandre.fabre@ap-hm.fr)

ABSTRACT

Background: Only few pediatric reports exist regarding the prevalence, cause and evolution of liver and renal injury in patients with anorexia nervosa (AN). The aim of this study is to describe the prevalence and the risk factors of hepatic and renal failure at admission and during hospitalization, especially during refeeding in a cohort of hospitalized adolescents with AN.

Methods: In a retrospective cohort study of adolescents with AN in a single hospital of Marseille from 2013 to 2019, we compared four groups on admission: elevated aminotransferases (AT)/normal AT and renal injury/no renal injury to analyze the differences between them (demographic factors, anthropometric factors, disease duration, initial prescribed calories, speed of refeeding, aminotransferase level, glomerular filtration rate). We observed the evolution of AT and renal injury for these four groups during refeeding (by the increase of kilocalories).

Results: A total of 29 subjects with AN met eligibility criteria (age: 14.2 years, female (86.2%), BMI at admission (Z-score= -2.8 standard deviation (SD)) with elevated AT (20.7 %) and renal injury (13.8 %) on admission. Lower Z-score BMI (-4.05 vs -2 SD, $p = 0.013$), lower expected weight for height (69% vs 76%, $p = 0.034$) and longer disease duration (2.1 vs 0.9 years, p =0,032) were significantly associated with elevated liver enzymes at admission. Lower Z-score BMI (-3.35 vs -2.5 SD, $p = 0.002$), lower expected weight for height at admission (69% vs 74,5%, $p = 0.002$) and loss of weight before admission (0.66 vs à 0.20 kg per day, $p = 0.002$) were associated with renal injury at admission. Time nadir BMI (13.5 vs 6.5 days, $p = 0.034$) and duration of hospitalization (55 vs 41 days, $p = 0.036$) were longer in elevated enzymes on admission group. During refeeding, liver enzymes (95% confidence interval (CI), odds ratio (OR) aspartate aminotransferase: -0.07 [-0.11; -0.03] and OR alanine aminotransferase: -0.16 [-0.27; -0.06]) and renal injury

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(95% CI, OR creatinine: -0.013 [-0.017; -0.008]) have normalized with the increase of calories, with significant association.

Conclusions: The results of this study suggest that degree of malnutrition is associated with liver and renal injury on admission. Theses failures disappeared with refeeding. In the future, prospective multicentric studies could examine evolution of renal and hepatic failure undergoing refeeding in large pediatric cohort of AN.

Keywords: Anorexia; adolescents; pediatric; liver injury; aminotransferase; renal injury; refeeding

1. Introduction

Anorexia nervosa (AN) is a psychiatric disorder characterized by significant weight loss, morbid fear of weight gain and severe body image disturbance, according to DSM-5. [1].

Bulik at al. [2] reported the prevalence of AN in females to be 1.2%, in males 0.29%, and prevalence in the population of 14-year-olds was estimated at 3.2% in females, and 1.6% in males [3]. The onset of AN most commonly occurs during adolescence, within 15–19-years old. While the incidence rates are stable in the adult group, they seem to be increasing in adolescents and children [4]. AN is a severe mental disorder with a high mortality rate (approximately 5 deaths per 1000 persons-years [5]).

Among all the complications of AN [6], hepatic and kidney failures remain poorly characterized.

In the literature, there are few reports regarding the prevalence, cause and evolution of liver injury in patients with AN. The only pediatric study [7] reported a 37% prevalence of elevated liver enzymes on admission in a large cohort ($n = 356$) of hospitalized adolescents, with an additional 4.1% of patients who developed elevated liver enzymes after admission. But the time course, evolution, and physiopathology of elevated aminotransferases during hospitalization for AN still remain unclear. In particular, the etiology of elevated aminotransferases is controversial. The two hypotheses regarding the etiology are malnutrition or refeeding.

No renal disorder is precisely characterized whereas over 70% of AN patients have renal complications in their lifetime [9], with a 5.2% prevalence of severe kidney disease [10]. Recently, a study [11] found that kidney failure was the cause of death in 2 out of 31 AN patients. Only one recent pediatric study [13] exists at our knowledge.

Therefore, the principal objective of this study was to describe the prevalence and the risk factors of elevated liver enzymes at admission, their evolution during hospitalization and examine whether the development of elevated liver enzymes at admission affects the therapeutic course in a cohort of hospitalized adolescents with AN.

The second objective was to describe the prevalence of renal injury and the risk factors of renal failure at admission, and the evolution of renal failure during hospitalization.

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2. Methods

2.1. Study population

The study was in single-center, retrospective cohort study of hospitalized patients at CHU Timone (Marseille, France) from 2013 to 2019. The study was approved by the GFHGNP ethics committee (GFHGNP 02-13-2019).

Criteria for study eligibility included adolescents younger than 18 years old, admitted with diagnostic of AN (according to DSM-5 criteria), hospitalized in Pediatric Multidisciplinary Unit of Timone's Hospital in Marseille between January 2013 and February 2019 for malnutrition due to restrictive AN which was defined as weight loss above 20% or Z-score BMI < - 2 standard deviation (SD).

Only the first admission was included if patients were readmitted during the study period to ensure that the aminotransferase and creatinine levels analyzed in this study would not reflect previous medical interventions. Nutritional rehabilitation therapy at Timone Hospital was commenced using oral feeding. Enteral refeeding by nasogastric tube was additionally used for patients who had insufficient weight gain. No parenteral nutrition has been used. Refeeding was started with the administration of 600-1000 kcal/day, in consideration of the amount of energy intake prior to admission. Refeeding was followed by a progressive increase of 200 kcal about every week.

Exclusion criteria were eating disorders other than anorexia and duration hospitalization under 5 days. Other not eligible patients were those with missing important data (over 60% among weight and height on admission, loss of weight before admission, initial calories prescribed, speed of refeeding, blood test on admission and during refeeding).

2.2. Study design

The data collected were: sex; age of illness beginning and age at admission (years); duration of the eating disorder (years); anthropometric measures (height and weight) at admission; BMI on admission and at the end of hospitalization (kg/m^2); Z-score BMI (SD); expected weight for height (%); loss of weight before hospitalization (in % and kg per day with last anterior weight during 3 last months), time to nadir BMI during hospitalization (days); initial prescribed calories (kcal); speed of caloric increase (kcal/days) and duration of hospitalization (days).

BMI was calculated using weight in kilograms divided by the square of height in meters (kg/m^2). Z-score BMI and expected weight for height (%) were calculated with Epinut software (http://epinut.fr/). Liver function was estimated by the level of aminotransferase (AT): aspartate aminotransferase (AST) and alanine aminotransferase (ALT). ALT and AST above 30 IU/L were considered elevated, according to our standard's laboratory hospital. Renal function was estimated by calculating the glomerular filtration rate (GFR) using Schwartz formula (**Annex 1**) and CKD (Chronic Kidney Disease) classification [14]. GFR below 90

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ml/min/1.73 m^2 was considered as renal failure. Liver and renal blood tests were checked at admission and every following weeks (during refeeding). The prescribed calories at the moment of the blood test were noted. We compared four different groups on admission: elevated AT(n = 6)/normal AT(n = 23) and renal injury(n = 4)/no renal injury(n = 25) to analyze the differences between them (Fig. 1). We observed the evolution of AT and renal injury for these four groups during refeeding.

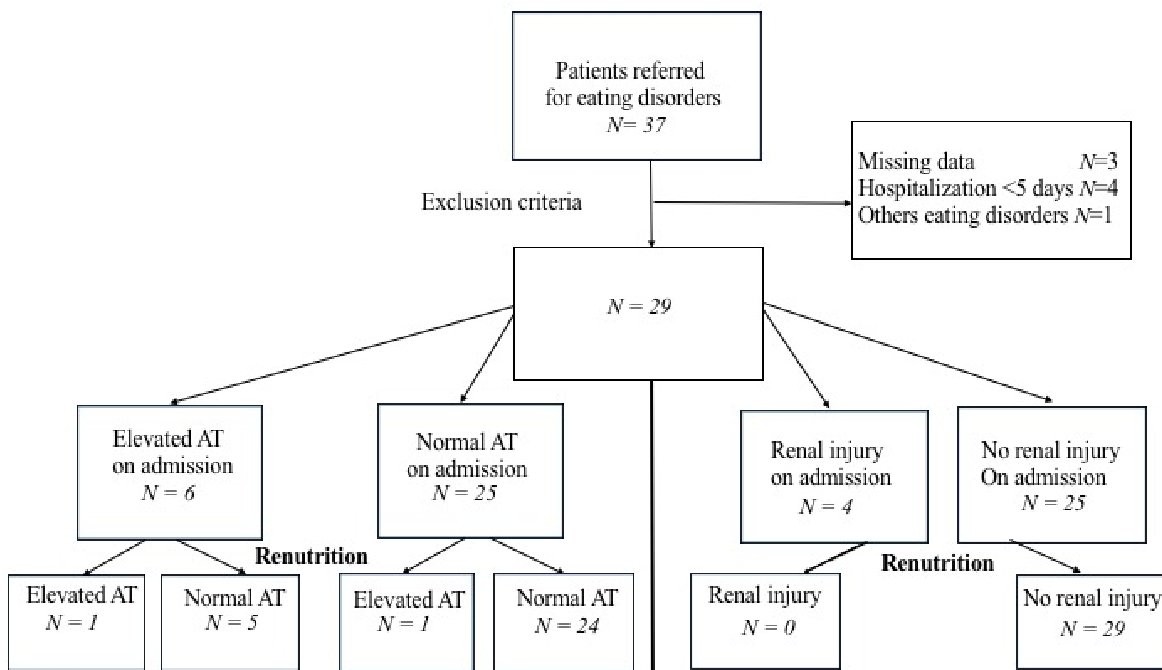

Figure 1. Flow chart. AT, Aminotransferases**.** Elevated AT was defined by ALT and AST above 30 IU/L (above hospital laboratory's range)**.** Renal injury was defined by GFR under 90 ml/min/1.73 m^2.

2.3. Statistical analysis

Categorical variables were described using numbers and percentages, and quantitative variables were described using medians and ranges. Comparisons between groups (elevated AT vs normal AT on admission / renal injury vs no renal injury on admission) were performed using Mann-Whitney tests for quantitative variables and Fisher tests for qualitative variables.

Linear mixt models were performed to examine evolution AT and creatinine undergoing refeeding.

All analyses were performed using the R software. Values of $p < 0.05$ were considered significant and the tests were two-sided.

3. Results

During the study period, 37 patients referred for AN were admitted to Pediatric Multidisciplinary Unit of Timone Hospital. After applying the exclusion criteria, 29 subjects met eligibility criteria between 2013 to 2019 and were included in the study (one patient excluded for bulimia and 4 for duration hospitalization

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inferior than 5 days). 3 patients were not eligible for missing data. No significative difference on age at admission, sex and Z-score BMI between these 3 patients with our population (Fig. 1).

They were predominantly female (86.2%). Median age was 14.2 ± 1.5 years old and median age of illness beginning was 13 ± 1.9 years old. Disease duration was 1 ± 1.2 year. Median rate of weight loss before admission was 0.1 ± 0,5 kg per day and 21.4 ± 11,8 %. They were malnourished on admission: Z-score BMI was -2.8 ± 1.6 SD, 58.6 % under 3rd percentile. The weight for height was 74.5 ± 10.7 %. The initial prescribed calories were 600 ± 145 kcal/day and the speed of refeeding was 33 ± 15,6 kcal/day. Time to nadir BMI was 7 ± 8 days and the duration of hospitalization was 45 ± 32.5 days (Table 1).

Age of illness beginning and age of hospitalization was earlier for boys than for girls (Table 1) with significative difference (respectively $p = 0.049$ and $p = 0.039$). However, no significative difference was observed between the sex on Z-score BMI ($p = 0.268$).

Table 1. Patient's characteristics ($n = 29$).

	Median	**Range**
Age on admission (years)	14,2	11-16,4
Boys	12,3	11,2-14
Girls	14,5	11-16,4
Age of beginning illness (years)	13	8-15,5
Boys	11,5	9-12,5
Girls	13,5	8-15,5
Disease duration (years)	1	0,1- 5
Weight loss (kg/days)	0,1	0,01-2,5
Weight loss (%)	21,4	9-68
BMI on admission (kg/m^2)	14	11-20,8
Z-score BMI (SD)	-2,8	-4,7- +2,6
Boys	-3,25	-4,6- -2
Girls	-2,5	-4,7- +2,6
Weight for height (%)	74,5	56-100
Initial prescribed calories (kcal/day)	600	400-1000
Speed of refeeding (kcal/day)	33	16.6-67
Time nadir BMI (days)	7	0-32
Z-score BMI end hospitalization (SD)	-2	-4- +2,7
Hospitalization duration (days)	45	5-127

BMI Body Mass Index, SD Standard Deviation

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Between the groups elevated AT (20.7 %, $n = 6$) and normal AT on admission (79.3%, $n = 23$), no significative difference has been observed concerning the age on admission, age of illness beginning and sex. Disease duration was significantly longer in the elevated AT on admission group. Lower Z-score BMI was significantly (-4.05 vs -2 SD, $p = 0.013$) associated with elevated liver enzymes at admission (Fig. 2). As a marker of malnutrition, lower expected weight for height was still significantly associated with elevated liver enzymes at admission (69% vs 76%, $p = 0.034$). However, there was no significative difference between elevated AT and loss of weight (in % and kg/days). The time of nadir BMI and the duration of hospitalization were significantly longer in the elevated AT on admission group (respectively 13.5 vs 6.5 days, $p = 0.034$ and 55 vs 41 days, $p = 0.036$) (Tab. 2).

Of the 6 patients who had cytolysis at admission, 4 had a blood test for viral hepatitis (hepatitis A, B, C, and E, EBV, CMV), autoimmune hepatitis (anti-nuclear antibody), thyroid and celiac disease. All of these laboratory tests were negative.

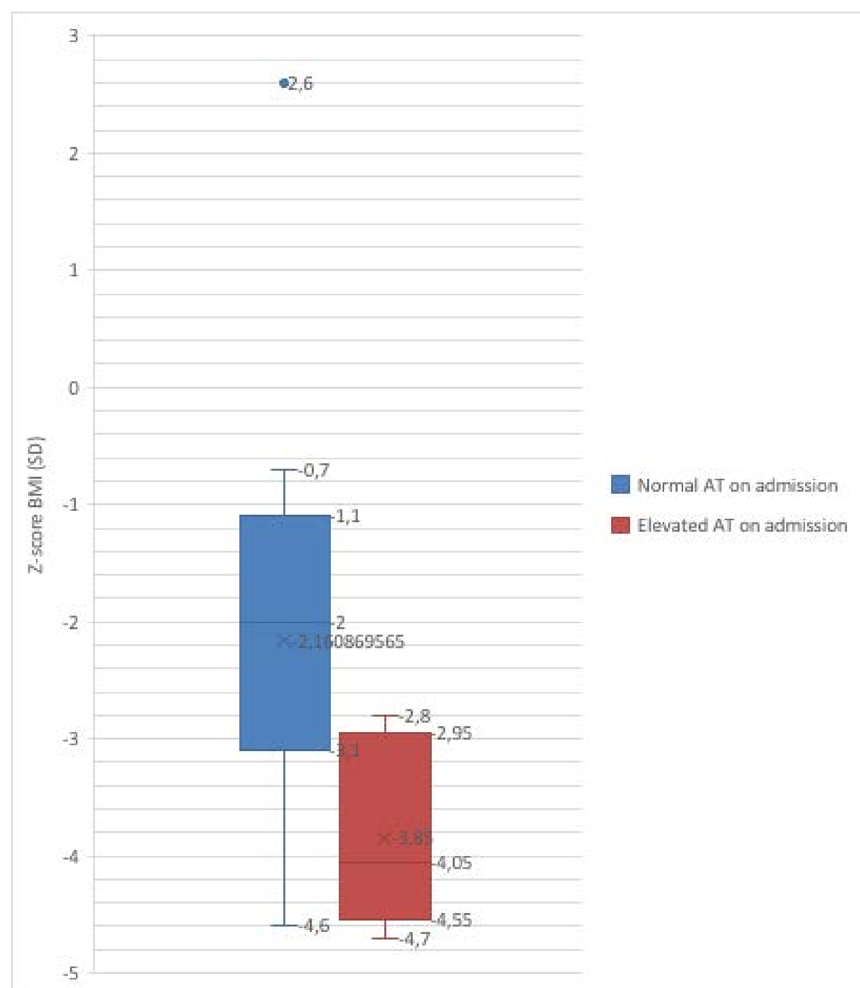

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Figure 2. Comparison of Z-score BMI in normal AT and elevated AT group on admission. BMI Body Mass Index, SD Standard Deviation, AT Aminotransferases. Z-score BMI is lower in the group elevated AT on admission. Patients with Z-score above -2 SD have loss of weight above 20%.

Table 2. Comparison of group elevated AT/normal AT and renal injury/no renal injury on admission. AT Aminotransferases, BMI Body Index Mass, [a] Mann-Whitney U test.

	Elevated AT on admission *n = 6* **Median** **Range**	**Normal AT on admission** *n = 23* **Median** **Range**	**p values [a]**	**Renal injury on admission** *n = 4* **Median** **Range**	**No renal injury on admission** *n = 25* **Median** **Range**	**p values [a]**
Age hospitalization (years)	15,4 11.2-16.4	14 11-16	0.224	13.9 13-16	14.2 11-16.4	0.824
Age beginning of illness (years)	13.3 9-15	13 8-15.5	0.913	12.8 10-14	13.5 8-15.5	0.611
Disease duration (years)	2.1 0.5-4.8	0,9 0.1-5	**0,032**	0.8 0.1-1	1 0,1-5	0,293
Loss of weight (%)	17.5 9-47	21.9 11.9-68	0.695	22.5 9-27	20 11.9-68	0.973
Loss of weight (kg/day)	0.075 0.01-2.5	0.12 0.03-1.08	0.674	0.66 0.03-2.5	0,20 0,01-1,08	**0.002**
Z-score BMI (- DS)	-4.05 -4.7- -2.8	-2 -4.6- +2.6	**0.013**	-3.35 -4.7- -1.2	-2,5 -4.6- +2.6	**0.002**
Weight for height (%)	69 56-78	76 57-100	**0.034**	69 56-89	74,5 56-100	**0.002**
Time nadir BMI (days)	13.5 7-30	6.5 0-32	**0.044**	7 0-32	14 6-30	0.163
Hospitalization duration (days)	55 46-78	41 3-97	**0.036**	49 5-97	45 3-127	0.467

During refeeding for the elevated AT on admission group, liver enzymes have normalized with increase of calories (time for normalization AT was 51.3 (18-61) days), with significant association: 95% confidence interval (CI), odds ratio (OR) AST: -0.07 [-0.11; -0.03] and OR ALT: -0.16 [-0.27; -0.06] except for one patient. He was a 13 years old boy, with BMI 12.4 kg/m^2 (Z-score= -3.7 SD) on admission, with the longest time nadir BMI (30 days), 600 kcal at initial refeeding and a speed of refeeding of 28.5 kcal/day.

For the normal AT on admission group, only one patient had cytolysis (2xN ALT) during refeeding beyond 30 days of hospitalization. She was a 16 years old girl and had an admission BMI of 18 kg/m2 (Z-score= -1 SD) with 21 % loss of weight before admission. We initiated her refeeding with 600 kcal a day but the speed of refeeding was higher than average (63 kcal/day).

Between the groups: renal injury (13.8%, *n*=4) /no renal injury (86.2 %, *n*=25), there were no significant difference in age on admission, age of illness beginning, sex, disease duration, time nadir BMI and duration of hospitalization. But, there was a significant difference for loss of weight before admission (0.66 vs à 0.20 kg per day, $p = 0.002$) and expected weight for height (69 vs 74,5%, $p = 0.002$) on admission. As the elevated

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enzymes, renal injury was significantly associated with lower Z-score BMI on admission (-3.35 vs -2.5 SD, $p = 0.002$) (Tab. 2).

The 4 patients who had renal injury at admission presented stage 2 CKD with a median GRF of 116 (71-181) ml/min/m^2. They normalized their renal function after 4 (2-5) days. In fact, creatinine has normalized with increase of calories with a significant association (95% CI, OR creatinine: -0.013 [-0.017; -0.008]). No other patient (with normal initial GRF) presented renal injury during hospitalization.

No association between renal injury and cytolysis has been observed (OR was 1.32, 95% CI [0.02-21.20]).

4. Discussion

4.1. Concerning liver injury

In the present study, we reported a 21 % prevalence of elevated liver enzymes on first admission for AN, with an additional 24% of patients who developed elevated liver enzymes after admission. The unique previous pediatric study [7] reported a prevalence of 37 % ($n = 356$). However, the difference with our study was not statistically significant.

Degree of malnutrition (lower Z-score BMI and expected weight for height) was significantly associated with elevated liver enzymes at admission. These results confirmed the previous findings [7, 12, 13].

Male sex predicted elevated liver enzymes on admission in previous study [7] but our study didn't confirm this result. The small size of our population could explain this difference. A previous study [15] with cohort of adults showed that the early age is a predictor of elevated AT on admission. Our study confirms this finding showing that longer disease duration is significantly associated with elevated AT on admission.

Only one study reported that early illness onset may be a risk factor for elevated AT levels during refeeding [16] whereas our study showed only one patient (with normal AT on admission) presenting cytolysis during refeeding. The illness age's onset of this patient was 15,5 years and disease duration 6 months. That is why, we cannot confirm the previous finding.

This same precedent study [16] found that elevated AT levels during refeeding were significantly associated with delay in the start of weight gain. But, in our study, it was elevated liver enzymes at admission that were associated with long delay of weight gain. And they were also associated with longer duration of hospitalization. To our knowledge, this is the first study to report these findings.

The physiopathology of elevated AT in AN remains unclear and source of debate. Starvation-induced autophagy (which can lead to hepatocyte injury and death) is the current proposed mechanism of liver dysfunction in those with AN [17,18]. But other studies suggest that elevated aminotransferases can occur after the refeeding process due to hepatic steatosis [19, 20]. Liver ultrasound can be helpful in distinguishing starvation-induced hepatitis from hepatic steatosis that can develop during refeeding [21]. We reported only one patient who had normal AT on admission and developed cytolysis afterward. Ultrasonography was normal

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for this patient. Therefore, we can't confirm hypothesis of previous studies [19, 20]. Again, the small size of our study could explain these differences.

For the 6 patients with cytolysis at admission, transaminases have normalized during refeeding with significant association (which mean we lost 7 points of ASAT and 16 points of ALAT when we increased refeeding of 100 kcal). As far as we know, this is the first study to report this association.

4.2. Concerning renal injury

Secondly, we reported in our study a prevalence of 13,8% renal failure whereas a prevalence of 4% renal failure was reported in the only recent pediatric study [11] with the same formula. These differences were not statistically significant. The major mechanism of chronic renal damage in young AN patients (besides hypokaliemia) is probably intravascular volume depletion due to energy restriction that causes chronic interstitial nephritis [8, 22].

We used Schwartz equation to estimate the GFR because it is the standard for pediatric patients [23, 24, 25]. However, no formula is a reference method for GFR in the adolescent anorexic population as far as we know. A recent study (n = 34) suggests that Cockroft-Gault formula is the most relevant formula to estimate renal function in malnourished adolescent with anorexia nervosa [26].

The recent pediatric study [11] revealed a strong association between the standard deviations of BMI and glomerular filtration impairment, independent of the formula used. Our study confirmed this finding and added new finding: loss of weight before admission is associated with renal injury at admission.

Our study reported that renal failure has normalized during refeeding with significant association (which mean we lost 1 point of creatinine when we increased refeeding of 100 kcal). No previous study examined the evolution of renal failure. Therefore, refeeding seems to be important to correct renal injury.

4.3. Limitations

The major limitations of this study are its retrospective nature in single-center, its small size and its inability to prove causality given its noncontrolled settings. However, except case reports, it is the second pediatric study to examine prevalence and risk factors of hepatic and renal injuries in a pediatric AN cohort as far as we know in the literature, and the first pediatric study to examine evolution of liver enzymes and renal failure undergoing refeeding.

5. Conclusion

In conclusion, elevated liver enzymes are frequent in AN of adolescents and may be a factor in determination of the disease's severity, prolonging delay of weight gain and duration of the hospitalization. Degree of malnutrition is associated with elevated liver enzymes on admission. The physiopathology remains unclear. It might be useful to do more investigations for the understanding of liver failure in AN.

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Renal complications in pediatric AN patients have to receive adequate attention. Degree of malnutrition is associated with renal failure on admission. We can suggest integrating the use of estimated GFR to the use of measured creatinine clearance for most severe patients.

In future, prospective multicentric studies could examine evolution of renal and hepatic failure undergoing refeeding in pediatric cohort of AN.

Conflict of interest: None declared.

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Authors contribution: CM served as primary author, collected the clinical data and samples and wrote the draft of the manuscript. GS, RR and SC followed anorexic patients. CM and AF analyzed, interpreted, and discussed the results. JB and CF revised the statistical analysis paragraph. MT and RR critically edited and revised the initial draft of the manuscript with regard to important intellectual content. AF was responsible for supervision, guidance, and final approval of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate: The GFHGNP ethics committee approved the study protocol (GFHGNP 02-13-2019).

I. ANNEXE

Annex 1

Schwartz equation:

eGFR 1⁄4 k   height = serum creatinine;

where k = 0.55 for children 1–13 years. k = 0.55 for adolescent females 13–18 years. k = 0.7 for adolescent males 13–18 year

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