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Selenium deficiency is associated with disease severity, disrupted reward processing, and increased suicide risk in patients with Anorexia Nervosa

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ABSTRACT

Background & Aims: Patients with Anorexia Nervosa (AN) present many nutritional deficiencies (macro- and often also micro-nutrients), possibly explained by their inadequate food intake. Previous studies reported that selenium (Se) deficiency is common in the general population. As Se can be easily added as a supplement, the goal of this study was to evaluate the clinical impact of Se deficiency in patients with AN.

Methods: This cross-sectional study concerned 153 patients with AN (92.9% women) followed at the Eating Disorder Unit of Lapeyronie Academic Hospital, Montpellier, France. Patients underwent an extensive neuropsychological assessment, and completed validated questionnaires. Blood samples were collected for Se quantification. Results were compared with the t-test, Mann-Whitney U, and Chi square tests, and univariate linear and multivariate logistic regression models.

Results: Se plasma levels were below the cut-off of 80 µg/L in 53.6% (N = 82) of patients. AN onset was earlier in patients with Se deficiency, ($p = .005$), whereas disease duration was comparable between groups ($p = .77$). General eating disorder symptomatology in the past 28 days (Eating Disorder Examination Questionnaire) was more severe in patients with Se deficiency ($p = .010$). The suicide risk (MINI International Neuropsychiatric Evaluation) tended to be higher ($p = .037$), and suicide attempt history was more frequent (28.39% vs 9.85%, $p = .004$) in patients with low Se levels. Se plasma concentration was negatively correlated with the performance in the temporal delayed discounting task ($p = .006$).

Conclusions: Our findings suggest that in patients with AN, Se plasma concentration might be implicated in disease severity and suicide risk. The finding that Se deficiency in patients with AN was associated only with reward-related processes, but not with other psychological functions suggests the selective involvement of dopamine-related pathways. Our results suggest that it might be useful to monitor the plasma micronutrient profile in patients with AN. Future studies should determine whether Se supplementation in AN might improve clinical outcomes.

1. Introduction

Selenium (Se) is a micronutrient with antioxidative properties that is

essential for human health. It is implicated in the neutralization of oxidative stress, immune system, thyroid homeostasis, and brain function. Many studies have focused on Se involvement in the immune

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system (Avery and Hoffmann, 2018; Sahebari et al., 2019). Moreover, Se deficiency might play a role in cancer development because it has been associated with increased risk of lung and laryngeal cancer (Duntas and Benvenega, 2015; Jaworska et al., 2013). Se deficiency has been associated also with several brain disorders, particularly cognitive decline (Cardoso et al., 2015; Vinceti et al., 2019). In agreement, daily intake of Brazilian nuts (a natural source of Se) improves cognitive performance in elderly patients with mild cognitive impairment (Rita Cardoso et al., 2016). Se deficiency is also implicated in the development of major depressive disorder (Zongyao Li et al., 2018). It has been suggested that Se exerts its functions mainly through participation in antioxidative processes. Glutathione peroxidase, one of the most important antioxidants in the human body, needs sufficient Se levels to function properly (Lubos et al., 2011). Glutathione peroxidase belongs to a class of molecules called selenoproteins that act as antioxidants and participate in the cellular response to oxidative stress, redox signaling, cellular differentiation, immune response, and protein folding (Steinbrenner et al., 2016). Se-rich foods include Brazil nuts, seafood, organic meat, eggs, and some bread types. However, epidemiological data shows that Se intake and plasma concentrations are suboptimal in Europe and in the Middle East (Stoffaneller and Morse, 2015). Moreover, in conditions of starvation, which is frequently self-induced in patients with Anorexia Nervosa (AN), the concentration of this essential micronutrient is drastically reduced with negative effects.

AN is a severe psychiatric disorder with the highest mortality rate among psychiatric diseases (Chesney et al., 2014). To date, there is no medical treatment specifically approved for AN, and the effectiveness of the existing psychological and nutritional management strategies is limited. It is important to better understand how insufficient nutrient intake affects disease outcomes to ensure good nutritional rehabilitation. Particularly, it is crucial to determine what micronutrients and supplements are necessary for these patients. Indeed, as they are generally more likely to accept micronutrient supplementation than caloric refeeding, this could increase treatment adherence and improve their long-term outcomes (Marzola et al., 2013). A previous study reported that a deficit of at least one trace element can be observed in almost half of patients with AN, particularly Se deficit (40% of patients) (Achamrah et al., 2017). Another study observed Se deficiency in 20.5% of patients with AN (REF). Finally, it has been shown that in AN, antioxidant activity increase and weight restoration are tightly linked (Oliveras-López et al., 2015).

The aims of the present study were: 1) to confirm the widespread Se deficiency in patients with AN; and 2) to determine Se role in the clinical course of AN by assessing Se deficiency association with the clinical course and neuropsychological functioning of patients with AN.

2. Materials & methods

2.1. Participants

The cross-sectional study included 153 patients with AN that were followed at the Eating Disorder Unit of Lapeyronie Academic Hospital, Montpellier, France. The following inclusion criteria were used: (1) age between 15 and 45 years, (2) native or fluent in French, (3) diagnosis of AN according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, (DSM-5) criteria, and (4) ability to provide informed consent. Patients with any AN type (restrictive or binge-purging) were included. Exclusion criteria were: (1) inability to understand and complete the clinical evaluation, (2) pregnancy or breastfeeding, and (3) deprivation of liberty by judicial or administrative decision. The study was carried out according to the Declaration of Helsinki. The informed consent was signed by all participants, and also by the official caregivers if the participant was younger than 18 years. This was an ancillary study in the framework of a larger project that was approved by the local ethics committee (Clermont Ferrand CPP).

2.2. Clinical assessment

All patient assessments were performed by a senior psychiatrist and a senior nutritionist with experience in AN evaluation and management. Besides the structured evaluation of AN, the presence of psychiatric comorbidities was evaluated with the Mini-International Neuropsychiatric Interview (MINI, version 5.0.0, (Lecrubier et al., 1997)), and sociodemographic and clinical data were collected from the medical records and from relatives, when possible. All clinical diagnoses (current and lifetime) were confirmed by consensus. The MINI suicide module was used to assess the suicide risk.

All study participants completed the following questionnaires:

Eating Disorders Examination Questionnaire (EDE-Q) (Luce and Crowther, 1999): a 33-item screening tool to evaluate the core clinical dimensions of the eating disorder (ED) over the last 28 days. For scoring, questions are subdivided into four subscales that explore four ED dimensions: eating concern, body shape concern, weight concern, and restraint. The total score is calculated by adding the scores of the four subscales and dividing the sum by four. In the present study, the Cronbach alpha value for the four subscales and total score was .95.

Eating Disorder Quality Of Life (EDQOL): a 25-item questionnaire that evaluates the quality of life in patients with ED in the last 30 days. The questionnaire is subdivided into four subscales: psychological, physical/cognitive, financial, and work/school related domains. The final score is obtained by adding all scores (Engel et al., 2006). In this study, the Cronbach alpha value for the four subscales and total score was .88.

Body shape questionnaire 34 (BSQ-34): is a 34-item questionnaire to measure the patients' attitudes towards their body shape and body image in general. The answer to each question is scored from 1 (never) to 6 (always). The final score is the sum of all subitem scores. Higher scores indicate impaired body image. In the present study, the Cronbach alpha value for all items and final score was .76 (Cooper et al., 1987).

Sociocultural Attitudes Towards Appearance Questionnaire-4 (SATAQ-4): is a 22-item scale that measures societal and interpersonal aspects of appearance ideals. It is subdivided into five subscales: relationships to body fat, to muscles tissue, to family, to peers, and to media. In this study, only the subscale scores were used (Schaefer et al., 2015). The Cronbach alpha value for the five sub-items was .63.

Patients also answered three questions on body-related cognitions (vision of weight, fear of gaining weight, and how often they weigh themselves) using a Likert-type scale (from 1 to 5).

2.3. Selenium levels in plasma

Se concentration was measured in plasma samples that were obtained during a standard follow-up visit at the Eating Disorders Unit. Blood was collected in Vacutainer tubes with K-EDTA. As different cut-offs for Se deficiency have been reported, for the present study, the most accepted cut-off value (i.e. ≤ 80 $\mu\text{g/L}$) was chosen (Duntas and Benvenega, 2015). Indeed, the optimal cut-off for Se deficiency is a matter of discussion. Our hospital laboratory uses an interval between 60 and 100 $\mu\text{g/L}$, with a mean value of 80 $\mu\text{g/L}$. In a large prospective study in Denmark, an increased risk of ischemic heart disease (relative risk 1.55) was observed among patients with serum Se concentration < 80 $\mu\text{g/L}$ (Suadicani et al., 1992). Conversely, Thomson (2004) concluded that a blood Se concentration of 80–95 $\mu\text{g/L}$ is sufficient for optimum selenoprotein activity. In their review, Duntas et al. suggest that the optimal range should be considered between 80 and 120 $\mu\text{g/L}$. Therefore, 80 $\mu\text{g/L}$ was chosen as the optimal cut-off. As our sample included very few children and men (most participants were adult women), the population heterogeneity was considered low, and no cut-off adjustment was necessary.

2.4. Neuropsychological assessment

2.4.1. Delayed discounting task

The delayed discounting task (DDT) was used to measure reward processing. It includes a probabilistic discounting and a temporal discounting task. Probabilistic discounting measures the patients' cognitive capacity to calculate risks. Temporal discounting measures the participants' proneness to choose between a bigger but later reward and a lower but quicker reward. In other words, it measures impulsivity and self-control. The questions presented to participants provide scenarios in which they have to choose, for example, €100 now, or €200 after one month. Subsequently, the sums remain the same, but the delay for the higher sum is increased (e.g. two years). The goal of this task is to find the time and the monetary value for which participants prefer the immediate and delayed (for example, 100€ now or 105€ after one year) options equally. This point is expressed as the coefficient "k", and "k value" is calculated with the following formula:

$$V = A / (1 + kD)$$

V is the present value of the delayed reward A at delay D, and k is a free parameter that determines the discount rate. With various time delays and values, multiple k values were calculated for each individual, and their mean score was taken for further analysis.

2.5. D2 attention test

The D2 test of attention is a validated, widely used instrument to measure sustained attention and concentration. Patients perform a *Cancellation Test* that is composed of 14 lines, each with 47 characters (a mixture of "p" and "d"). Each character has one to four dashes that are positioned individually or in pairs above and/or below each letter. The target symbol is a "d" with two dashes (above or below or both). Thus, a "p" with one or two dashes and a "d" with one, three, or four dashes are distracters. Participant must cross out (i.e. cancel) as many target characters as possible by moving from left to right (Bates and Lemay, 2004; Brickenkamp and Zillmer, 1998). There are many indexes to interpret the test results. The three most widely used are: d2 score 1 (or GZ), which is the number of characters handled, d2 score 2 (or F), which is the number of mistakes (omission or confusion), and the d2 ratio, which is calculated with the formula $GZ/F \times 100$ and is the global score of this test. Lower scores indicate better attention and concentration. In the final analyses, the d2 ratio was used.

2.6. Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation Test (BSAT) was used to evaluate executive functions and mental flexibility. Participants are asked to predict the position of the filled-in circle after viewing a series of pages in which the position of one filled-in circle among multiple empty circles changes. This test measures the capacity to detect changing patterns. The total number of correct answers is converted into a score. Higher scores indicate better mental flexibility and executive functions (Burgess and Shallice, 1997).

2.7. Iowa gambling task

The Iowa gambling task (IGT) is a classic measure of the decision-making capacity. In this test, the participant receives 2000 game money. Then, during the 100 trials, by taking one of four cards from one deck, the participant is asked to increase this sum as much as possible. Two decks are more profitable in the short term, but less valuable in the long run, and the inverse is true for the other two decks. The IGT performance was measured by calculating the global net score (the total number of advantageous selections minus the disadvantageous selections). Lower scores represent poor performance, and negative scores

indicate a relative preference for the disadvantageous decks (Bechara et al., 1994).

2.8. Rey-Osterrieth complex figure test

The Rey-Osterrieth complex figure (ROCF) test assesses the visual memory and the visuospatial constructional capacity. Participants are given a ROCF stimulus card and they are asked to copy it immediately and then to draw it from memory after 30 min. The score is calculated on a scale from 1 to 4, where 1 is the best performance. The scoring system includes accuracy, organization, location, and reproduction time (Shin et al., 2006). As few patients scored 4, patients with scores 3 and 4 were grouped.

2.9. Statistical analysis

The normal distribution of variables was evaluated. Quantile-Quantile plots were used to identify significant outliers, and when appropriate, outliers were trimmed or winsorized. When the Shapiro-Wilk test was > 0.05 , distribution was considered normal. Otherwise, non-parametric tests were used. Categorical data were analyzed with the Student's *t*-test or Mann Whitney U, the Chi square for 2×2 tables, and continuous data with univariate and multivariate linear regression models. The level of significance was set at $p < .05$. In univariate analyses, the Benjamini-Hochberg procedure was used to correct for multiple comparisons.

3. Results

The present study included 153 patients with AN among whom 142 (92.9%) were women. Se plasma levels were below the cut-off of 80 µg/L in 82 patients (53.6%). Se plasma concentrations were not different among patients with restrictive AN and binge-eating/purging AN ($p = .36$, independent samples *t*-test). Table 1 shows the results in function of the Se concentration (above and below the cut-off value of 80 µg/L).

Plasma Se concentration was not associated with sociodemographic variables (sex, age, education level, and marital status) (Table 1). In women, hormonal contraception was associated with higher Se plasma concentration ($85.19 \mu\text{g/L} \pm 16.52 \mu\text{g/L}$ in users vs $79.55 \mu\text{g/L} \pm 14.01 \mu\text{g/L}$ in non-users, $p = .049$). On the other hand, current and minimum lifetime (lowest since the onset of AN) body mass index (BMI) were not different in patients with normal and low plasma Se concentration ($p = .46$ and $p = .17$, respectively). The number of patients at risk of suicide, evaluated with the MINI screening questionnaire, was higher in the group with Se concentration below the cut-off (25/75, 33%, vs 10/58, 17.24%; $p = .040$, not significant after correction for multiple testing), as well as the number of patients with history of suicide attempt (23/81, 28.39%, vs 7/71, 9.85%; $p = .006$).

In the linear regression analysis, plasma Se concentration $< 80 \mu\text{g/L}$ was associated with earlier age at AN onset ($p = .005$), history of hospitalization for ED ($p = .029$), and poorer performance in the following self-assessed body-related cognitions: vision of weight ($p = .034$), higher fear of gaining weight ($p = .008$), and higher frequency of self-weighting ($p = .042$). Patients with Se deficiency also had lower vitamin B12 concentration (308.31 ± 122.87 vs 378.18 ± 162.73 , $p = .004$).

The EDE-Q and BSQ-34 questionnaire total scores were lower in patients with low than in patients with normal Se concentration ($p = .010$ and $p = .004$, respectively). There was no difference between groups in the SATAQ-4 and EDQOL total scores ($p = .165$ and $p = .089$, respectively).

Plasma Se concentration was also negatively correlated with the temporal DDT score ($p = .006$, sample $N = 111$), but not with the other neuropsychological tests (see Fig. 1 and Table 1).

In the multivariate models (Table 2) adjusted for confounders (i.e. the variables associated with Se deficiency in Table 1), EDE-Q total score

Table 1

Differences of sociodemographic, clinical and neuropsychological variables in patients with low versus normal selenium concentrations.

	Low selenium Mean \pm SD or N (%)	Normal Selenium Mean \pm SD or N (%)	T-statistic, U score, or χ^2	P- value
Sociodemographic and clinical characteristics				
Age, years	25.48 \pm 9.20	26.76 \pm 11.17	2777.0	0.623
Age at AN onset, years	16.24 \pm 2.93	19.04 \pm 6.25	-2.96^t	0.005*
Disease duration, years	8.42 \pm 8.78	8.58 \pm 9.58	2650.5	0.77
Education, years	14.19 \pm 9.98	13.63 \pm 2.31	2137	0.18
BMI	18.12 \pm 3.07	17.75 \pm 2.40	0.83 ^f	0.41
BMI, minimal lifetime	15.31 \pm 2.17	15.9 \pm 2.09	-1.66 ^f	0.10
Calorimetry	1183.60 \pm 220.54	1120.67 \pm 197.4	1.79 ^f	0.07
Fat mass	21.99 \pm 7.99	20.16 \pm 6.94	1.43 ^f	0.15
Vitamin B12	308.31 \pm 122.87	378.18 \pm 162.73	-2.94^t	0.004**
Irregular menstruation	17/41 (41.46%)	7/35 (20.00%)	4.03	0.045*
Suicide attempt history	23/81 (28.39%)	7/71 (9.85%)	8.2^{x2}	0.004**
Violent suicide attempt history	6/22 (27.27%) 25/75 (33%)	0/7 (0%) 10/58	2.4 ^{x2} 4.37	0.121 0.037*
Suicide risk (MINI)	19/82 (23.17%)	(17.24%)	4.78	0.029*
Hospitalization history		7/71 (9.8%)		
Clinical questionnaires scores				
EDEQL score	1.58 \pm .803	1.32 \pm .729	1.72 ^f	0.089
SATAQ-4 score	62.65 \pm 15.96	58.84 \pm 15.61	1.40 ^f	0.165
BSQ-34 score	122.09 \pm 44.22	99.17 \pm 40.40	1477.5^u	0.004**
EDE-Q score	3.63 \pm 1.34	2.82 \pm 1.73	1.59^{6u}	0.010**
Neuropsychological characteristics				
Delayed discounting score (log)	0.98 \pm 3.39	0.03 \pm 0.07	1163.5^u	0.006**
Probabilistic discounting task score (log)	1.07 \pm 2.09	0.84 \pm 1.46	1568.5 ^u	0.636
IGT score	5.13 \pm 30.42	2.69 \pm 33.01	0.394 ^t	0.694
BSAT score	7.53 \pm 2.047	7.41 \pm 1.90	1987 ^u	0.551
D2 test of attention score	0.4 \pm .31 1.97 \pm 0.88	0.4 \pm 0.25	1728.0 ^u 1928.5 ^u	0.418 0.546
ROCF Copy		1.87 \pm 0.85		

Abbreviation: AN, anorexia nervosa; BSAT, Brixton spatial anticipation test; BSQ-34, body shape questionnaire 34; EDE-Q, eating disorder examination questionnaire; EDEQL, eating disorder quality of life questionnaire; IGT, Iowa gambling task; ROCF, Rey-Osterrieth complex figure; SATAQ-4, sociocultural attitudes towards appearance questionnaire 4; BMI – body mass index; SD, standard difference; MINI, Mini international neuropsychiatric interview.

** Significant after Benjamini-Hochberg correction, adjusted p-value (family wise error rate), with critical p value < 0.01

* significant after standard unadjusted p value < 0.05

(p = .005), k value of DDT (p = .016), and history of suicide attempt (p = .045) remained significantly associated with low Se concentration, but not suicide risk (p = .157).

Then, to avoid confusion concerning the cut-off variable, data on plasma Se concentration were divided into quartiles and then the relationship with the DDT, EDE-Q, and BSQ-34 scores was evaluated again.

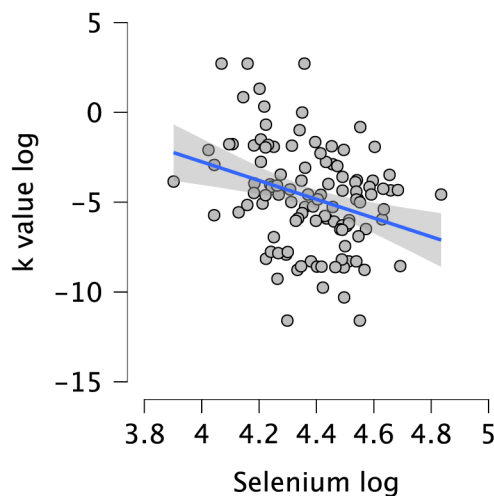


Fig. 1. Relationship between log selenium concentration and log k value (p = .006).

In all cases, the relationship between score and Se levels was confirmed (p = .001 for DDT, p = .014 for EDE-Q, and p = .011 for BSQ-34) (Figs. 2–4).

Lastly, after correction for current depression, plasma Se concentration remained associated with suicide attempt history (p = .005), but not with suicide risk (measured with the MINI) (p = .078).

4. Discussion

4.1. General observations

The present study offers the first evidence that plasma Se concentrations < 80 μ g/L, found in half of patients with AN, are negatively associated with several health-related parameters. Patients with Se deficiency had earlier AN onset, more severe general ED pathology, and higher number of past hospitalizations for AN, and more frequently reported history of suicide attempts. Previously, one case report implicated Se in the development of myopathy in a patient with AN (Ishihara et al., 1999), but no other study precisely analyzed the link between Se and AN.

Our observation that Se concentration was below the cut-off in half of patients with AN is in line with previous studies on AN (Achamrah et al., 2017; Hanachi et al., 2019) and also with reports suggesting that Se deficiency could be implicated in various psychiatric disorders (e.g. depression, schizophrenia, cognitive decline) (Cardoso et al., 2015; Zhe Li et al., 2018; Zongyao Li et al., 2018; Rita Cardoso et al., 2016; Vinceti et al., 2019). Notably, in our sample Se deficiency was associated with previous suicide attempts and suicide risk. The association with suicide attempt history remained after controlling for current depression. Unfortunately, we did not assess the current depression severity to better elucidate whether Se deficiency effect on suicidal behaviors is independent of depression. Given the high risk of suicidal behaviors and suicide in patients with AN, and the fact that previous suicide attempts are one of the most important predictors of future suicide attempts and death by suicide (Irigoyen et al., 2019), it is necessary to keep in mind the possibility of higher risk of suicidal behaviors in patients with AN and Se deficiency.

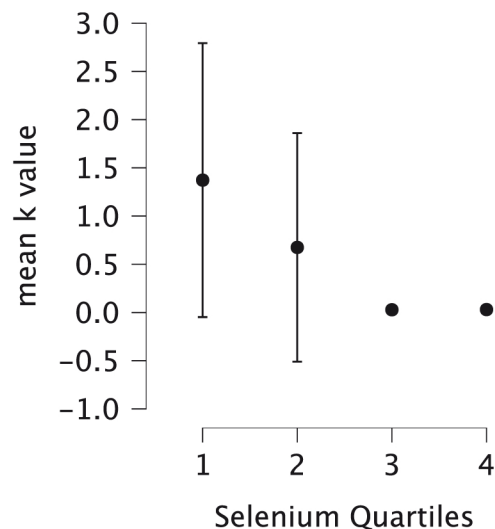
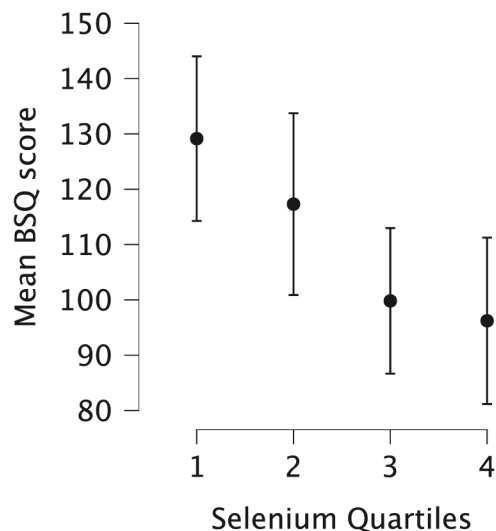
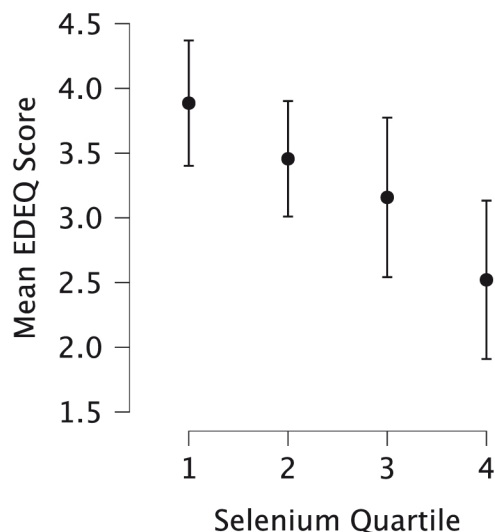
As this was a cross-sectional study, causality cannot be inferred. However, it can be hypothesized that in patients with AN, micronutrient intake is not adequate and this might lead to micronutrient concentration alterations that affect various neuropsychological functions, ultimately increasing the risk of suicidal behaviors. Another hypothesis is that in AN, the pathophysiology of which is primarily mediated increased dopamine (REF), the need of Se as an antioxidant is increased

Table 2

Adjusted and unadjusted logistic regression models with most important variables as a dependent variable in patients with low versus normal selenium concentrations.

Logistic regression model			Model 1		Model 2 ^a			
Outcome variable	Low Selenium Mean ± SD	Normal Selenium, Mean ± SD	Wald	P-value	OR	Wald	P-value	OR
EDE-Q score	3.63 ± 1.34	2.82 ± 1.74	8.39	0.004	1.41	7.80	0.005	1.48
DDT score	0.98 ± 3.39	0.029 ± 0.07	7.35	0.007	1.22	5.83	0.016	1.24
Suicide attempt	23/30 (76.7%)	58/122 (47.5%)	7.58	0.006	3.62	4.00	0.045	4.65
Suicide risk	0.33 ± 0.48	0.17 ± 0.38	4.24	0.040	2.40	2.01	0.157	2.81

Abbreviations: EDE-Q, Eating Disorder Examination Questionnaire; OR, odds ratio; SD, standard deviation.

^a Adjusted for: age, current body mass index, minimal lifetime body mass index, disease duration, age at AN onset, calorimetry score and fat mass, suicidal attempt**Fig. 2.** Mean k value in 4 selenium quartiles ($p = .001$).**Fig. 4.** Mean BSQ-34 score in 4 selenium quartiles ($p = .011$).**Fig. 3.** Mean EDEQ score in 4 selenium quartiles ($p = .014$).

to counteract dopamine toxicity (see below). In this case, Se deficiency could be a putative biomarker of disease severity. In our population, the EDE-Q and BSQ-34 scores decreased with the increasing Se concentration (divided in quartiles). If these results are replicated, Se concentrations could serve as a measure of AN severity. The overall results underline the need to monitor the micronutrient status in AN in order to propose relevant supplementation interventions, although interventional studies are needed to test these approaches.

4.2. Neuropsychological data

Among the different neuropsychological tests, only poorer performance in the DDT with the monetary stimulus was associated with plasma Se concentration $< 80 \mu\text{g/L}$. Patients with AN generally perform better in DDT than patients with bulimia nervosa, binge eating disorder, and even healthy controls (Steinglass et al., 2017). The absence of associations with the other neuropsychological tests (IGT, D2, ROCF, and BSAT) could be explained by the fact that the DDT investigates the reward processing in the brain by taking into account the time value, while other tests do not measure time. Time perception in the human brain is processed by dopamine (Berke, 2018), and Se levels and dopaminergic function are tightly related. High dopamine levels make people underestimate time intervals. A study in mice showed that time judgments are regulated by dopamine neurons and suggested that patients with AN underestimate time perception (Soares et al., 2016), as later demonstrated in a study on adolescents with AN (Vicario and Felmingham, 2018). Dopamine seems to be crucial for AN development, as suggested by the widely used "activity-based anorexia" rodent model (Gorrell et al., 2020; Schalla and Stengel, 2019; Verhagen et al., 2009). For instance, a study that investigated various pharmacological treatments for activity-based anorexia found that D2/D3 receptor antagonism is associated with decreased mortality and increased weight, unlike 5-HT2A antagonism. Better outcomes are observed with amisulpride, a selective D2/D3 antagonist, than with olanzapine that has a more broad receptor affinity profile (Klenotich et al., 2015).

Delayed discounting capacity can be influenced behaviorally by strengthening cognitive functions with behavioral or pharmacological interventions. Although reward delaying is better in patients with AN (Amlung et al., 2019) there is intra-disease heterogeneity (Ritschel et al., 2015). In AN, the immediate reward might be conceptualized as low body weight, perceived body shape, and possible social rewards

associated with appearance, compared with the long-term health benefits of healthy weight. Initially it may be seen as an adaptive behavior: better chances of attracting partners and succeeding in society if the attractive body shape is reached by delaying the gratification of the immediate palatable food in favor of thinness (i.e. sexual competition hypothesis of ED) (Nettersheim et al., 2018). However, this behavior becomes maladaptive when the individual who reaches the goal (target weight) cannot delay gratification for later health benefits and longevity instead of the current body-focus and the compliance with the current perfect self-image (Gatward, 2007). The implication of Se concentration in this possibly maladaptive progress is novel.

4.3. Reward system, oxidative stress, and dopaminergic pathway

Previous research has shown that reward system alterations are one of the core aspects of AN, leading to the hypothesis that AN might be a reward-related disorder (Duriez et al., 2019). In patients with AN, seven *de novo* missense variants have been identified among which four concern genes (*CSMD1*, *CREB3*, *PTPRD*, and *GAB1*) that belong to a signaling pathway implicated in neuron differentiation and dopamine pathway (Clarke et al., 2016). The Val66Met polymorphism in brain derived neurotrophic peptide (BDNF) is associated with neurogenesis impairment and also with higher reward value of starvation imagery, further supporting the hypothesis of the reward system implication (Clarke et al., 2016). Furthermore, mounting evidence suggests that many neuroendocrine hormones involved in homeostasis and body weight regulation also play roles in the food reward valuation and learning through their interactions with the mesolimbic dopamine system (Berner et al., 2019; Simon et al., 2020).

In agreement, our results show that in patients with AN, reward functions were heterogeneous and this variability was related to plasma Se concentration. The reward system is primarily mediated by dopamine neurons that are very sensitive to oxidative stress. Moreover, oxidative stress in dopaminergic pathways has been linked to various diseases. Dopamine is stored in intra-neuronal pre-synaptic vesicles where the pH is lower than the normal cellular pH (~5.5 versus 7.2) to increase its stability and to keep it separated from molecules with which it might react (Eiden and Weihe, 2011). Once dopamine is released into synapses or the neuronal cytoplasm, where the pH is higher, it is much more reactive and might induce oxidative damage (Qi et al., 2010). Se, by mediating the antioxidative action of glutathione peroxidase, can, in part, neutralize this damage (Solovyev, 2015). For instance, methamphetamine, a dopamine releaser in neurons, increases dopamine oxidation that causes neuronal damage, during which the concentration of glutathione peroxidases decreases. However, high Se concentrations counteract this effect (Barayuga et al., 2013). We hypothesize that similar mechanisms could be at play during the initial stages of AN.

Another interesting finding of the present study was the association between low Se and low vitamin B12 levels. A plausible hypothesis is that vitamin B12 also is implicated in oxidative stress (Bito et al., 2017). A systematic review found that lower vitamin B12 concentration might be associated with increased pro-oxidant and decreased antioxidant status (van de Lagemaat et al., 2019). This is in line with our hypothesis of increased oxidative stress in AN due to the hyperdopaminergic state, and suggests that vitamin B12, like Se, could be used for antioxidative purposes.

Pharmacological studies also indirectly suggest dopaminergic abnormalities in AN. Indeed, it has been reported that the dopaminergic antagonist olanzapine and the dopamine system modulator aripiprazole are the most effective drugs for ED symptom control (Marzola et al., 2015). In AN, patients tend to gradually lose their ability to obtain pleasure from food, one of the most important rewards from an evolutionary viewpoint, and develop an aversive reaction to food, as indicated by the increased activity of the amygdala rather than of the hedonic pathways (Kaye et al., 2011). Patients with AN do not lose the pleasure of food completely, but they lose its relative value, because other

rewards (e.g. body image and low weight) become more gratifying than food. In our study, lower Se concentration was associated with poorer DDT performance, altered body image-related cognition, significant changes in the BSQ-34, and more severe ED symptomatology. This suggests that Se might be involved in the dopaminergic reward pathway. However, it must be kept in mind that excess Se also might be toxic. Some evidences show specific Se toxicity to dopaminergic neurons and the dopamine system in general (Naderi et al., 2018), suggesting that Se concentration must be finely regulated for optimal reward-related decision making.

Basic science studies also support the link between dopamine dysregulation and AN. In rats fed a diet with low Se, dopamine turnover in prefrontal cortex and hippocampus is increased (Castaño et al., 1997, 1995). Moreover, potassium-induced dopamine release is enhanced in the striatum of mice with Se deficiency (Watanabe et al., 1997). Finally, a study in juvenile mice reported that Se deficiency impairs cognition, sensorimotor gating, and energy homeostasis (Kilonzo et al., 2021). These pathways might be implicated in AN because its onset is mainly in adolescence or early adulthood. Our finding that AN onset was earlier in patients with Se deficiency indirectly supports this hypothesis. Finally, it has been suggested that tumor necrosis factor (TNF) alpha and oxidative stress are implicated in AN maintenance (Agnello et al., 2013). As Se supplementation reduces TNF alpha expression, this also may contribute to explain the importance of an adequate Se intake in patients with AN (Jamilian et al., 2018; Lee et al., 2014; Zhang et al., 2002).

5. Limitations

This study presents some limitations. First, the cross-sectional observational study design does not allow drawing any conclusion about causality. Second, although statistical analyses were controlled for several confounders, some important confounders might have been overlooked. For instance, depression severity was not measured. Third, due to the lack of a depression questionnaire and specific suicidality-related measures (e.g. Beck Suicide Ideation Scale or Columbia Suicide Severity Rating Scale), reliable associations between suicidal behavior and Se deficiency could not be made. Fourth, Se was measured only in plasma samples, and we do not know how these findings translate to brain Se concentrations. Lastly, the choice of cut-off for Se deficiency could have been different, and the chosen value may be not applicable to all patients.

6. Conclusion

Our results suggest that Se deficiency is frequent in AN, and is associated with less optimal reward processing and higher suicide risk and disease severity. In clinical practice, it should be important to monitor plasma Se concentration in patients with AN. Future studies should investigate the causality of these associations and whether Se supplementation could translate into better clinical outcomes.

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Author Contribution

RS conceived the idea. RS and AL and wrote and revised the

manuscript. EO made critical improvements, MS organized and cleaned the data, KDM performed neuropsychological tests, AAC calculated k values from raw data, PL and ER performed endocrinological tests, including Se concentrations, LM and PC provided their expert opinions, and SG supervised the whole process.

Declaration of Competing Interest

The authors declare no conflict of interest.

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