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Research Article

Sociodemographic Factors, Nutritional Status, and Inflammatory Markers in Patients with Postural Orthostatic Tachycardia Syndrome

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Objectives. Postural orthostatic tachycardia syndrome (POTS) is characterized by cardiovascular autonomic dysfunction of unknown etiology with high a prevalence of gastrointestinal symptoms. The aim of the present study was to examine sociodemographic, lifestyle, and nutritional factors as well as inflammatory markers in patients with POTS. *Materials and Methods*. Forty-three patients with POTS and 61 healthy controls completed questionnaires about sociodemographic factors, lifestyle habits, and gastrointestinal symptoms. Blood samples were analyzed for serum levels of cobalamins, folic acid, iron, total iron-binding capacity (TIBC), ferritin, sodium, potassium, magnesium, phosphorus, albumin, high-sensitive C-reactive protein (CRP), and 25-hydroxyvitamin D (25-OH vitamin D). *Results*. POTS patients were predominantly women with a lower education level and were more often working part-time, on sick leave, and living alone compared with healthy controls. They reported lower alcohol intake and physical activity levels than controls. The nutrient intake was in general similar in both groups, but POTS patients had a higher intake of different drinks and reported more gastrointestinal symptoms than controls. POTS was associated with higher CRP levels (β: 1.370; 95% CI: 0.004–2.737; $p = 0.049$), lower albumin levels (β: -1.443; 95% CI: -2.648–(-0.238); $p = 0.019$), and higher sodium levels (β: 1.392; 95% CI: 0.559–2.225; $p = 0.001$). Abdominal pain ($p = 0.004$) and intestinal symptoms' influence on daily life ($p = 0.025$) were negatively associated with albumin levels. Abdominal pain ($p = 0.011$), vomiting and nausea ($p = 0.003$), and intestinal symptoms' influence on daily life ($p = 0.026$) were associated with higher sodium levels. Serum levels representing iron and vitamin metabolism were equal between groups. *Conclusions*. POTS is associated with poorer sociodemographic status, but malnutrition cannot explain POTS or related gastrointestinal symptoms. Higher CRP and lower albumin levels suggest low-grade inflammation as one possible etiological factor.

1. Introduction

Postural orthostatic tachycardia syndrome (POTS) is characterized by pronounced symptoms of orthostatic intolerance and a heart rate increase > 30 beat per min (bpm) from a recumbent to a standing position or more than 120 bpm in standing, in the absence of orthostatic hypotension [1, 2]. The diagnosis can be confirmed by either an active stand test for 10 min or tilt table testing. The heart rate increase must occur in the absence of orthostatic hypotension [1, 2]. The prevalence of POTS is significantly higher among women in their fertile age compared with men. The

etiology and pathophysiology of this cardiovascular autonomic dysfunction are unknown [3]. It is well described that patients with POTS often have abdominal pain and nausea [4], but also a wide range of other gastrointestinal symptoms have been described [5]. Similar gastrointestinal symptoms of unknown origin in young women have been reported in irritable bowel syndrome (IBS) and endometriosis [6, 7]. IBS is associated with female sex, smoking, and unemployment [6], whereas endometriosis is associated with lower alcohol intake and lower physical activity [7]. These factors have never been examined in POTS, which may be of importance in the care planning of the patients.

Previous studies have shown that IBS patients have poor dietary habits, with a low intake of vegetables and fruits and a high intake of fast food, candy, and soda [8]. The gastrointestinal symptoms are correlated with poor dietary intake, and improvement of dietary habits leads to markedly reduced symptoms [8, 9]. Malnutrition may cause neuropathy, e.g., vitamin B12 deficiency and iron deficiency are well-known etiologies of autonomic neuropathy and orthostatic hypotension [10, 11]. Low levels of B12 have been described in adolescents with POTS [12], but the degree of malnutrition has not been studied in adult POTS patients.

Low-grade inflammation is another hypothesis for gastrointestinal symptoms in IBS [13], and a high prevalence of autoantibodies and abnormal cytokine levels have been described in POTS [14].

While most studies on POTS have focused on regulatory molecular mechanisms, few studies have examined the sociodemographic factors and lifestyle habits. It has been proposed that lifestyle habits and poor nutrient intake could explain the autonomic neuropathy and gastrointestinal symptoms. Accordingly, the aim of the present study was therefore to examine sociodemographic factors, lifestyle habits, nutritional factors, and inflammatory markers in patients with POTS and explore associations between these factors and gastrointestinal symptoms.

2. Materials and Methods

2.1. Study Design. Study participants were recruited for this cross-sectional study at the Department of Gastroenterology, Skåne University Hospital, Malmö, Sweden, between October 2020 and January 2022. Invitations including study information were sent by regular mail to patients with previously confirmed POTS at the Department of Cardiology of the same hospital, as described previously [15]. The patients were contacted by telephone to give further information and book a visit. During the same time frame, healthy controls were recruited among hospital staff and students. All study participants were asked to complete a 4-day food diary at home. During the first study visit, the participants were asked to fill in study questionnaires, and a clinical examination was performed. Blood samples were drawn and kept frozen at -20°C. The blood sample analyses were performed at the Department of Clinical Chemistry. At the time of the examination and blood sampling, none of the participants had any symptoms indicative of a viral or bacterial infection.

2.2. Study Population

2.2.1. Patients. The Syncope Study of Unselected Population in Malmö (SYSTEMA) cohort, with over 3000 patients investigated for syncope and severe orthostatic intolerance at the Skåne University Hospital, was conducted during 2008–2021. Details of the SYSTEMA cohort are described elsewhere [16]. The patients underwent cardiovascular autonomic tests with head-up tilt (HUT) testing with continuous hemodynamic monitoring, as well as other cardiac tests including ambulatory electrocardiogram (ECG) or 24 h ambulatory blood pressure monitoring, when appropriate [16]. The HUT testing protocol included supine rest for 10 min preceding table elevation to 60-70° for 20 min [17]. POTS diagnosis was defined as symptoms of orthostatic intolerance lasting for ≥ 6 months associated with a pathological HUT test showing a heart rate (HR) increase > 30 bpm from a supine position or more than 120 bpm in standing, in the absence of orthostatic hypotension [1]. Moreover, all patients had been thoroughly evaluated by a senior expert (AF) to exclude other primary causes of the hemodynamic findings. As part of the clinical follow-up, POTS patients had been given lifestyle advice, including increased water and sodium intake.

From the SYSTEMA cohort, 93 patients with a clinically confirmed POTS diagnosis were included in the POTS substudy. These patients were further examined at the Clinical Research Unit, Department of Internal Medicine, to reconfirm the POTS diagnosis. If possible, from the clinical status of the included patients, blood pressure and heart rate were measured twice in the supine position by a validated automated oscillometer device (Omron, Kyoto, Japan), and then after 1, 3, 5, and 10 min of standing. An average of two measurements in the supine position was used for group comparisons. For the orthostatic heart rate increase, the difference between standing heart rate after 3 min and supine heart rate was calculated. All cardiovascular pharmacological agents such as beta-blockers, ivabradine, midodrine, and droxidopa were discontinued 72 h prior to the examination. If patients were unable to abstain from medication due to pronounced symptoms, the POTS diagnosis established during previous tilt-testing and characteristic symptoms were considered valid [17].

Patients from the POTS substudy obtained written information about the present study if they were living within a reasonable proximity to Malmö ($n = 82$) (Supplementary Figure 1). The patients were later contacted by telephone by one of the authors (HT) to give more information about the study. The inclusion criteria were age 18–70 years and the ability to fully understand the study information.

2.2.2. Control Subjects. Healthy control participants were recruited among hospital staff and medical students at Skåne University Hospital through personal invitation and advertisement. The controls were not allowed to have any current chronic or acute illness or significant gastrointestinal symptoms. Intake of multivitamins and hormonal contraceptive medicines was accepted, but otherwise, only temporary use of medications, such as seasonal allergy medicines, was allowed.

2.3. Clinical Examinations. During the first study visit, POTS patients were examined for heart, lung, abdominal, and neurological status. Neurological sensory testing was performed distally at the feet and distal leg with touch and by 10 g monofilament (Bailey Instruments, UK). A neurothesiometer (Horwell, London, UK) examination was performed to assess vibratory thresholds bilaterally at the medial malleolus and the tip of the big toe. A tendon hammer was used to assess the Achilles and patellar reflex. The current weight was obtained, as well as resting blood pressure from the right arm, in a supine position after approximately 5 min of rest. The healthy controls were examined with neurological sensory testing in the same way as the patients.

2.4. Questionnaires

2.4.1. Study Questionnaire. All study participants were asked to complete a questionnaire regarding sociodemographic factors, lifestyle habits, pregnancies and childbirth, previous and current illnesses, family history, current pharmacological treatment, and specific lifestyle modifications in case of gastrointestinal complaints.

2.4.2. Food Diary Questionnaire. The study participants were asked to keep a dietary record of all ingested food and drinks as well as associated gastrointestinal symptoms for 4 days. Each ingested item should be as thoroughly described as possible. Details about how to keep a food diary have been published previously [18]. The food intake during the 4 days was grouped into categories of meat, fish, vegetables/legumes, fruits/berries, dairy products, cereals, candies, soda, juice, protein drinks, and energy drinks including fluid replacement by a senior physician (BO). The number of times they ingested any fast food or calorie-containing liquid was registered, as well as whether they had regular or unregular food habits.

2.4.3. The Visual Analog Scale for Irritable Bowel Syndrome. The visual analog scale for irritable bowel syndrome (VAS-IBS) is a validated questionnaire regarding gastrointestinal symptoms common in IBS [19]. The respondent marks their degree of symptoms on a VAS between 0 and 100 mm, where 100 mm means very severe symptoms. The items covered are abdominal pain, diarrhea, constipation, bloating and flatulence, vomiting and nausea, psychological well-being, and the intestinal symptoms' influence on daily life. The scales are inverted from the original version [19]. Reference values for 52 healthy women are published [20].

2.5. Blood Samples. Serum levels of cobalamins, folic acid, iron, total iron-binding capacity (TIBC), ferritin, sodium, potassium, magnesium, phosphorus, albumin, high-sensitive C-reactive protein (CRP), and 25-hydroxyvitamin D (25-OH vitamin D) were analyzed according to clinical routines at the Department of Clinical Chemistry [21].

2.6. Statistical Analyses. Statistical analyses were performed using the software SPSS©, version 25 for Windows (IBM, New York, USA). Comparisons between groups were performed by the Mann–Whitney *U* test or Fisher's exact test as appropriate. Spearman's correlation test was used to assess correlations between food intakes, serum levels of nutrients and inflammatory parameters, and symptoms. Since age and sex differed between groups, a generalized linear model was used to calculate associations with continuous variables after adjustments for these confounders, using significantly different nutrient and inflammatory parameters, weight, and body mass index (BMI) as dependent variables, and cohort group or gastrointestinal symptoms as predictors, and gastrointestinal symptoms as dependent variables and nutrient intake as predictors. For adjustment of age and sex in categorical variables, logistic regression was used with groups as dependent variables and sociodemographic and lifestyle habits as independent variables. Due to the low number of participants, p for trend was calculated except for marital status. Values are presented as median and interquartile range, numbers and percentages, β-value with a 95% confidence interval (CI), or odds ratio (OR) with a 95% CI. $p < 0.05$ was considered statistically significant. $p < 0.01$ was considered statistically significant in correlation tests due to several calculations.

3. Results

3.1. Basal Characteristics. In total, 61 controls and 43 patients with POTS were included. The time from symptom onset to POTS diagnosis was 3 [1–10] years, and the time from diagnosis to study inclusion was 3 [1–7] years. The patients were slightly younger than the controls ($p = 0.030$), with a higher prevalence of female sex ($p = 0.019$). After the adjustment for age and sex, weight was higher in patients, but BMI did not differ between groups. POTS patients had a lower education level, seldom worked full time, and were more often on sick leave or unemployed than healthy controls. They more often lived alone compared with healthy controls. Both groups had a low prevalence of smokers, whereas the patients drank less alcohol and had less physical activity than the controls (Table 1). The patients reported they felt sick from drinking alcohol.

The most common comorbidities among patients were the Ehlers-Danlos syndrome ($n = 12$; 27.9%), IBS ($n = 12$; 27.9%), asthma ($n = 8$; 18.6%), migraine ($n = 7$; 16.3%), neuropsychiatric disorders (ADHD/ADD/autism spectrum disorders) ($n = 6$; 14.0%), endometriosis ($n = 5$; 11.6%), and myalgic encephalomyelitis ($n = 5$; 11.6%). Sporadic cases of other diseases were observed such as celiac disease and inflammatory bowel disease. In the control group, allergy was found in four participants. The most common drugs in the POTS patients were antihypotensive drugs (midodrine and droxidopa) ($n = 17$), ivabradine ($n = 16$), beta blockers ($n = 13$), histamine H1 blockers ($n = 13$), and combined hormonal contraceptives ($n = 8$). A complete list of drugs used during inclusion is given in Supplementary Table 1. Several patients were taken vitamins such as B12 ($n = 6$), D-vitamin ($n = 4$), multivitamins ($n = 3$), and folic acid ($n = 2$). Sporadic users of antiallergic treatment ($n = 2$), contraceptives ($n = 4$), and multivitamins ($n = 2$) were found among healthy controls.

Table 1: Basal characteristics.

	Healthy controls $N = 61$	POTS $N = 43$	p value	β or OR (95% CI)	p value
Age (years)	38 (29–44)	31 (26–41)	0.030		
Women (n, %)	45 (73.8)	40 (93.0)	0.019		
Weight (kg)	65.0 (57.5–76.2)	70.0 (60.0–82.6)	0.132	7.031 (2.012–12.050)	0.006*
BMI (kg/m^2)	22.7 (21.4–25.3)	24.2 (21.3–27.0)	0.416	1.330 (-0.382–3.042)	0.128*
Education (n, %)			<0.001		
Primary school (9 years)		3 (7.0)			
Secondary school (3 years)	4 (6.6)	14 (32.6)			
At least 1 year of higher education	10 (16.4)	9 (20.9)			
University	47 (77.0)	17 (39.5)			
p for trends				0.386 (0.216–689)	0.001**
Occupation (n, %)			<0.001		
100%	41 (67.2)	6 (14.0)			
99-51%	9 (14.8)	5 (11.6)			
50%		1 (2.3)			
Sick leave		19 (44.2)			
Retired	1 (1.6)	1 (2.3)			
Unemployment		3 (7.0)			
Studying	10 (16.4)	8 (18.6)			
p for trends				1.368 (1.108–1.688)	0.004**
Marital status (n, %)			0.023		
Living alone	15 (24.6)	20 (46.5)		1.00	
Married/living together	46 (75.4)	23 (53.5)		0.451 (0.184–1.110)	0.083**
Smoking (n, %)			0.361		
Never smoked	42 (68.9)	32 (74.4)			
Quit smoking	12 (19.7)	5 (10.9)			
Sometimes	4 (6.6)	1 (2.2)			
Regularly	3 (4.9)	5 (11.6)			
p for trends				0.975 (0.614–1.548)	0.914**
Weekly alcohol consumption (standard glasses)			<0.001		
<1	19 (31.1)	38 (88.4)			
1-4	32 (52.5)	4 (9.3)			
5-9	8 (13.1)	1 (2.2)			
9-14	2 (3.3)				
p for trends				0.116 (0.043–0.312)	<0.001**
Weekly physical activity (min)			0.025		
No time at all	3 (4.9)	8 (18.6)			
<30	7 (11.5)	6 (14.0)			
30-60	13 (21.3)	10 (23.3)			
60-90	9 (14.8)	11 (25.6)			
90-120	11 (18.0)	2 (4.7)			
>120	18 (29.5)	6 (14.0)			
p for trends				0.691 (0.525–0.910)	0.009**

POTS: postural orthostatic tachycardia syndrome. Values are given as number and percentages or median and interquartile ranges. Differences are calculated by Fisher's exact test and Mann–Whitney U test. β Coefficient and 95% confidence interval (CI) (continuous variables) or odds ratio (OR) and 95% CI (categorical variables) are given after adjustment for age and sex by generalized linear model* or logistic regression**. p for trend was given for dichotomous variables, except for marital status. $p < 0.05$ was considered statistically significant.

3.2. Nutrient Intake. Only 20 (32.8%) of the controls and 24 (55.8%) of the POTS patients returned diary books, with no differences in age ($p = 0.080$) or sex distribution ($p = 0.118$) between groups. Patients had a lower intake of vegetables and legumes compared with controls, and a tendency to have a lower intake of candies and cakes (Table 2). On the other hand, the intake of sugar-rich soda was higher in patients. There was a more frequent intake of different drinks such as energy drinks, protein drinks, and juice in patients than in controls, although not statistically significant for each drink. However, when calculated together, the higher drink intake in patients reached statistical significance (Table 3). When studying the diary books, several meals were replaced by energy-rich drinks in the POTS group (data not shown).

Table 2: Nutrient intake.

	Healthy controls $N = 20$	POTS $N = 24$	p value
Meat	4.00 (1.25–7.75)	4.00 (1.25–5.75)	0.794
Fish/seafood	1.00 (0–2.00)	1.00 (0–2.00)	0.712
Vegetables/legumes	6.00 (4.00–8.00)	5.50 (3.00–7.00)	0.042
Fruits/berries	4.00 (2.25–5.00)	3.00 (0.25–6.50)	0.550
Dairy products	6.00 (3.25–9.50)	5.50 (2.5–8.00)	0.531
Cereals	9.00 (7.25–11.75)	7.00 (3.25–9.00)	0.333
Candies	3.00 (3.00–5.00)	2.00 (1.25–4.00)	0.051

POTS: postural orthostatic tachycardia syndrome. Values are given as median and interquartile ranges. Mann–Whitney U test. $p < 0.05$ was considered statistically significant.

3.3. Serum Levels of CRP and Nutrient Parameters. Although only three (7.3%) patients and one (2.0%) control had CRP levels above the reference value, the levels of high-sensitive CRP were higher in patients than in controls (Table 4) (Figure 1). CRP levels correlated inversely with the levels of albumin (rs = −0.470, $p < 0.001$) and iron (rs = −0.348, $p = 0.004$). All participants had albumin levels within reference values, but the levels were lower in patients than in controls (Table 4) (Figure 1), and albumin levels correlated with levels of iron (rs = 0.268, $p = 0.010$) and ferritin (rs = 0.293, $p = 0.005$).

Sodium levels were higher in patients than in controls, with corresponding lower potassium levels (Table 4) (Figure 1).

Among the controls, three (5.9%) had low iron levels, eight (15.7%) had higher TIBC levels, and eight (15.7%) had low ferritin levels. Among patients, four (9.8%) had low iron levels ($p = 0.119$), seven (17.1%) had high TIBC levels ($p = 0.190$), and six (14.6%) had ferritin levels below reference values ($p = 0.211$). Regarding 25-OH vitamin D, 36 (70.6%) controls and 29 (70.7%) patients had levels below reference values ($p = 0.204$). When adjusting for sex and age, which may affect levels of ferritin and phosphorus, there were still no differences between controls and patients (β: -8.980; 95% CI: -29.859–11.900; $p = 0.399$ and β: 0.052; 95% CI: -0.029–0.132; $p = 0.209$, respectively).

There were no correlations between nutrient intake and nutrient levels in serum (data not shown).

3.4. Gastrointestinal Symptoms. POTS patients had more gastrointestinal symptoms than healthy controls (Table 5). Bread was the only food intake which correlated with symptoms and showed negative correlations with vomiting and nausea (rs = −0.443, $p = 0.003$) and psychological well-being (rs = −0.406, $p = 0.006$). Dietary habits did not associate with any symptoms after adjustments for the confounders' age and sex (data not shown).

CRP levels correlated with diarrhea (rs = 0.379, $p = 0.002$), bloating and flatulence (rs = 0.397, $p = 0.001$), and the intestinal symptoms' influence on daily life (rs = 0.336, $p = 0.006$). Albumin correlated negatively with abdominal pain (rs = −0.327, $p = 0.001$), vomiting and nausea ($rs = -0.276$, $p = 0.008$), and the intestinal symptoms' influence on daily life ($r = -0.280$, $p = 0.007$). Sodium levels correlated with abdominal pain (rs = 0.291, $p = 0.005$), vomiting and nausea (rs = 0.304, $p = 0.003$), and the intestinal symptoms' influence on daily life (rs = 0.292, $p = 0.005$). Potassium levels correlated negatively with diarrhea (rs = −0.316, $p = 0.002$) and vomiting and nausea (rs = −0.275, $p = 0.008$).

3.5. Associations with Serum Levels of CRP and Nutrient Parameters. Since levels of CRP, albumin, sodium, and potassium differed between patients and controls (Figure 1), calculations were performed after adjustments for the confounders; age and sex. POTS was associated with higher CRP levels (β: 1.370; 95% CI: 0.004–2.737; $p = 0.049$), lower albumin levels (β: -1.443; 95% CI: -2.648–(-0.238); $p = 0.019$), and higher sodium levels (β: 1.392; 95% CI: 0.559–2.225; $p = 0.001$). There was no association between POTS and lower potassium levels (β: -0.084; 95% CI: -0.188–0.021; $p = 0.117$).

CRP levels were not associated with any gastrointestinal symptoms after adjustment for confounders (data not shown). Abdominal pain (β: -0.004; 95% CI: -0.052–(-0.010); $p = 0.004$) and intestinal symptoms' influence on daily life (β: -0.020; 95% CI: -0.038–(-0.003); $p = 0.025$) were negatively associated with albumin levels. Abdominal pain (β: 0.020; 95% CI: 0.005–0.035; $p = 0.011$), vomiting and nausea (β: 0.021; 95% CI: 0.007–0.035; $p = 0.003$), and intestinal symptoms' influence on daily life (β: 0.014; 95% CI: 0.002–0.027; $p = 0.026$) were associated with higher sodium levels. Diarrhea (β: -0.002; 95% CI: -0.004–(-0.001); $p = 0.006$) and vomiting and nausea (β -0.002; 95% CI: -0.004–(-0.001); $p = 0.011$) were negatively associated with potassium levels.

4. Discussion

The main findings of the present study were the associations of POTS with sociodemographic factors, signs of low-grade inflammation, and higher sodium levels compared with healthy controls.

The current findings suggest that POTS patients more often are living alone, less often complete any education, and less often are working full time compared with healthy subjects. Although it may be suspected that the disease

Table 3: The number of participants who ingested the food or beverage at any time for 4 days.

	Healthy controls $N = 20$	POTS $N = 24$	p value
Regular meals	16 (80.0%)	15 (62.5%)	0.321
Fast food	6 (30.0%)	8 (33.3%)	1.000
Soda			
Sugar-rich	2 (10.0%)	9 (37.5%)	0.044
Sugar-free	3 (15.0%)	3 (12.6%)	1.000
Juice	5 (25.0%)	8 (33.3%)	0.742
Protein drinks	1 (5.0%)	3 (12.6%)	0.614
Energy drinks	0	4 (16.6%)	0.114
All drinks together	7 (35.0%)	17 (70.8%)	0.032

POTS: postural orthostatic tachycardia syndrome. Values are given as number and percentage of participants in each group. One participant could ingest several different drinks. Fisher's exact test. $p < 0.05$ was considered statistically significant.

may contribute to these associations, no causality can be confirmed in this cross-sectional study. The low intake of alcohol and lower degree of physical activity are also suggested to be secondary effects of the disease. The patients said that they felt sick when they drank alcohol and therefore avoided or reduced alcohol intake. Low physical activity may further impair their health and their psychological and physical capacities since physical activity has been shown to reduce the burden of gastrointestinal unhealth and depression [22, 23]. Low physical activity is also a risk factor for physical deconditioning, which may worsen symptoms in POTS [2].

IBS was present in one-third of the POTS patients, and endometriosis was present in 12% of patients. These comorbidities are much more frequent than expected since the prevalence in the society of IBS is 4–11% [24, 25] and the prevalence of endometriosis is 6–10% [26]. Some of the patients may have got diagnosis with IBS due to their gastrointestinal symptoms, since the physician may not have recognized POTS as associated with such symptoms. Self-reported IBS in the general population showed the strongest associations with female sex and smoking, and gastrointestinal symptoms were associated with unemployment and inversely associated with age ≥ 50 years [6]. In POTS patients, a female predominance is at hand, but there were no differences in smoking habits between groups, and the differences in age, education, occupation, marital status, alcohol intake, and physical activity cannot explain the development of gastrointestinal symptoms [6]. In endometriosis, low alcohol intake and low physical activity were observed, but education, occupation, and marital status did not differ between endometriosis patients and controls from the general population [7]. These observations suggest that patients with POTS are more affected by this condition with a greater impact on daily life than what is observed in patients with IBS and endometriosis. This may be due to that POTS patients do not only have gastrointestinal symptoms but also have symptoms of cardiovascular and, possibly, another autonomic dysfunction. The sociodemographic consequences are most likely secondary to the severity of symptoms and do not have a causal role. There is a delay from symptom onset to diagnosis, and the inability to work full-time or complete higher educational levels remains years after diagnosis.

The higher levels of sodium in POTS than in controls are in accordance with other studies [27], which may indicate hypovolemia and increased intake of salt by patients following common POTS recommendations [28]. POTS often have a reduced intravascular volume [29–31] and high-standing plasma norepinephrine [32]. A radiolabeled serum albumin investigation found a plasma volume deficit of nearly 13% [29]. A reduced plasma volume should stimulate the renin–angiotensin–aldosterone system (RAAS) to promote sodium retention. Although POTS patients have been shown to have lower sodium excretion than healthy controls [33], the regulatory RAAS might be defective in POTS [29]. Elevation in plasma norepinephrine suggests an increase in the neural tone of the sympathetic nervous system, leading to deficient RAAS activity [34]. However, the affected sodium levels may also depend on gastrointestinal disturbances with dysregulated electrolytes as a result.

Intravascular hypovolemia may be exaggerated in the upright position by blood pooling in the abdomen, pelvis, and legs [35]. The decreased return of blood to the heart and the reduced cardiac output lead to less stimulation of carotid and aortic baroreceptors, triggering an increase in sympathetic outflow [36, 37]. The high sympathetic activity renders a hyperadrenergic state with palpitations, tachycardia, near syncope, chest pain, and dyspnea, as well as symptoms from other organs like the gastrointestinal system, the genitourinary system, and psychological effects of high sympathetic activity such as anxiousness [38]. This may start a negative spiral since gastrointestinal symptoms of diarrhea and vomiting may worsen dehydration and electrolyte imbalance with the loss of potassium and albumin. The sympathetic activation continues until the patient is supine, or until the patient increases plasma volume through hydration [38]. In accordance with the hypovolemia theory, POTS patients experienced a reduction in heart rate acceleration and standing plasma norepinephrine upon upright position following a short-term period of elevated dietary sodium intake [27]. The current finding with the replacement of a meal of fast food with liquid intake in POTS may depend on increased thirst as a response to hypovolemia.

Previous studies have suggested POTS to be an autoimmune disease, with high a prevalence of autoantibodies and abnormal cytokine levels [14]. Although within reference values in most patients, CRP levels were associated with POTS but not with gastrointestinal symptoms, in contrast to potassium levels which were associated with gastrointestinal symptoms but not with POTS. A normal CRP value does not the exclude presence of low-grade inflammation [39]. For comparison, CRP levels did not differ between controls and IBS patients, which are also considered a low-grade inflammatory disease [18]. The findings of higher CRP and lower albumin levels, in correlation with altered levels of iron, TIBC, and ferritin, support the hypothesis that low-grade inflammation is common in POTS [40]. If the patients

Table 4: Serum levels of CRP and nutrient parameters.

	Healthy controls $N = 61$	POTS $N = 43$	p value
High-sensitive CRP (<5 mg/L)	0.68 (0.35–1.38)	1.35 (0.62–2.98)	0.006
Albumin (36–48 g/L)	44 (41–45)	41 (40–44)	0.014
Cobalamin (156–672 pmol/L)	294 (231–362)	300 (244–363)	0.549
Folic acid (>8 nmol/L)	19 (15–24)	18 (12–27)	0.503
25-OH vitamin D (>75 nmol/L)	63 (49–80)	68 (54–80)	0.292
Iron (9–34 μmol/L)	18 (14–22)	17 (12–22)	0.719
TIBC (47–80 μmol/L)	67 (61–73)	69 (60–76)	0.692
Ferritin (men: 22–322 μg/L) (women: 10–291 μg/L)	34 (15–74)	31 (14–50)	0.574
Sodium (137–145 mmol/L)	141 (139–142)	142 (141–143)	0.003
Potassium (3.5–4.4 mmol/L)	4.0 (3.8–4.2)	3.9 (3.8–4.0)	0.029
Magnesium (0.70–0.95 mmol/L)	0.78 (0.75–0.83)	0.80 (0.76–0.84)	0.169
Phosphorus (men 18-50 år: 0.70–1.6 mmol/L; women ≥18 år: 0.80–1.5 mmol/L)	1.2 (1.1–1.3)	1.1 (1.0–1.3)	0.103

Two missing values in POTS and 10 missing values in controls. CRP: C-reactive protein; POTS: postural orthostatic tachycardia syndrome; TIBC: total iron-binding capacity. Reference values within brackets are taken from the Department of Clinical Chemistry, Skåne University Hospital, Malmö, Sweden [21]. Values are given as median and interquartile ranges. Mann–Whitney U test. $p < 0.05$ was considered statistically significant.

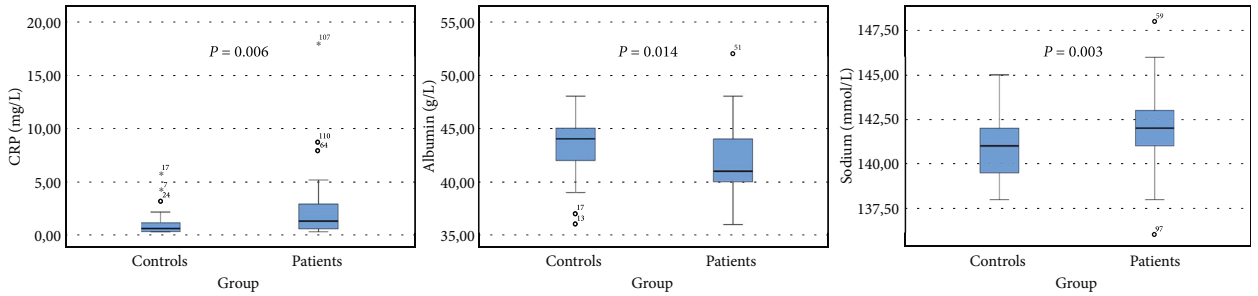

Figure 1: Serum levels of C-reactive protein, albumin, and sodium in healthy controls and patients with postural orthostatic tachycardia syndrome. Mann–Whitney U test. $p < 0.05$ was considered statistically significant.

Table 5: Gastrointestinal symptoms.

	Controls $N = 61$	POTS $N = 43$	p value
Abdominal pain (5 (1-15))	0	30 (11–62)	<0.001
Diarrhea (3 (0–10))	0	28 (0–64)	<0.001
Constipation (9 (1–22))	0 (0–13)	53 (7–74)	<0.001
Bloating and flatulence (14 (1–29))	0 (0–10)	65 (14–88)	<0.001
Vomiting and nausea (2 (0–3))	0	44 (21–70)	<0.001
Intestinal symptoms influence on daily life (2 (0–18))	0 (0–7)	50 (22–61)	<0.001
Psychological well-being (4 (0–16))	3 (0–18)	52 (20–76)	<0.001

POTS: postural orthostatic tachycardia syndrome. Gastrointestinal symptoms were assessed by the visual analog scale for irritable bowel syndrome, 0–100 mm, where 0 represents no symptoms and 100 maximal symptoms [19]. Reference values for VAS-IBS from healthy women are shown within brackets [20]. Values are given as median and interquartile ranges. Mann–Whitney U test. $p < 0.05$ was considered statistically significant.

were hypovolemic, the true albumin levels could be even lower than observed.

A previous study has found lower levels of B12 in adolescents with POTS [12]. This could not be found in the present study in adults. Furthermore, although POTS patients ingested several energy-rich and sugar-rich drinks, they had overall similar dietary habits to the healthy controls; they had similar serum levels of micronutrients; and their dietary habits did not associate with any gastrointestinal symptoms. We could thus not find any evidence that malnutrition could explain the pathophysiology behind POTS and related gastrointestinal symptoms, as we have found in IBS patients [9]. However, more patients than controls ingested vitamin tablets, which may have improved the circulating levels of nutrients. The high intake of drinks was based on individual experience and not prescribed by the physician.

The strength of the present study is the comparison between patients and controls from the same region. One limitation is the low-reported frequency of diary books and the differences in age and sex between the two groups. However, these differences were adjusted for in the statistical calculations. Another limitation is that the study was conducted in a tertiary hospital setting and that the included POTS patients may not be representative of findings in milder forms of POTS. On the other hand, the study of well-phenotypic POTS patients may increase the sensitivity for finding differences in the examined factors between POTS and healthy controls.

5. Conclusion

In conclusion, the diagnosis of POTS is associated with sociodemographic factors in the form of less often being married or living together, less often having completed an education, and an impaired ability to work full time. POTS patients drink less alcohol and demonstrate low physical activity but have adequate dietary habits. Malnutrition may not explain the neuropathy in POTS. Low-grade inflammation may be involved in the pathophysiology of POTS and its related symptoms, as well as dysregulation of sodium levels and hypovolemia.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The present study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Review Board at Uppsala University, Dnr 2020-02432 and 2021-00049. The Regional Ethical Committee in Lund, Sweden, approved the SYSTEMA project (82/2008) and the POTS-substudy (2017/295).

Consent

All study participants provided informed written consent prior to inclusion.

Conflicts of Interest

The authors have no conflict of interest to declare.

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Supplementary Materials

Supplementary 1. Supplementary Figure 1: flow chart of the recruitment of study participants. SYSTEMA: the Syncope Study of Unselected Population in Malmö; POTS: postural orthostatic tachycardia syndrome.

Supplementary 2. Supplementary Table 1: medication treatment in the group of patients with postural orthostatic tachycardia syndrome.

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