Behçet's syndrome, gender and lifestyle factors

P. Leccese, A.A. Padula, N. Lascaro, S. D'Angelo, M.C. Padula

Rheumatology Department of Lucania, San Carlo Hospital, Potenza and Madonna delle Grazie Hospital, Matera

Pietro Leccese, MD
Angela Anna Padula, MD
Nancy Lascaro, MD
Salvatore D'Angelo, MD, PhD
Maria Carmela Padula, PhD

Please address correspondence to:
Maria Carmela Padula
Rheumatology Department of Lucania, San Carlo Hospital,
Via Potito Petrone,
85100 Potenza, Italy.
E-mail: mcpadula25@gmail.com

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ABSTRACT

Objective. *Behçet's syndrome (BS) is a chronic, relapsing inflammatory disease characterised by various clinical manifestations. Emerging literature evidence supports the role of a healthy lifestyle as an environmental factor able to modulate disease activity, severity and quality of life. We aim to evaluate gender differences in the main lifestyle-related aspects within a cohort of patients with BS.*

Methods. *We collected data on demographics (age, sex), anthropometric measures (weight, height), lifestyle factors (dietary habits, physical activity, smoking, and alcohol consumption) and the impact of the disease on professional life in a group of consecutive BS patients.*

Results. *We recruited 105 BS patients (55M:50 F). Males recorded significantly higher rates of grade I obesity (9.1%M vs. 0.0%F, p<0.005) and greater alcohol consumption (58.3%M vs. 26.6%F, p<0.005), despite reporting higher levels of physical activity (29.0%M vs. 10.0%F, p<0.005). Female exhibited significantly less pro-inflammatory dietary habits, characterised by higher fruit consumption p<0.005) and a lower intake of refined products (p<0.005). The occupational impact was higher in female group compared with males (no work repercussions were recognised in 76.4%M vs. 28.0%F, p<0.005).*

Conclusions. *This study highlights gender-specific patterns in BS. In men, pro-inflammatory dietary habits and BMI alterations was found. Conversely while women maintain a nutritionally healthier lifestyle, the disease is related to a significant occupational burden. Although our tests are preliminary and our data need to be validated in a larger study cohort, the present study emphasises the importance of a personalised and holistic approach for BS management also considering the disease heterogeneity.*

Introduction

Behçet's syndrome (BS) is a rare, chronic and relapsing multisystemic vasculitis characterised by oral and genital ulcers, skin lesions, and ocular, neurological and gastrointestinal involvement. Although the exact etiopathogenesis remains unclear, it is widely recognised that environmental triggers act upon genetically susceptible individuals (*e.g.*, HLA-B51 carriers) to initiate and perpetuate the disease (1-5). Infectious agents and microbiome dysbiosis are strongly implicated (6, 7); for instance, HSV-1 DNA and specific strains of *Streptococcus* (such as *S. sanguinis* and *S. salivarius*) have been frequently isolated from oral ulcers, suggesting that microbial antigens may trigger an abnormal hypersensitivity response (6, 7). Moreover, an altered gut microbiome, characterised by a severe reduction in butyrate-producing bacteria, is believed to upregulate Th-17 cells and downregulate regulatory T (Treg) cells, thereby driving systemic inflammation (8-10). Recent literature has increasingly highlighted a significant impact of environmental factors and lifestyle habits on disease activity, severity, and the health-related quality of life (HRQoL) of BS patients (11-15). Nutrition plays a pivotal role: diets rich in anti-inflammatory components, such as fruit, vegetables, and butyrate, have been shown to modulate systemic inflammation and improve antioxidant capacity. Conversely, specific histamine-rich or sour foods have been frequently reported by patients as direct triggers for oral mucosal lesions. Alongside diet, oral hygiene is a crucial modifiable factor. Poor oral health

and chronic dental infections can exacerbate both cutaneous and systemic symptoms, whereas the regular use of topical interventions, such as specific mouthwashes, has proven highly effective in controlling oral ulcers and significantly improving patients HRQoL (3, 6, 16-19).

Gender differences also shape the clinical phenotype of BS with evidence indicating that the disease is often more frequent and severe in male patients (2), as previously reported by our group. This discrepancy may be linked to hormonal influences where testosterone could drive neutrophil activation and polarize the immune response towards a pro-inflammatory Th-1 pattern, upregulating IL-2 and IL-12 while the levels of oestrogens are able to modulate immune activity (20, 21).

Lifestyle habits such as tobacco consumption also present complex interactions with the disease. While smoking is a universally recognised cardiovascular risk factor and may worsen the neurological and vascular manifestations of BS, some studies have reported a paradoxical reduction in recurrent oral and genital aphthosis among smokers, potentially due to nicotine localised anti-inflammatory effects on keratinocytes (22-25). However overall tobacco use remains a significant risk factor for a severely decreased HRQoL and increased stress (3, 6, 16-19).

Consequently, modern management pathways for BS, which broadly follow the 2018 EULAR recommendations, increasingly emphasise the need for a holistic approach that pairs pharmacological treatments with targeted lifestyle, oral hygiene, and psychological interventions (26).

Furthermore, socioeconomic factors and occupational status represent a critical dimension of the disease burden. Chronic symptoms like arthropathy, severe fatigue and neurological involvement heavily compromise daily functioning. Consequently, unemployment and the necessity to give up work significantly reduce HRQoL in these patients (13, 27-29).

Therefore, this preliminary study aims to evaluate gender differences concerning crucial lifestyle-related aspects, such as dietary habits, physical activity, alcohol consumption, and the impact of the disease on work, within a cohort of consecutive patients with BS.

Materials and methods

An observational, cross-sectional study was conducted on a cohort of 105 consecutive adult patients (55 males and 50 females) diagnosed with BS according to International Study Group's criteria for Behçet's Disease (30). Patients were asked to complete an anonymous questionnaire designed to collect data across several the following items:

- Socio-demographics and anthropometrics: data included gender and age (stratified into range from 19-30 years to over 70 years);
- Body mass index (BMI) was calculated using the standard formula (weight in kilograms divided by the square of height in meters, kg/m^2) and categorised as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), or obese (grade I: 30–34.9, grade II: 35–39.9, grade III: ≥40);
- Dietary habits: patients reported their weekly intake of fruit and vegetables (classified as 0, 1–15, 16–29, or >30 portions per week). The survey also measured the consumption frequency of refined/ultra-processed products (*e.g.*, ready meals, baked goods, sweets) and sugary drinks, ranging from never to daily intake.
- Voluptuous habits: tobacco use was categorised into never, current smoker, former smoker, and e-cigarette user, alongside the daily quantity of cigarettes. Alcohol consumption was recorded as yes/no, with specific frequencies evaluated in weekly units.
- Physical activity: Activity levels were classified into: sedentary (no heavy physical work and no moderate/intense leisure-time exercise), partially active (light leisure-time physical activity), and physically active (heavy occupational labour, or ≥30 minutes of moderate activity for at least 5 days/week, or intense activity for >20 minutes ≥3 days/week).
- Socioeconomic/work impact: impact of the disease on employment was assessed through specific categories: no impact, reduced working hours, changed to a less stressful job, stopped working activity, or non-worker/unemployed.

All subjects gave their informed consent to this study, that has been conducted according to the Good Clinical Practices (GCP) and the Declaration of Helsinki. The Regional Ethics Committee (CEUR - Comitato Etico Unico Regionale) approved the study (permit number: 705/2017).

Statistical analysis

Data were analysed to identify gender-specific differences and lifestyle patterns. Categorical variables were expressed as frequencies and percentages. Statistical comparisons between the male and female subgroups (*e.g.*, dietary intake, BMI classes, physical activity, and occupational impact) were performed to determine significant differences. The chi-squared goodness-of-fit test was used to assess the association. The strength of association was expressed by the odds ratio (OR) with 95% confidence interval (CI). A p-values <0.05 was considered statistically significant.

Results

The survey included a total of 105 patients (55 males and 50 females). The analysis revealed several statistically significant gender differences across lifestyle parameters. Our results are summarised in Table I.

BMI and activity levels varied by gender. Grade I obesity was observed exclusively in the male group (9.1% M *vs*. 0.0% F, p=0.0289). In terms of physical activity, males were significantly more active (29.0% *vs*. 10.0%, p=0.0146), while a higher proportion of females were classified as sedentary (48.0% F *vs*. 25.5% M, p=0.0164).

Regarding dietary habits, female patients demonstrated a significantly higher consumption of fruit, with 26.0% consuming 16-29 portions per week compared to 10.9% of males (p=0.0478). Females also consumed fewer refined products, with 30.0%

Table I. Socio-demographic characteristics, body mass index and lifestyle parameters of patients with Behçet's disease in the male and female groups.

	Overall (105) n (%)	Males (55) n (%)	Females (50) n (%)	*p*-value
Age (classes)				
19-30 years	11 (10.5)	8 (14.5)	3 (6.0)	
31-40 years	24 (22.9)	10 (18.2)	14 (28.0)	
41-50 years	29 (27.6)	15 (27.3)	14 (28.0)	
51-60 years	29 (27.6)	17 (30.9)	12 (24.0)	
61-70 years	10 (9.5)	5 (9.1)	5 (10.0)	
Over 70 years	2 (1.9)	0 (0.0)	2 (4.0)	
BMI (classes)				
Underweight	2 (1.9)	0 (0.0)	2 (4.0)	NS
Normal weight	66 (62.9)	35 (63.6)	31 (62.0)	NS
Overweight	23 (21.9)	13 (23.6)	10 (20.0)	NS
Obese (grade I)	5 (4.8)	5 (9.1)	0 (0.0)	***0.0289****
Obese (grade II)	6 (5.7)	2 (3.6)	4 (8.0)	NS
Obese (grade III)	3 (2.9)	0 (0.0)	3 (6.0)	NS
Portions of fruit/week				
0	13 (12.4)	10 (18.2)	3 (6.0)	NS
1-15	73 (69.5)	39 (70.9)	34 (68.0)	NS
16-29	19 (18.1)	6 (10.9)	13 (26.0)	***0.0478****
Portions of vegetables/week				
0	7 (6.7)	5 (9.1)	2 (4.0)	NS
1-15	81 (77.1)	44 (80.0)	37 (74.0)	NS
16-29	14 (13.3)	4 (7.3)	10 (20.0)	NS
>30	3 (2.9)	2 (3.6)	1 (2.0)	NS
Consumption of refined products/week				
0	22 (20.9)	7 (12.7)	15 (30.0)	***0.0299****
1-2	44 (41.9)	24 (43.6)	20 (40.0)	NS
3-4	21 (20.0)	12 (21.8)	9 (18.0)	NS
5-6	9 (8.6)	6 (10.9)	3 (6.0)	NS
Daily	9 (8.6)	6 (10.9)	3 (6.0)	NS
Consumption of sugary drinks/week				
0	38 (38.5)	18 (16.7)	20 (73.3)	NS
1-2	40 (30.8)	24 (41.7)	16 (13.3)	NS
3-4	13 (12.8)	6 (16.7)	7 (6.7)	NS
5-6	4 (5.1)	3 (4.2)	1 (6.7)	NS
Daily	10 (12.8)	4 (20.8)	6 (0.0)	NS
Smoking				
Never	56 (53.3)	27 (49.1)	29 (58.0)	NS
Yes (currently)	16 (15.2)	9 (16.4)	7 (14.0)	NS
Yes (in the past)	22 (20.9)	13 (23.6)	9 (18.0)	NS
Yes (e-cigarette)	11 (10.5)	6 (10.9)	5 (10.0)	NS
Alcohol				
Yes	38 (46.2)	30 (58.3)	8 (26.6)	***0.0000****
No	67 (53.8)	25 (41.7)	42 (73.3)	***0.0000****
Physical Activity				
Sedentary subject	38 (36.2)	14 (25.5)	24 (48.0)	***0.0164****
Partially active	46 (43.8)	25 (45.5)	21 (42.0)	NS
Physically active	21 (20.0)	16 (29.0)	5 (10.0)	***0.0146****
Impact on Work				
No	56 (53.3)	42 (76.4)	14 (28.0)	***0.0000****
Yes (reduced working hours)	16 (15.2)	2 (3.6)	14 (28.0)	***0.0005****
Yes (changed to less stressful job)	5 (4.8)	2 (3.6)	3 (6.0)	NS
Yes (stopped working activity)	11 (10.5)	6 (10.9)	5 (10.0)	NS
No worker	17 (16.2)	3 (5.5)	14 (28.0)	***0.0017****

*Statistically significant ($p<0.05$).
NS: not significant; BMI: body mass index.

reporting zero weekly consumption versus 12.7% of males ($p=0.0299$). Conversely, alcohol consumption was significantly more prevalent among males, as 58.3% reported drinking alcohol compared to 26.6% of females ($p=0.0000$).

The impact of the disease on employment showed significant differences. A significant majority of males (76.4%) reported that the disease had no impact on their work, compared to only 28.0% of females ($p=0.0000$). Female patients challenged significantly greater occupational challenges, presenting higher rates of reduced working hours (28.0% F *vs*. 3.6% M, $p=0.0005$) and a higher prevalence of non-workers (28.0% F *vs*. 5.5% M, $p=0.0017$).

Variables such as smoking, consumption of vegetables or sugary drinks showed no statistically significant differences between the genders.

Discussion

This study underlines significant gender-specific lifestyle patterns among patients with BS. Our analysis reveals that men exhibit a lower intake of anti-inflammatory foods (such as fruit), a higher consumption of alcohol, and higher rates of grade I obesity, despite reporting greater levels of physical activity. In contrast, women reported a healthier dietary profile characterised by a higher intake of fruit and fewer refined products; however, they experienced a markedly higher socioeconomic burden, as the disease severely impacted their employment status.

Comparing these findings with the existing literature, we observed a complex interplay between lifestyle, gender, and Health-Related Quality of Life (HRQoL) in BS. Regarding dietary habits, previous surveys by Senusi et al. found that the consumption of fruit and vegetables appeared to have no direct statistical impact on HRQoL outcomes (28, 29). However, more recent literature strongly supports the biological relevance of nutrition. Di Cianni *et al*. (31) and Emmi *et al*. (3) demonstrated that an anti-inflammatory, butyrate-enriched diet improves total antioxidant capacity and reduces leukocyte oxidative stress in BS patients. In our data, male patients consume significantly less fruit and more refined, sugary products and this finding suggests that men may be more exposed to pro-inflammatory dietary triggers, potentially exacerbating the disease.

The biological severity of BS in males is well-documented and may also be driven by hormonal factors. Current evidence indicates that testosterone in male BS patients can influence neutrophil activation and polarize the immune response towards a pro-inflammatory Th-1 pattern (upregulating IL-2 and IL-

12), which might explain the generally increased disease severity in male cohort (2, 20). This biological predisposition, combined with our observed poorer dietary choices in the male group emphasizes the need for targeted nutritional interventions in male patients.

Interestingly, our study found a significantly higher prevalence of alcohol consumption among males. While alcohol is generally considered detrimental in autoimmune conditions, Senusi *et al*. reported an unexpected positive association between moderate alcohol consumption (such as wine) and better HRQoL scores in BS patients (28). This paradox was interpreted not as a direct biological benefit, but rather as an indicator that patients who consume alcohol are likely more socially integrated and active, which positively skews their self-perceived QoL.

An interesting data appears from the analysis of the male cohort regarding physical activity and metabolic outcomes. Despite men reporting significantly higher levels of physical activity compared to women (29.0% vs. 10.0%, p=0.0146) and lower sedentary rates (25.5% vs. 48.0%, p=0.0164), grade I obesity was observed exclusively among male patients (9.1% vs. 0.0%, p=0.0289). The clinical explanation for this discrepancy likely lies in their nutritional habits, which reflect a highly pro-inflammatory lifestyle. Male patients reported significantly higher alcohol consumption (58.3% vs. 26.6%, p=0.0000), lower intake of fruit (only 10.9% consuming 16-29 portions per week compared to 26.0% of females, p=0.0478), and greater consumption of refined products (p=0.0299). This suggests that the metabolic and anti-inflammatory benefits of physical activity may be severely offset by poor dietary choices. While regular exercise is an independent protective factor that significantly improves HRQoL in patients with BS, the lack of anti-inflammatory foods undermines systemic inflammation control. Recent literature confirms that an anti-inflammatory diet, particularly one enriched with butyrate and antioxidants, is crucial for reducing leukocyte oxidative stress and managing disease activity (16-19, 31-37).

A sub-analysis qualitative analysis of the dataset was conducted to evaluate lifestyle habits across BMI categories, specifically comparing normal weight *versus* overweight and obese patients. Interestingly, the data revealed a "normal-weight inflammatory paradox". While overweight and obese patients exhibited expected metabolic risk factors, such as higher alcohol intake and lower physical activity in some cases, a substantial portion of normal-weight patients, particularly younger subjects, reported highly pro-inflammatory dietary habits. These included the daily or highly frequent consumption of refined, ultra-processed foods and sugary drinks, coupled with an inadequate intake of protective, anti-inflammatory foods like fruits and vegetables (mostly confined to 1-15 portions per week across both groups). This finding is of critical clinical relevance and suggests some preliminary hypotheses to be further explored in future studies, also considering the role of patient body composition. It highlights the significance of adhering to an anti-inflammatory lifestyle in young people in order to mitigate the body systemic inflammation beyond BMI. In fact, in BS patients the frequent consumption of simple sugars and processed foods acts as a strong immunological trigger, altering the gut microbiome and increasing oxidative stress. The finding also underlines that, while BMI is a standard and widely used tool for classifying weight categories, it presents significant clinical limitations as it cannot distinguish between fat mass and lean muscle mass, nor does it assess the anatomical distribution of adipose tissue. Consequently, BMI may fail to identify individuals who are Metabolically Obese Normal Weight (MONW) whose phenotype is characterised by high visceral fat, insulin resistance, and elevated cardiovascular disease risk subjects who maintain a statistically normal weight but exhibit high visceral adiposity, metabolic dysregulation, and a pro-inflammatory state. In the context of BS, assessing actual body composition is particularly important because adipose tissue acts as an active endocrine organ and the lack of this test in the current dataset is both one of the study limitations and a point to address in future studies. Evidence shows that altered levels of adipose tissue-produced peptides (adipokines), such as leptin, resistin, and adiponectin, are actively involved in the regulation of immune processes, upregulating the production of proinflammatory cytokines and promoting the differentiation of immune cell responses in autoimmune diseases, including BS (5, 10, 17, 18, 31, 37- 39). This biological mechanism strongly supports the "normal-weight inflammatory paradox" observed in our cohort, where many normal-weight patients reported highly pro-inflammatory dietary habits, including the frequent intake of refined products and sugary drinks. Therefore, evaluating true body composition rather than relying exclusively on BMI is crucial to accurately stratify the metabolic and inflammatory risk in BS patients, as a normal weight does not preclude an underlying pro-inflammatory metabolic profile driven by poor lifestyle choices.

A significant gender disparity in our cohort was observed in the context of the disease occupational impact. While the majority of males (76.4%) reported no impact on their work, women experienced significant occupational challenges, including a higher prevalence of reduced working hours and unemployment. This finding aligns perfectly with longitudinal data from Senusi et al., which consistently demonstrated that unemployment, giving up work, or claiming disability benefits due to BS symptoms drastically reduces HRQoL (28). Furthermore, Senusi *et al*. reported that female BS patients generally have significantly lower HRQoL scores compared to males (29). The disproportionate occupational burden borne by women directly translates to financial insecurity and reduced social wellbeing, which are known drivers of poor HRQoL.

We highlight both the exploratory and preliminary nature of our findings and the study limitations: the relatively small sample size; the need to support our data by future additional analyses for stronger interpretations and conclusions; the need to better characterise the concept of the "normal-weight in-

flammatory paradox", also considering patient body composition; the need to in-depth analyse the correlation between occupation burden and disease severity in particular in female group. The evaluation of possible confounding factors (in a larger cohort), such as comorbidities, organ involvement, disease duration, disease severity could also increase the strength of our preliminary evidence.

Conclusions

Our findings highlight the critical need for targeting environmental factors in BS patients. Among the modifiable lifestyle factors, nutrition plays an essential role for human health: a diet rich in anti-inflammatory foods, such as fruit and vegetables, omega-3 fatty acids, combined with a reduction in processed foods, represents a significant factor in modulating inflammation, with a positive impact on disease activity and quality of life. The study underlines that a gender-specific approach must address biological and lifestyle factors, like improving the pro-inflammatory diet in male patients, while providing targeted socioeconomic and psychological support to mitigate the severe occupational impact observed in female patients. Nutritional screening and counselling should be implemented in BS management, targeting the correction of pro-inflammatory dietary choices not just for weight loss in obese patients, but for systemic inflammation control also in normal-weight individuals. Although these preliminary data need to be validated in larger cohorts of both BS patients and healthy controls, this study highlights the critical need for a personalised and holistic approach for a tailored management of disease.

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