



Effectiveness of the Nutraceutical *Prunella vulgaris* on Autoimmunity and Quality of Life in Women with Hashimoto Thyroiditis: Case-control Pilot Study*

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Abstract: Background: In Hashimoto's thyroiditis (HT), symptoms and impaired quality of life (QoL) are described even when thyroid hormones are in the normal range. In Chinese medicine, the nutraceutical *Prunella vulgaris* is used for its supposed anti-inflammatory and immunomodulatory activity. Aim: To evaluate the effects of *Prunella vulgaris* on autoimmunity, mainly thyroid peroxidase antibodies (TPOAb) and QoL, in HT women. Methods: Prospective open-label case-control study in 62 adult HT women randomized to the nutraceutical (group 1) or not (group 2). *Prunella vulgaris* (Tireomab-H®; 1 pill: stock 4:1 194.4 mg, powder 155.6 mg) was given at the dosage of 2 + 2 pills/day for 3 months. The women's usual therapy was not changed. Some clinical and laboratory data were collected, as were QoL scores on the ThyPRO questionnaire. TPOAb levels were evaluated as xULNR (upper limit normal range). Results: Thirty-one group 1 women and 27 group 2 women completed the study. On two ThyPRO scales (Tiredness, Emotional Susceptibility) no differences between the groups were initially noted. TPOAb xULNR values were 13.6 (median; IQR 9.1-37.8) in group 1 and 14.7 (3.6-40.0) in group 2. After 3 months, TPOAb had significantly dropped in group 1 (10.1; 4.4-36.0; P=0.002) but not in group 2 (16.3; 3.0-55.6). In group 1, 12 ThyPRO scales had significantly improved, while in group 2, all but one scale were unchanged. The other clinical and laboratory data did not change in either group. Percentage changes in TPOAb levels did not correlate with percentage changes in ThyPRO scales in either group. No adverse events were reported. Conclusions: In HT women, *Prunella vulgaris* significantly reduces TPOAb levels and improves QoL. The absence of correlation between percentage changes in TPOAb and percentage changes in ThyPRO suggests that the effect on QoL could be a direct neuroendocrine effect of the nutraceutical. More studies are needed.

Keywords: Hashimoto thyroiditis, women, *Prunella vulgaris*, autoimmunity, QoL.

INTRODUCTION

Hashimoto thyroiditis (HT) is the most common autoimmune disease and is due to the formation of anti-thyroid antibodies. Its prevalence in the general population ranges between 5% and 20%, with a 4:1 female-to-male prevalence [1]. The aetiology of HT involves genetic, environmental, nutritional and other factors [1]. Cytotoxic T cells infiltrate the

thyroid, promoting inflammation and the subsequent destruction of the follicular thyroid and inducing autoantibodies, mainly thyroid peroxidase antibodies (TPOAb), via the B cell-mediated response [2]. Normal thyroid functions, as well as a wide range of thyroid dysfunctions, may be observed at the time of HT diagnosis. Levo-thyroxine (L-T4) replacement is needed when overt hypothyroidism develops in HT [3]. By contrast, there is no strong evidence for L-T4 treatment in subclinical hypothyroidism (elevated TSH but normal thyroid hormones), especially in elderly subjects [3, 4].

Interest in non-conventional treatments of HT is increasing [5]. Among trace-elements, selenium is the most frequently used. A systematic review and meta-analysis found that selenium was effective and safe in lowering TSH, TPOAb and malondialdehyde levels in HT subjects with subclinical hypothyroidism [6]. The effect of selenium supplementation on quality of life (QoL), however, seems to be less consistent. In two studies, in which QoL was evaluated by means of an unspecified questionnaire [7] or the short-form 12 health survey questionnaire [8], marked improvements were reported. In other studies, which utilised short-form 12 or short-form 36, these data were not confirmed [9-11]. Among nutritional supplements, *Prunella vulgaris* (Pv), a perennial herbaceous plant of the *Lamiaceae/Labiateae* family with a wide range of pharmacological applications [12] has long been used in Chinese traditional medicine. Pv seems to possess antioxidant, anti-inflammatory and immunosuppressive properties, and is increasingly playing a therapeutic role in thyroid diseases [13]. In rat plasma, injection of an aqueous extract of Pv has been reported to down-regulate TSH and thyroid antibodies [14]. Moreover, rosmarinic acid, one of the bioactive compounds identified in Pv, has been seen to reduce pro-inflammatory cytokines both *in vivo* and *in vitro* [15]. In addition, in experimental studies involving human thyrocytes, some other bioactive components of Pv (quercetin, luteolin, morin and β -sitosterol) have proved to exert anti-inflammatory and anti-apoptosis effects that are potentially useful in HT treatment [16].

Despite of these interesting experimental data and the proposed use of Pv in HT in randomized clinical trials [17], to our knowledge, no published data are as yet available. Our aim was to carry out a pilot study in women with HT in order to evaluate the potential effect of Pv on some clinical and laboratory parameters. In addition, considering the above-reported inconclusive results regarding QoL in HT patients on selenium supplementation, we also investigated the potential effect of Pv on QoL. The patient-reported outcome (PRO) measure for benign thyroid disorders (ThyPRO) questionnaire was employed. ThyPRO is a validated instrument for use in patients with thyroid diseases [18, 19], and in a group of HT subjects - mainly women, 77% of whom were on L-T4 treatment - Watt et al. [20] observed that some QoL scores were significantly positively related to TPOAb levels.

MATERIALS AND METHODS

Patients

Eighty-one adult women (>18 years of age) with a history of HT were asked to participate in the study at the time of their scheduled endocrinological examination in our private setting. Inclusion criteria were: written consent to the study, positive TPOAb levels, non-pregnant condition in pre-menopausal women, absence of other acute diseases, non-use of other nutraceuticals, including selenium-containing products, and the availability of an e-mail address. Sixty-five women accepted and were randomized 1:1 to receive the nutraceutical

Pv, in addition to their usual therapies if already prescribed (group 1), or nothing, if no other usual medicines were prescribed (group 2). Three women withdrew their consent before the study began. Thirty-two women were assigned to group 1 (cases) and 30 to group 2 (controls). During the study, one woman in group 1 and two in group 2 were lost to follow-up. Another group-2 woman was excluded as routine breast screening proved suspicious for malignancy. Table 1 reports some clinical data of the women fully evaluable (group 1 $n=31$, group 2 $n=27$).

Protocol

The study consisted of two scheduled clinical examinations three months apart. During the first examination, the women randomized to group 1 received the nutraceutical *Pv* (Tireomab-H®; Phytoitalia, Corbetta. Italy) in pill form. Each pill contained 194.4 mg of dry extract (4:1) and 115.6 mg of powder. The daily dosage was: 2 pills early in the morning and 2 pills late in the evening for 3 months. The timing and dosage of any other ongoing drugs, including L-T4, were not changed. Thyroid sonography was performed to calculate thyroid volume (TV). At both the initial and final examinations, the ThyPRO questionnaire was administered in order to obtain a self-report of QoL. After 1 month, all patients were contacted by e-mail in order to assess their adherence to the protocol, to record possible adverse events and, in group 1, to obtain consent to provide further pills. Fasting blood samples were drawn before the initial and final examinations in order to collect plasma, which was stored frozen and shipped to the University of Padua for cytokine and TgAb evaluation. Blood samples for TPOAb and other laboratory variables were simultaneously collected and analysed locally.

Outcome Variables

In this case-control prospective open-label protocol, we mainly evaluated TPOAb and QoL. QoL was assessed by means of the ThyPRO questionnaire. The clinical variables recorded were: body mass index (BMI; kg/m^2), sitting blood pressure (mmHg), resting heart rate (beats/min) and TV (ml). A detailed list of ongoing therapies was requested. Sensitivity C-protein reactive (PCR; ng/ml) levels were evaluated in order to exclude active inflammatory conditions. Free-thyroxine (f-T4; pg/ml), TSH (mIU/l) and thyroglobulin antibodies (TgAb: IU/ml) were evaluated in order to monitor the function and autoimmunity of the thyroid. Chemokine ligands 9 (CXCL9; pg/ml) and 11 (CXCL11; pg/ml) were evaluated, as these are reported to be increased in HT [21].

Measurements and Assays

Changes in QoL were measured by means of the Italian version of ThyPRO [19]. This questionnaire consists of 85 questions, grouped into 13 multi-item scales. The ThyPRO scales cover the following domains: Goiter symptoms, Hyperthyroid symptoms, Hypothyroid symptoms, Eye symptoms, Tiredness, Cognitive problems, Anxiety, Depressivity, Emotional susceptibility, Impaired social life, Impaired daily life, Impaired sex-life, and Cosmetic complaints. Each item is rated on a 5-point scale from 0 (not at all) to 4 (very much), and refers to the last 4 weeks. Linearly transformed scores range from 0 to 100, with higher

scores indicating more severe thyroid-related complaints. TV was measured as already reported [22]. Several commercial assays were used to evaluate TPOAb levels, each applying different upper limits of the normal range (ULNR). Data are reported as xULNR, to reduce inter-assay variability. When TPOAb values were unexpectedly low or high, samples were re-evaluated by means of Liaison®Anti-TPO (DiaSorin, Saluggia, Italy). TgAb were evaluated by means of Liaison®Anti-Tg (DiaSorin, Saluggia, Italy) and reported as IU/ml, with a 5-100 IU/ml range. Plasma concentrations of CXCL9 and CXCL11 were measured by means of commercially available quantitative sandwich enzyme-linked immunosorbent assays (RayBIO® Human MIG/CXCL9 and RAYBIO® Human I-TAC/CXCL11; Ray Biotech, Norcross, GA, USA). The minimum detectable amounts of CXCL9 and CXCL11 were 20 pg/ml and 2 pg/ml, respectively. TSH and f-T4 were evaluated by chemiluminescence immunoassay methods. Normal regional TSH values in women have been published [23], the normal f-T4 range being 8.0-17.0 pg/ml. PCR was evaluated by means of a turbidimetry method (QuantILab, Instrumentation Laboratory, Ascoli Piceno, Italy), normal values and sensitivity being <5 mg/l and 0.1 mg/l, respectively.

Statistical Analysis

GraphPad Prism 11 software (GraphPad, San Diego, CA, USA) was used for statistical analysis. Data are reported as mean $\pm$ standard deviation (SD), median and IQR. Comparison between groups was performed by means of the non-parametric Mann-Whitney test. Comparison between data from the initial and final examinations was performed by means of the non-parametric Wilcoxon signed-rank test. Percentage changes in TPOAb and ThyPRO scales were calculated by applying the formula: (final value - initial value)/initial value $\times$ 100. Percentages were compared by means of Fisher's exact test. Correlations were evaluated by means of Spearman's rank correlation test. Significance was set at $P \leq 0.05$.

Ethics Approval

The administration of nutraceuticals is regulated differently from drugs, according to the European multilingual directives of 20 December, 2006 (<http://data.europa.eu/eli/reg/2006/1924/oj>). Local Ethics Committees do not require registration of studies involving nutraceuticals. Before randomization, our participants and their general practitioners received written information about the protocol and signed an informed consent form, thereby consenting to the management of data collected from their medical files and to their use for scientific purposes. Data were managed anonymously. Data collection and subsequent analysis were performed in compliance with the Declaration of Helsinki. A retrospective registration on Chinese Clinical Trials 334646 2026-07-25 was requested.

RESULTS

Clinical Changes during the 3-month Protocol

At the initial clinical evaluation, BMI was slightly, but not significantly, higher in group 1 than in group 2 (Table 1). At the final evaluation, BMI had slightly decreased both in group 1 (24.0; 22.7-28.0; $P=0.23$) and in group 2 (23.0; 20.5-26.0; $P=0.17$), the difference between

the groups being significant ($P=0.05$). No significant differences in TV were noted. Regarding blood pressure and heart rate, no significant differences were noted between the groups (data not shown). In group 1, L-T4 was started in one patient. At the end of the study, the median L-T4 dosages per week were 500 µg (313-700 µg) in group 1 ($P=0.99$) and remained unchanged in group 2, without differences between the groups ($P=0.93$). No adverse events were reported in either group during the 3-month study.

Laboratory Changes during the 3-month Protocol

Serum f-T4 levels remained unchanged from the baseline (Table 1) to the end of the study both in group 1 (10.7 pg/ml; 9.3-12.0 pg/ml; $P=0.83$) and in group 2 (10.8 pg/ml; 9.3-13.8 pg/ml; $P=0.27$), without differences between the groups ($P=0.52$). At the end of the study, TSH levels were unchanged in group 1 (2.91 mIU/l; 1.74-4.20 mIU/l; $P=0.45$) and slightly, but not significantly ($P=0.07$), increased in group 2 (2.59 mIU/l; 1.58-5.15 mIU/l). However, at the end of the study, TSH levels were not significantly different ($P=0.99$) between the groups. Serum PCR levels were unchanged from the baseline (Table 1) to the end of the study both in group 1 (0.8 mg/l; 0.4-2.0 mg/l; $P=0.99$) and in group 2 (0.5 mg/l; 0.3-0.9 mg/l; $P=0.62$), without differences between the groups ($P=0.23$). TPOAb levels, expressed as xULNR at the beginning and end of the protocol in both groups, are reported in Figure 1. A slight but significant decrease in TPOAb levels was noted in group 1 ($P=0.02$) but not in group 2 ($P=0.58$). At the end of the study, no significant difference was observed between the groups ($P=0.62$). The percentage of subjects in whom TPOAb levels decreased during the protocol was significantly higher in group 1 (74.2%) than in group 2 (33.3%; $P=0.003$). TgAb levels were unchanged in group 1 (140.6 IU/ml; 65.9-274.7 IU/ml; $P=0.779$) and in group 2 (139.9 IU/ml; 56.4-767.6 IU/ml; $P=0.66$), and were superimposable between the groups ($P=0.99$). CXCL9 (536.5 pg/ml; 356.8-1783.0 pg/ml; $P=0.83$) and CXCL11 (10.8 pg/ml; 4.7-569 pg/ml; $P=0.69$) levels were unchanged in both groups (CXCL9 659.6 pg/ml; 384.0-944.3 pg/ml; $P=0.38$. CXCL11 10.2 pg/ml; 3.6-44.5 pg/ml; $P=0.70$) and were superimposable between the groups (CXCL9 $P=0.78$; CXCL11 $P=0.47$).

QoL Changes during the 3-month Protocol

Four ThyPRO questionnaires were not filled in at the final evaluation ($n=3$ in group 1, $n=1$ in group 2). Radar plots (Figure 2) report the median changes in the 13 ThyPRO scales from the beginning to the end of the study in both groups. Figure 2 shows a reduction in scales only in group 1. No significant difference in scales was noted between the groups at the start of the study, except for the Tiredness symptoms scale (group 1: 39.3; 32.1-57.4; group 2: 31.6; 28.6-42.9; $P=0.02$) and the Emotional susceptibility scale (group 1: 38.9; 27.8-55.6; group 2: 25.4; 16.7-41.7; $P=0.03$). A significant reduction was noted in group 1 in all but one scale (Impaired social life: start 0.0; 0.0-31.3; end 0.0; 0.0-12.5, $P=0.089$). Regarding the scales, the level of significance of the reduction in scores ranged from $P=0.02$ (Goitre symptoms, Impaired sex life) to <0.0001 (Hypothyroid symptoms, Tiredness symptoms, Cognitive problems, Anxiety, Emotional susceptibility, Cosmetic complaints). In group 2, all but one ThyPRO scale were non-significantly changed during the protocol; the Tiredness symptoms scale showed significant worsening (initial 32.1; 28.6-42.9; final 39.3; 28.6-57.1; $P=0.05$). The ThyPRO questionnaires collected the end of the study showed significantly ($P=0.03$) lower scores on the scale of Cognitive problems in group 1 (8.3; 0.5-20.9) than in

group 2 (16.7; 7.3-50.0). Except for the Depressivity and Impaired social life scales, the median scores were lower in group 1 than in group 2 on all other scales. On the scales Anxiety ($P=0.07$) and Impaired daily life ($P=0.06$), the difference was near to significance.

ThyPRO and QoL Correlations

At the beginning of the study, ThyPRO scales were not related to TPOAb levels when all subjects were evaluated together. However, when the correlation between ThyPRO and TPOAb was evaluated separately in each group, only the scale Impaired sex life was negatively related to TPOAb ($n=31$, $R_s -0.42$; $P=0.02$) in group 1. In both groups, changes in TPOAb xULNR were not related to changes in QoL scales. Only the Cognitive problems scale approached significance ($P=0.08$) in group 1.

DISCUSSION

Pv, a traditional Chinese medical herb, seems to exert beneficial effects in human beings in a wide spectrum of thyroid diseases. In a meta-analysis of 13 studies, a *Pv* preparation combined with L-T4 was seen to reduce the diameter of thyroid nodules more than L-T4 alone [24]. However, Han et al. [24] underlined the low quality of the studies included in their meta-analysis. Another systematic review and meta-analysis, involving 17 randomized controlled trials, showed that treating autoimmune hyperthyroidism with *Pv* (from 2 to 24 months; median 3 months) in combination with anti-thyroidal drugs was superior to drug treatment alone in improving thyroid function, thyroid antibodies, thyroid gland size, inflammation and the incidence of adverse effects [25]. A potential use of *Pv* in thyroid-associated ophthalmopathy has emerged from *in vitro* studies with fibroblasts collected from patients with thyroid-related eye disease [26]. Cell growth was inhibited and apoptosis was promoted when *Pv* polysaccharides ($>400 \mu\text{g/ml}$) were added in co-culture to dexamethasone and interferon- γ [26]. Finally, in a study of 89 tissue samples of papillary thyroid cancer, *Pv* was seen to target genes associate with β -sitosterol, thereby reducing mechanisms linked to cell-growth and metastasis-related behaviour [27].

Our case-controlled open study conducted in two groups of adult women seems to be the first attempt to test the effects of *Pv* [194.4 mg of dry extract (4:1) and 115.6 mg of powder] in HT, in which a potential role has been hypothesized [17] but never demonstrated *in vivo*, to our knowledge. TPOAb, but not TgAb, were significantly reduced in women after 3-month *Pv* administration. Although spontaneous oscillations of TPOAb titres cannot be excluded, such changes seem to be prevalent in *Pv*-treated women. Few HT women were involved in this pilot study, and no sub-analysis of women also treated/untreated with L-T4 was done. A similar TPOAb reduction after 3-month selenium supplementation has been noted in both L-T4-treated and non-L-T4-treated HT subjects [28]. The effect of selenium or *Pv* on immunomodulation for longer periods of administration is unclear, and it remains to be seen whether these effects, both in our study and in others [6, 28], correlate with clinically relevant effects.

Chronic thyroid diseases, such as HT, impair thyroid function [1] and QoL [29, 30] and the role of selenium supplementation on QoL is debated [7-11]. In our pilot study, 3-month *Pv* administration significantly improved QoL, as evaluated by means of the ThyPRO questionnaire, independently of TPOAb changes and TSH/f-T4 levels. Interestingly, the

Tiredness scale significantly improved in group 1 and significantly worsened in group 2, further indicating the positive effect of *Pv* on QoL in HT women.

The ThyPRO questionnaire was tested in HT by Cui et al. [31], who found a slight positive correlation between the Tiredness scale and TSH levels and an association between greater QoL deterioration and lower free-triiodothyronine concentration. Like us, Watt et al. [20] observed that some symptom scales (Goitre symptoms, Depressivity and Anxiety) in HT patients with a wide range of TPOAb levels (0-21952 U/l) were positively related with TPOAb levels but not with thyroid function. We can hypothesize that one or more chemical compounds present in Tirogab H® exerted a central effect, alleviating the subjective symptoms which impaired QoL in our HT women. The impact of anti-thyroid antibodies in brain tissues as a possible explanation for psycho-neurological disorders in patients with HT is debated [32]. We have no data to support this hypothesis, and testing TPOAb in liquor was beyond the scope of our study.

While *Pv* is reported to suppress the gene expression of inflammatory cytokines in human thyrocytes *in vitro* [16], *in vivo* studies on inflammatory factor in HT subjects on *Pv* treatment are largely heterogeneous; indeed, unchanged IL-6 and TNF- γ , increased IL-10 and reduced TNF- α have been reported [25].

Chemokines are small cytokines involved in the immune response [33]. CXCL9 and CXCL11 have been reported to be increased in HT [21]. Our study, however, did not show any effect of *Pv* on these chemokines, though these results need to be confirmed in a larger group of HT women. Similarly, other clinical and laboratory variables evaluated did not yield significant information. In contrast, some authors have reported changes in thyroid nodules and TV on *Pv* administration and changes in BMI. In the paper by Wei et al. [25], changes in thyroid dimensions during *Pv* administration were evaluated, but TV was not reported and the observation of a reduced length of the right thyroid lobe remains inconclusive. Similarly, the quality of studies aimed at assessing the beneficial effect on thyroid nodules of *Pv* added to L-T4 makes this research inconclusive [24].

It is well known that obesity promotes inflammation and is related to several autoimmune diseases, including HT [34]. In our study, PCR, as an index of low-grade inflammation, was normal and was not influenced by *Pv*. Moreover, BMI did not change in either group during the study, though it was slightly greater in *Pv*-treated women than in controls at the final examination. This phenomenon seems to be linked to the individual's life-style. As yet, no specific diet is recommended for patients with HT, though a protective effect of an anti-inflammatory diet rich in vitamins and minerals and low in foods of animal origin has been suggested [35]. To date, there are no data on *Pv* supplementation and BMI. The role of the caffeic acid extract in *Pv*, which is reported to increase serum insulin levels [13], on BMI has not been studied in HT. The role of quercetin extract from five herbs, including *Pv*, on efferocytosis -a process in which macrophages recognize and engulf apoptotic cells [36]- can only be hypothesized in HT-associated obesity [37].

The present study has several limitations. The positive findings on QoL observed in women under *Pv* must be taken into consideration that study employs an open-label, non-placebo-controlled design. Therefore, without blinding and a placebo arm, could be more difficult to distinguish a genuine pharmacological effect of *Prunella vulgaris* on QoL from a non-specific placebo response driven by positive expectation. No pairwise analysis of L-T4-treated and L-T4-untreated women was performed, owing to the small size of the subgroup.

Some variables were not considered (e.g. income, family status, education, smoking) and only a few variables were centralized in a single laboratory.

CONCLUSIONS

In conclusion, our pilot study underlines the potential role of *Pv* in HT, confirming preliminary data in autoimmune thyroid disease [17, 25, 26]. The herbal properties of *Pv* significantly reduce TPOAb levels. The effects of *Pv* on TPOAb are similar to those reported for selenium supplementation [6, 28]. The significant improvement of QoL on *Pv* administration, which was not related to a reduction in TPOAb titres, suggests a direct neuroendocrine effect of neuro-trophic substance(s) contained in the nutraceutical. Our data need to be confirmed in a larger number of subjects, in order to overcome the limitations of the present preliminary study. A further step could be a multicentre randomized case-control prospective study in which the effects of *Pv* could be monitored over a longer period of time and assessed after *Pv* withdrawal.

ABBREVIATIONS

HT: Hashimoto's thyroiditis

QoL: Quality of life

ThyPRO: Thyroid Patient-reported outcome

ULNR: Upper limit normal range

TPOAb: Thyroid peroxidase antibodies

TSH: Thyroid-Stimulating Hormone

L-T4: Levo-thyroxine

Pv: *Prunella vulgaris*

BMI: Body mass index

TV: Thyroid volume

PCR: C-protein reactive

F-T4: free-thyroxine

TgAb: thyroglobulin antibodies

CXCL9: chemokine ligands 9

CXCL11: chemokine ligands 11

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Data Availability Statement: The dataset used or analysed during the current study is available from the corresponding author upon reasonable request.

Compliance with Ethics Guidelines: All procedures were carried out in accordance with the ethical standards of the institution and with the 1975 Helsinki Declaration, as revised in 2008. Informed consent was obtained from all participants. The authors declare that they have no conflicts of interest. This article does not include any studies involving human or animal subjects conducted by any of the authors.

Consent to Participate: All study participants provided informed consent.

Consent for Publication: All study participants have consented to the publication.

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Table 1: Some clinical and laboratory data collected at the initial evaluation of the *Pv* study in group 1 (n=31 cases) and group 2 (n=27 controls) women with HT history. Data are reported as median and IQR if not already reported. Exact P values are reported.

	Group 1	Group 2	Significance P
Age, years (mean $\pm$ SD)	53.2 $\pm$ 9.4	52.7 $\pm$ 11.9	0.87
Years since HT diagnosis	11.5 (3.0-20.0)	5.5 (3.0-9.8)	0.18
BMI, kg/m ²	24.8 (22.4-29.7)	23.6 (20.8-26.2)	0.07
Thyroid volume, ml	8.1 (6.3-12.0)	8.9 (5.8-12.3)	0.98
Women on L-T4 (percentage)	61.3	62.9	0.99
L-T4 μ g/week	600 (300-700)	480 (350-650)	0.78
f-T4, pg/ml	10.1 (9.7-11.8)	10.0 (8.3-12.4)	0.68
TSH, mIU/l	2.40 (1.32-4.30)	2.18 (1.34-3.95)	0.77
PCR, mg/l	0.9 (0.4-1.6)	0.6 (0.3-0.92)	0.14
TPOAb, xULNR	13.6 (6.4-37.8)	14.7 (3.6-40.0)	0.52
TgAb, IU/ml	146.0 (59.9-261.2)	145.3 (65.8-646.1)	0.79
CXCL9, pg/ml	548.0 (351.0 - 1050.0)	778.5 (392.0-1044.0)	0.47
CXCL11, pg/ml	12.8 (5.8-59.6)	11.4 (4.9-31.2)	0.35

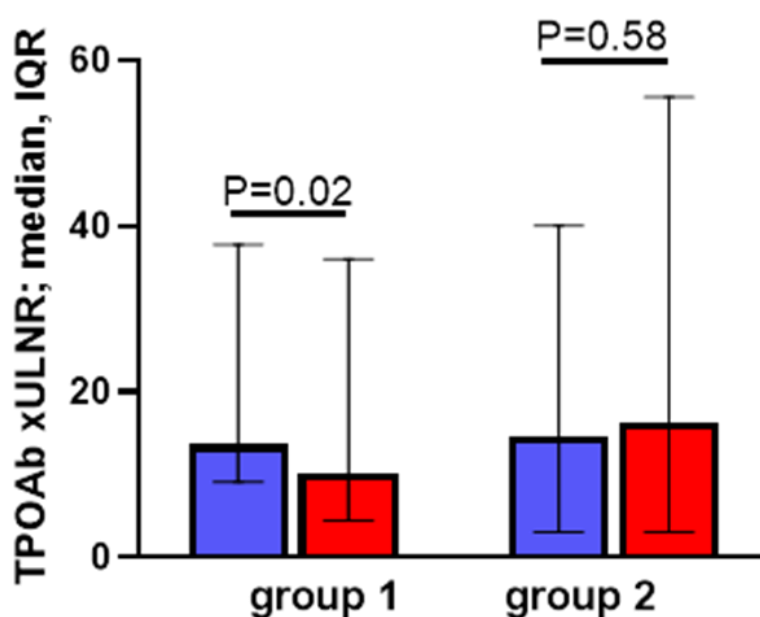


Figure 1: Median (IQR) of TPOAb levels, expressed as xULNR, in group 1 and group 2 at the beginning (blue boxes) and end (red boxes) of the *Pv* study.

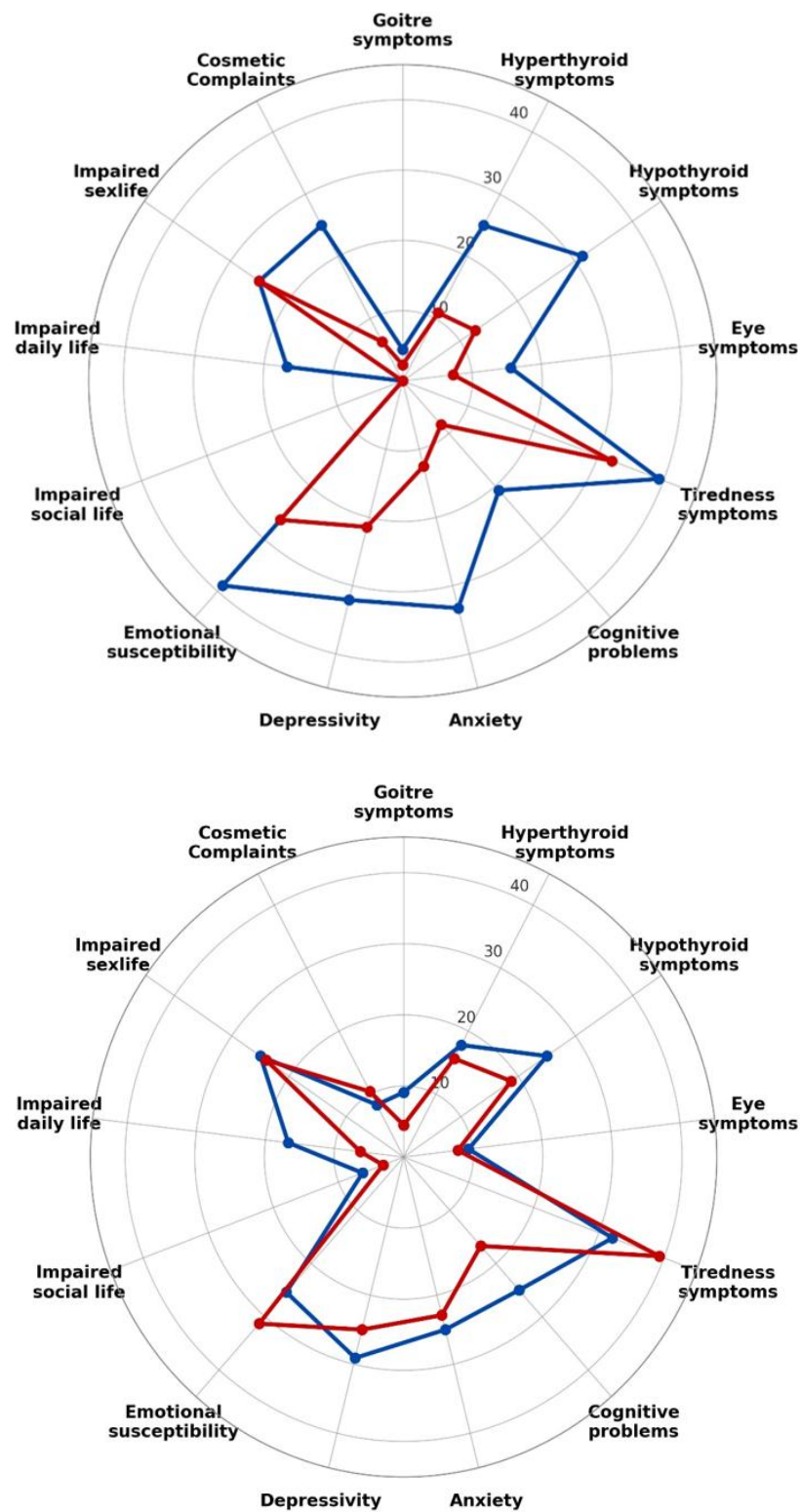


Figure 2: Radar plots of the median of the ThyPRO scales in group 1 (upper panel) and group 2 (lower panel). Blue and red lines indicate the median of the first and last questionnaires fitted.