Marked improvement of thyroid function and autoimmunity by Aloe barbadensis miller juice in patients with subclinical hypothyroidism

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**A B S T R A C T**

Some natural compounds decrease serum levels of thyroid autoantibodies, but results are inconsistent and thyroid function has been evaluated infrequently; moreover, the effects of Aloe on thyroid autoimmunity and function have been examined in very few studies. This study stems from the observation of one co-author, who has Hashimoto’s thyroiditis (HT)-related subclinical hypothyroidism (SCH). Upon checking her biochemical thyroid panel when taking daily Aloe barbadensis Miller juice (ABMJ) for thyroid-unrelated reasons, she noticed a decrease in serum thyroperoxidase autoantibodies (TPOAb) and thyrotropin (TSH) and an increase in serum free thyroxine (FT4). Based on this observation, we enrolled 30 consecutive HT women with levothyroxine-untreated SCH and high TPOAb levels. All of them took ABMJ (50 ml daily) for nine months and were tested for serum TSH, FT4, free triiodothyronine (FT3) and TPOAb. Measurements were performed at baseline and at months 3 and 9. TSH, FT4 and TPOAb improved significantly already at month 3 and further (~61%, +23% and −56%) at month 9. However, FT3 decreased significantly at month 3 (~16%) with no further decrease at month 9, so that the FT4:FT3 ratio increased significantly (+33% and +49%). At baseline, 100% of women had TSH > 4.0 mU/L and TPOAb > 400 U/ml, but frequencies fell to 0% and 37%, respectively, at month 9. In contrast, a control group (namely, 15 untreated SCH women of comparable age and baseline levels of TSH, FT4, FT3 and TPOAb) had no significant changes in any index. We conclude that the daily intake of 100 ml ABMJ for 9 months in women with HT-related SCH decreases the burden of thyroid autoimmune inflammation. In addition, ABMJ rescues thyrocyte function, with decreased need for conversion of the prohormone T4 into the more active T3 through ABMJ-induced inhibition of T4 deiodination.

**Introduction**

*Aloe* is a very old plant with medicinal properties that was discovered by the ancient Egyptians, who called it “the plant of immortality” [1]. The botanical name of *Aloe vera* is *Aloe barbadensis* Miller. It belongs to the Asphodelaceae (Liliaceae) family, and is a shrubby or arborescent, perennial, xerophytic, succulent, pea-green color plant. It grows mainly in the dry regions of Africa, Asia, Europe and America [1]. Records of its use were engraved in tablets thought to be from 2100 B.C. *Aloe* then travelled to various parts of the globe, and starting from the 17th century it had become a common medicinal plant [2]. The name *Aloe vera* derives from the Arabic word “Alloeh” meaning “shining bitter substance” and from the Latin word “vera” meaning “true.” Two millennia ago, Greek scientists regarded *Aloe vera* as the universal panacea [1]. Egyptian queens Nefertiti and Cleopatra used *Aloe* as part of their regular beauty regimes. Alexander the Great and Christopher Columbus used it to treat soldiers’ wounds. The first reference to *Aloe vera* in the English literature dates back to 1655, when John Goodyer translated the Dioscorides’ Medical treatise *De Materia Medica*. By the early 1800s, *Aloe vera* was in use as a laxative in the United States, and in the mid-1930s it was successfully employed to treat chronic and severe radiation dermatitis [1].

*Aloe Barbadensis* leaf juice is extracted from the leaves of the aloe plant. *Aloe Barbadensis* leaves contain over 200 nutritional substances, including 20 minerals (particularly iron, chromium, zinc, selenium, copper, manganese, magnesium, sodium, potassium, and calcium), 20
Aloe vera, a common comestible plant, belongs to the Xanthorrhoeaceae family and is native to the Indian subcontinent. This plant has been used by humans for centuries due to its many health benefits. It contains many bioactive compounds, such as saponins, salicylic acids, and others [1]. Interestingly, the thyroid hormone-forming tyrosine is the rarest amino acid present in Aloe Barbadensis leaves (28 µmol/100 g), while arginine is the main one (449 µmol/100 g) [3]. The anti-oxidant and/or anti-inflammatory properties of Aloe vera are explained by its content in vitamin A, C, and E, in the glycoprotein C-glucosyl chromone, in certain sterols (campesterol, β-sitosterol, and lupeol), vegetable hormones (auxins and gibberellins) and bradykinin. Campesterol, β-sitosterol, lupeol and two antrachinones (aloin and emodin) act as analgesics and antiseptics [1]. These sterols are also found in shea butter and sabal/saw palmetto (Serenoa repens) [4,5]. Further details can be found in the Volume 1 of WHO (World Health Organization) Monographs on Selected Medicinal Plants [6]. As reviewed elsewhere [1], some uses of Aloe vera are based on scientific evidence in humans and/or animals, while other uses are based on tradition. Scientific-based therapies for Aloe vera include seborrhic dermatitis, psoriasis vulgaris, genital herpes, skin burns, wound healing, pressure ulcers, mucositis, radiation dermatitis, acne vulgaris, lichen planus, frostbite, apthous stomatitis, type 2 diabetes mellitus, HIV infection, cancer prevention, ulcerative colitis and constipation. Traditional-based therapies for Aloe vera include alopecia, bacterial and fungal skin infections, parasitic infections, chronic leg wounds, systemic lupus erythematosus, arthritis and tic douloureux.

A number of natural compounds/nutraceuticals are being used to treat autoimmune thyroid diseases (AIT), namely Graves’ disease (GD), GD-associated ophthalmopathy, HT and postpartum thyroiditis (PPT) [7–29]. Though an exhaustive list of these substances goes beyond the scope of the present paper, examples of them include omega-3 fatty acids-rich small oily fish [7,8], L-carnitine [9–11], selenium [12–29], and myoinositol [27–29]. However, the observation that prompted the present study stemmed from a fortuitous observation (Table 1). One of the authors of the present paper, who has a history of HT-associated initial, mild hypothyroidism (also called subclinical hypothyroidism [SCH]), decided to take Aloe Barbadensis Miller juice (ABMJ), at the dose of 50 ml every morning on an empty stomach, as a skin soother and laxative. No other medications or over-the-counter compounds were taken. She checks thyroid function and thyroxoperoxidase autoantibodies (TPOAb) semiannually, since in one relative progression to overt hypothyroidism was preceded by a frank fall in FT4 and increase in both TSH and TPOAb approximately six months earlier. At the biochemical check performed three months after having started taking ABMJ, she was struck by the remarkable improvement of all indices (Table 1). The improvement was even more impressive six months later (Table 1).

Based on this positive experience, we decided to test the effects of ABMJ administration in HT women with levothyroxine-un treated SCH and high levels of TPOAb.

Materials and methods

Materials

The ABMJ taken by all patients was Aloe Vera2 by ZUCCARI (Trento, Italy). Each 100 ml preparation of ABMJ, which has an energetic value of 7.40 kcal (31.20Kj), contains nonpasteurized and noncarbon filtered Aloe vera leaf juice and pulp (49.8 g), 0.2 g fats (0% saturated), 1.2 g carbohydrates, zero proteins, and 0.06 g minerals (of which, 0.02 g sodium). The juice also contains citric acid as an acidifier and sodium benzoate and potassium sorbate as typical preservatives with biocidal properties. Noteworthy, Aloe Vera2 is free of aloin, a substance primarily contained in the outer cuticles of the leaves that is irritating to the intestinal mucosa. Once opened, the one-liter bottle has to be stored in the refrigerator, as recommended by the producer.

Patients

Based on the observations summarized in Table 1, we aimed to recruit women, aged 30 to 55 years and with HT-associated SCH (TSH > 4.0 mU/L; high levels of TPOAb), who had never been treated with L-T4 and/or supplements. In addition to past and current treatment with L-T4 and/or supplements, exclusion criteria were: (i) concurrent diseases, including diabetes mellitus and other autoimmune diseases; (ii) use of any nutraceuticals/drugs that affect the hypothalamic-pituitary-thyroid axis and autoimmunity. These criteria were verified with the family physicians.

Patients were informed of the aforementioned initial observation and enrolled upon signing an informed consent form. Thirty women, aged 20 to 55 years, were enrolled and all of them completed the study. They were treated with 50 ml ABMJ (Aloe Vera2), which was taken in the morning on an empty stomach. To minimize confounding factors, all patients were directed to the same natural product health store where the said co-author bought ABMJ. The natural product health store personnel informed us that each patient had bought enough bottles to complete the study. Parallelizing the initial observation, the duration of study was 9 months, with serum TSH, FT3, FT4 and TPOAb measured at baseline (time zero), and 90 ± 3 days (3 months) and 180 ± 3 days (9 months) later. Measurement of FT3 was added for sake of completeness.

For the purpose of comparison with a group of Hashimoto’s thyroiditis women who were under no thyroid hormone replacement therapy and no supplementation with nutraceuticals, we took advantage of a database on patients with Hashimoto’s thyroiditis (Interdepartmental Program of Molecular & Clinical Endocrinology and Women’s Endocrine Health, University hospital of Messina). Based on age and levels of the fundamental indices (serum TSH and TPOAb) at time zero, the 30 Aloe-treated women could be matched to 15 women with SCH of comparable age (21–57 years) and baseline levels of serum TSH and TPOAb that had been measured with the same corresponding kits.

Assays

Serum TSH, FT4, FT3 and TPOAb were assayed using electrochemiluminescent kits (Roche, Mannheim, Germany). Reference values were 0.27–4.2 mU/L for TSH, 9.3–17.1 pg/ml (12–22 pmol/L) for FT4, 2.0–4.4 pg/ml (3.1–6.8 pmol/L) for FT3, and 0–100 U/ml for TPOAb. To avoid intra-assay variations, sera were stored at −20 °C, and all 90 sera for each analyte (30 patients × 3 time points) were assayed in one

| Table 1 | Summary of the Aloe vera barbadensis Miller juice-induced changes in the biochemical thyroid profile of one author of the present paper and that prompted the study described herein. |
| --- | --- |
| Follow-up | Before use of Aloe juice | During use of Aloe juice |
| Range (min - max) | Last value | First value | Last value |
| TSH, mU/L | 4.3–5.5 | 5.14 | 3.22 | 1.83 |
| FT4, pmol/L [7–19] | 7.9–8.3 | 8.3 | 8.9 | 11.44 |
| FT3, pmol/l [2.7–6.4] | 5.0–5.25 | 5.22 | 5.0 | 4.78 |
| TPOAb, U/ml [0–35] | 1,256–1,875 | 1,875 | 778 | 246 |

* Follow-up prior to use of the aloe juice (50 ml twice a day) spans 14 months, respectively. The first value of each thyroid index under the juice regimen was recorded 3 months after having started taking the juice; the last value was recorded 9 months after having started taking the juice. Numbers in brackets are the reference ranges.
Table 2

Changes observed in the specific biochemical thyroid indices (all analyzed as continuous variables) during and at the end of a 9-month duration administration of Aloe vera-barbadensis Miller juice in 30 women with Hashimoto’s thyroiditis-related subclinical hypothyroidism (HT-SCH), and in a control group of 15 women under no L-T4 therapy or any nutraceutical supplementation.\(^a\)

| Statistics (P value) | 3 Months vs baseline | 9 Months vs baseline | 9 vs 3 months |
|---------------------|----------------------|---------------------|--------------|
| **Study group**     |                      |                     |              |
| TSH, mU/L           | 5.20 ± 0.65 (5.12)   | 3.02 (3.12; -42%)   | 2.01 ± 0.57 (2.99; -40%) |
| FT4, pmol/L         | 9.63 ± 1.58 (9.17)   | 10.67 ± 1.31 (10.53; +11%) | 11.83 ± 1.50 (11.54; +23%) |
| FT4:FT3 ratio       | 1.83 ± 0.32 (1.80)   | 2.47 ± 0.46 (2.39; +35%) | 2.78 ± 0.63 (2.69; +52%) |
| TPOAb, U/ml         | 939 ± 140 (930)      | 914 ± 135 (902)     | 977 ± 178 (962) |
| **Control group**   |                      |                     |              |
| TSH, mU/L           | 5.44 ± 0.86 (5.40)   | 5.43 ± 0.78 (5.60)  | 5.80 ± 1.18 (5.84) |
| FT4, pmol/L         | 9.58 ± 1.48 (9.04)   | 9.65 ± 1.46 (9.03)  | 9.39 ± 1.59 (8.78) |
| FT4:FT3 ratio       | 1.81 ± 0.26 (1.78)   | 1.85 ± 0.30 (1.70)  | 1.75 ± 0.32 (1.69) |
| TPOAb, U/ml         | 993 ± 140 (990)      | 985 ± 135 (983)     | 977 ± 135 (982) |

\(^a\) Individual changes are illustrated in Fig. 1.

Statistics

- Differences between m ± SD of continuous variables were analyzed by ANOVA or by the Wilcoxon signed rank test for the indices with non-gaussian distribution (TSH and TPOAb). Differences between proportions were analyzed by the two-tailed Fisher’s exact test. The threshold for significance was set at a P value of < 0.05.

Results

**Biochemical thyroid data**

Data are summarized in Tables 2 and 3, and illustrated in Figs. 1 and 2.

In the control group (Table 2), all biochemical indices were statistically similar to the corresponding ones of the study group. In addition, they did not change significantly over time.

In sharp contrast, in the study group all indices changed significantly at the first evaluation (end of the third month) (Table 2). At this first post-treatment evaluation, serum TPOAb decreased by one-fourth, while FT4 increased by one-sixth and FT3 decreased by the same magnitude. As expected from the well-known linear-log relationship in the thyroid hormone-driven feedback regulation of TSH secretion, serum TSH changed in the expected direction (decrease) and to a greater extent (3 times more) than the 15% increase in serum FT4. The 3-fold greater change held six months later, in response to the further increase in serum FT4 (approximately 60% compared to 24% increase in serum FT4); TPOAb levels continued to fall. Changes of serum TPOAb, TSH and FT4 augmented over time, whereas FT3 did not decrease further at month 9 compared with month 3. As a result, the FT4:FT3 ratio continued to increase (Table 2). Figs. 1 and 2 show that, both in the patients and in the control group, changes for each given index were uniform, with virtually no outliers.

In brief, all the changes observed are consistent with an amelioration of the intrathyroid autoimmune process, with rescue of T4 synthesis by the thyrocyte (and subsequent decline in serum TSH) and simultaneous impairment of the deiodinase-mediated peripheral T3 formation.

Table 3 shows that euthyroidism (TSH ≤ 4.0 mU/L) was achieved in 83% of patients already at the end of the third month of treatment. This proportion becomes exactly one-third (33%) using the very stringent criterion of TSH ≤ 2.5 mU/L. At the end of the ninth month, 100% or 83% of women were euthyroid, depending on TSH threshold. In contrast, all control women retained their SCH status, with a TSH > 4.0 mU/L (data not shown).

The bottom part of Table 3 shows that the worst biochemical scenario based on the combination of three indices (TSH, FT4 and TPOAb) occurred at baseline in 40 or 60% of patients (depending on the TPOAb threshold used). However, already by the third month of treatment the scenario improved at the best possible level (disappearance) or improved significantly.

None of the 30 women complained of any side-effects during the nine months of study.

Discussion

As checked with a PubMed search on September 30, 2017 using the string “Aloe and thyroid”, except for a letter to the Editor reporting on a single patient [30] and one paper on male mice [31], there are no other studies describing the effects of Aloe on thyroid function. A 56-yr-old woman with lichen planus, who refused treatment with corticosteroids, took Aloe vera juice (10 ml/day) for 11 months [30]. No improvement run. Intra-assay coefficients of variations for all four thyroid analytes were < 3%.

Statistics

Data are given as mean ± standard deviation (SD) and median. Differences between m ± SD of continuous variables were analyzed by ANOVA or by the Wilcoxon signed rank test for the indices with non-gaussian distribution (TSH and TPOAb). Differences between proportions were analyzed by the two-tailed Fisher’s exact test. The threshold for significance was set at a P value of < 0.05.
Table 3
Changes observed in the specified biochemical thyroid indices (all analyzed as categorical variables) during and at the end of a 9-month duration administration of Aloe vera barbadensis Miller juice in 30 women with Hashimoto’s thyroiditis-related subclinical hypothyroidism.

| Statistics (P value) | Baseline | 3 Months | 9 Months | 3 Mos. vs baseline | 9 Mos. vs baseline | 9 Vs 3 months |
|---------------------|----------|----------|----------|-------------------|-------------------|--------------|
| TSH > 4.0 mU/L      | 30 (100%)| 5 (16.7%)| 0        | < 0.0001          | < 0.0001          | 0.05         |
| TSH < 4.0 mU/L      | 0        | 25 (83.3%)| 30 (100%)| OR = 0.003        | OR = 0.003        | OR = 0.08    |
| TSH > 2.5 mU/L      | 30 (100%)| 20 (66.7%)| 5 (16.7%)| < 0.0008          | < 0.0001          | 0.0002       |
| TSH ≤ 2.5 mU/L      | 0        | 10 (33.3%)| 25 (83.3%)| OR = 0.032        | OR = 0.0035       | OR = 0.10    |
| FT4 < 10 pmol/L     | 18 (60%) | 8 (26.7%) | 1 (3.4%) | < 0.0001          | 0.026             |              |
| FT4 ≥ 10 pmol/L     | 12 (40%) | 22 (73.3%)| 29 (96.6%)| OR = 0.24         | OR = 0.023        | 0.09         |
| TPOAb > 1000 U/ml   | 12 (40%) | 25 (83.3%)| 30 (100%)| OR = 0.13         | OR = 0.011        | OR = 0.08    |
| TPOAb ≤ 1000 U/ml   | 30 (100%)| 30 (100%)| 11 (37%) | 1.0               | < 0.0001          |              |
| TPOAb > 400 U/ml    | 0        | 0        | 19 (63%) | 0.0012            | < 0.0001          | 0.05         |
| TPOAb ≤ 400 U/ml    | 0        | 0        | 0        | < 0.0001          | < 0.0001          | 1.0          |
| TSH > 4 mU/L + FT4 < 10 pmol/L + TPOAb > 1000 U/ml | 12 (40%) | 0        | 0        | OR = 0.023       | OR = 0.023       |              |
| TSH > 4 mU/L + FT4 < 10 pmol/L + TPOAb > 400 U/ml | 18 (60%) | 8 (26.7%) | 1 (3.4%) | < 0.0001         | < 0.0001         | 0.026        |

* Differences between proportions analyzed by the Fisher’s exact test. Statistically significant differences are typed **bold-face**. Borderline significant differences (P values between 0.10 and 0.05) are typed *bold-face italics*. OR = Odds ratio.

Aloe vera juice can be measured on a clinical **vs** clinical relevant scale, namely return to the euthyroid status. Before supplementation, 100% of our patients were subclinically hypothyroid HT patients. Unlike the 4.5% increase in serum FT3 following a 6-month supplementation with selenomethionine plus myo-inositol [28], we found a 16% decrease after 3 months of supplementation with Aloe vera, this value did not change in either direction after another 6 months of supplementation (Table 2). Consequently, the FT4:FT3 ratio (pmol/L/pmnl/L) increased from 1.83 at baseline to 2.47 (+35%) at month 3 and 2.73 (+52%) at month 9 after Aloe vera supplementation, as did, but to a lower extent (2.95 to 3.21 [+9%]), after 6 months of supplementation with seleniummethionine plus myo-inositol [28]. Upon studying in *vitro* other HT patients’ circulating lymphocytes that were cultured in the presence of selenomethionine plus myo-inositol, our group has found a dose-dependent decline in the extracellular concentration of the hydrogen peroxide-stimulated lymphocyte-secreted chemokines (CCL2, CXCL9 and CXCL10) [32]. Because (i) circulating lymphocytes can be a proxy of the lymphocytes that infiltrate the thyroid in HT, (ii) the said chemokines are markers of functional damage of the thyrocyte [33,34], and (iii) increased peripheral deiodination of T4 into the more potent T3 is a compensatory mechanism for the diminished secretion of T4 from the thyroid gland, we propose the following interpretation for the amelioration of the thyroid autoimmune probe and hormone profile induced by either selenomethionine plus myo-inositol or Aloe vera juice. Upon supplementation, the decreased intrathyroid inflammation and decreased chemokine-mediated damage of the thyrocyte result in greater T4 secretion and decreased need to generate T3 in the periphery compared to the pre-supplementation period.

The benefit provided by the Aloe vera juice can be measured on a clinically relevant scale, namely return to the euthyroid status. Before supplementation, 100% of our patients were subclinically hypothyroid (TSH > 4.0 mU/L), but nine months after supplementation none was so. If the TSH threshold is lowered to 2.5 mU/L (which is relevant in the setting of the first trimester of gestation), after 3 and 9 months of Aloe vera supplementation two-thirds and one-sixth of women would have the undesirable level of TSH > 2.5 mU/L. Remaining in the obstetrical setting, the decline in TPOAb from the first week of gestation through 12 months postpartum upon supplementing Italian women with selenomethionine for all this time was beneficial [26], in that the decline of TPOAb (a well-known risk factor for PPT development) was followed by a 2-fold lower rate of PPT and hypothyroidism compared to the
Fig. 1. Individual changes of serum TSH, FT4, FT3, FT4 to FT3 ratio and TPOAb in 30 women with Hashimoto's thyroiditis-associated subclinical hypothyroidism who took Aloe Barbadensis Miller juice for 9 months.
Fig. 2. Individual changes of serum TSH, FT4, FT3, FT4 to FT3 ratio and TPOAb in 15 controls (women with Hashimoto's thyroiditis-associated subclinical hypothyroidism who did not take Aloe Barbadensis Miller juice).
untreated group. We speculate that the same outcome would very likely occur should women take Aloe vera juice for the entire duration of gestation and the first 12 months after delivery.

In conclusion, a 9-month treatment with 50 ml/day of Aloe vera juice restores euthyroidism in 100% of HT-related initial/mild hyperthyroidism (also known as subclinical hyperthyroidism), with appreciable results already evident after 3 months, and markedly decreases their highly elevated serum TPOAb levels (again already evident after 3 months). These beneficial results are comparable to, if not greater than, those reported in the literature for selenium alone or selenium associated with myo-inositol. In addition to an ameliorative effect on thyroid inflammation and subsequent rescue of the hormone biosynthesis by the thyrocytes, Aloe vera juice is likely to act on the peripheral deiodination of T4 into T3. Randomized, double-blind placebo-controlled trials are warranted.

Declarations of interest

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