Altered Intestinal Absorption of L-Thyroxine Caused by Coffee

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Objective: To report eight case histories, and in vivo and in vitro studies showing coffee’s potential to impair thyroxine (T4) intestinal absorption.

Design: Of eight women with inappropriately high or nonsuppressed thyroid-stimulating hormone (TSH) when T4 was swallowed with coffee/espresso, six consented to the evaluation of their T4 intestinal absorption. This in vivo test was also administered to nine volunteers. In three separate tests, two 100 μg T4 tablets were swallowed with coffee, water, or water followed, 60 minutes later, by coffee. Serum T4 was assayed over the 4-hour period of the test. Two patients and two volunteers also agreed on having tested the intestinal absorption of T4 swallowed with solubilized dietary fibers. In the in vitro studies, classical recovery tests on known concentrations of T4 were performed in the presence of saline, coffee, or known T4 sequestrants (dietary fibers, aluminium hydroxide, and sucralfate).

Main outcome: For the in vivo test, average and peak incremental rise of serum T4 (AIRST4 and PIRST4), time of maximal incremental rise of serum T4 (TMIRST4), and area under the curve (AUC) were determined. In patients and volunteers, the four outcome measures were similar in the water and water + coffee tests. In patients and volunteers, compared to water, coffee lowered AIRST4 (by 36% and 29%), PIRST4 (by 30% and 19%), and AUC (by 36% and 27%) and delayed TMIRST4 (by 38 and 43 minutes); bran was a superior interferer. In the in vitro studies, coffee was weaker than known T4 sequestrants.

Conclusion: Coffee should be added to the list of interferers of T4 intestinal absorption, and T4 to the list of compounds whose absorption is affected by coffee.

Introduction

Intestinal absorption of thyroxine (T4) takes place in the duodenum and upper tract of the small intestine (jejunum), is maximal when stomach is empty, and is affected by a number of gastrointestinal disorders, including Helicobacter pylori–related gastritis, as well as ingestion of drugs, dietary fibers, and herbal remedies (1,2). We have reported on delayed intestinal absorption of T4, a form of malabsorption due to a delayed kinetics of T4 uptake by the intestine (3). While persons with a normal kinetics can take oral levothyroxine (L-T4) 15–30 minutes prior to breakfast, persons with delayed absorption of T4 need to postpone breakfast by a minimum of 60 minutes after ingestion of T4. In addition to the five patients described in that paper (3), we have observed many other patients subsequently (Benvenga et al., unpublished data); in a few of these other patients, breakfast had to be delayed by 5 hours to bring down serum TSH to either normal or subnormal concentrations, depending on the replacement or TSH-suppressive purpose of L-T4 therapy (Benvenga et al., unpublished data).

After having observed the initial five cases with delayed intestinal absorption of T4 (3), we became alerted about issues of T4 intestinal absorption. Accordingly, we would collect a detailed history about other drugs and/or over-the-counter products taken by the patient, as well as dietary habits and modalities of ingestion of L-T4. Moreover, after publication of that paper (3) and related seminars given in our province, local general physicians and endocrinologists would refer to us patients treated with substitutive or

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TSH-suppressive doses of L-T4 whose serum TSH fails to normalize or become suppressed. Thus, as reported herein, we have been able to collect a number of such patients in whom the problem we disclosed was the ingestion of L-T4 with coffee/espresso (instead of water) or with water but soon followed by drinking coffee/espresso. Correction of the habit, results of acute test of intestinal absorption of L-T4, and simple in vitro experiments confirmed indeed that, with the exception of a single patient, coffee lowers the intestinal absorption of T4.

Materials and Methods

Patients (case reports)

The relevant data of the eight patients are summarized in Table 1. Unless specified otherwise, the coffee referred to the Italian-style one. This is prepared with the classical Italian coffeemaker ("caffettiera"), an aluminum stovetop brewer. The coffeemaker was always the Moka Express® by Bialetti (Cocconcio, Brescia, Italy), in agreement with the fact that Moka Express can be found in 90% of the Italian homes (4). When espresso was drunk, it was prepared with household espresso machines. Coffee or espresso was drunk hot in china cups, with no additions such as milk, whipped cream, or liquors. Several brands of ground coffee were used, and most patients switched from one brand to another depending on price at the supermarket.

Materials

For the in vivo study, serum T4 was measured with the chemiluminescent assay by Roche Diagnostics (Monza, Italy). Intraassay and interassay coefficients of variations (CV) in our laboratory are 2.9% and 4.2%, respectively.

Because of the many coffee brands involved, not only between patients but also within patients, it was not feasible to perform the in vivo test with all brands that each patient used to drink. On the other hand, the histories indicated that the effect of coffee or espresso was independent of brand (Table 1). Thus, we elected to use the espresso of a vending machine located in the floor of our division.

As described below in more detail, two patients and three volunteers accepted to have comparatively tested the effect of substances that are known to inhibit T4 intestinal absorption: dietary fibers from bran and antacids. Bran was Crusca Sohn (M. Antonetto, Turin, Italy), and antacids were aluminum hydroxide plus magnesium hydroxide (Maalox®, oral suspension; Aventis, Milan, Italy). Concentration of aluminum hydroxide and magnesium hydroxide in Maalox is 3.25% and 3.65%, respectively.

For the in vitro study, the solid-phase radioimmunoassay (RIA) kit from DSL Laboratories (Webster, TX) was used. Details of this kit are given below. In addition to coffee, bran, and aluminum hydroxide + magnesium hydroxide, sucralfate was tested. Sucralfate was Antepsin® (20% oral suspension; Baldacci, Pisa, Italy). The espresso used came from the aforesaid vending machine.

In vivo studies (intestinal absorption of L-T4)

The incremental rise of serum T4 after ingestion of an oral dose of L-T4, in lieu of radioisotopic techniques, can be used as a surrogate marker for intestinal absorption of L-T4 itself. To mimic the real situation, in which patients would ingest one or two tablets of L-T4, the test was partially modified with respect to the conventional tests using an oral load of ≥ 600 µg L-T4, such as the one described previously (3). The first change consisted, for both patients and volunteers, of using two tablets of 100 µg L-T4 instead of 10 tablets of 100 µg each. The second change consisted of swallowing the 200 µg L-T4 with one cup of espresso (25–30 mL).

As a control, after 4–6 weeks the test was repeated, and after another 4–6 weeks it was repeated again. The two repetitions differed for the fluid used to challenge the intestinal absorption of L-T4, and their sequence was random. In one repetition, the 200 µg L-T4 were swallowed with one glass of plain mineral water (approximately 200 mL). In the other repetition, the L-T4 was swallowed with one glass of plain mineral water, but 60 minutes later the patient or volunteer drank one cup of espresso. Each patient performed the test simultaneously with at least one volunteer. The 600 µg of L-T4 needed for the three tests in a given person (either patient or volunteer) came from the same lot.

Patients no. 1 and 2, and volunteers no. 1, 2, and 5 were willing to perform an additional test to compare the effect of espresso with that of known inhibitors of T4 intestinal absorption. These compounds were dietary fibers from bran in the two patients and volunteers no. 1 and 2, and antacids (aluminum hydroxide plus magnesium hydroxide) in volunteer no. 5. Two packs of bran (that is a total of 10.2 g dietary fibers) dissolved in 200 mL of plain mineral water or 20 mL (two soup spoons) of aluminum hydroxide plus magnesium hydroxide were taken 5 minutes after having swallowed the 200 µg L-T4 with 200 mL of plain mineral water. Because the results of volunteer no. 5 deviated from those of the other volunteers and patients as well, she repeated both the test of the 200 µg L-T4 swallowed with water and the test of the 200 µg L-T4 swallowed with espresso.

Aside from these specifications, the test was performed as described previously (3). After an overnight fast, an i.v. catheter was inserted in the forearm. Blood was taken at seven time points: –30 and 0 minutes for averaged baseline measurements of serum T4 (or endogenous T4), and then at +30, 60, 90, 120, 180, and 240 minutes (endogenous plus exogenous T4). Immediately after the 0-minute sampling, the patient or volunteer ingested two tablets of 100 µg L-T4 (Eutirox®, Bracco, Milan, Italy) according to one of the modalities detailed above. During the test, no food or drink was allowed except for the drinks under evaluation.

Results (mean ± SD) are expressed as ΔT4 (in nmol/L), namely, as incremental rise of serum T4 concentration over the baseline to correct for endogenous T4. Using large oral loads of L-T4, it was demonstrated that each 10% of the dose absorbed causes a 10.4 nmol/L increment in serum T4 (5).

The following indices were considered for each absorption curve, after having averaged the –30- and 0-minute time points to obtain a single baseline (or zero) point: (i) mean ± SD of the six ΔT4 values to obtain the average incremental rise of serum T4 (AIRST4); (ii) ΔT4 peak as indicative of the maximal incremental rise of serum T4 (MIRST4); (iii) time point at which this ΔT4 peak is reached as indicative of the time of the maximal incremental rise of serum T4 (TMIRST4); (iv) area under the curve (AUC) (nmol/L · 240 minutes). These indices were compared within groups of subjects, using as reference values the values
Table 1. Interference of Coffee on the Intestinal Absorption of L-T4, Based on Relevant History and Serum TSH, in the Eight Patients (All Women) Who Were Brought to Our Attention for Inappropriately High or Nonsuppressed TSH

<table>
<thead>
<tr>
<th>Case no. (age$^a$)</th>
<th>Relevant history</th>
<th>TSH (mU/L)$^b$ when L-T4 swallowed with</th>
<th>Water</th>
<th>Coffee$^c$</th>
<th>Water</th>
<th>Coffee$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (62 years)</td>
<td>A bank employee with primary hypothyroidism (TSH = 32 mU/L) due to Hashimoto’s thyroiditis. Treated with 100 mg/day L-T4 (1.7 μg/[kg BW·day]), which she swallowed with water 1 h prior to breakfast, TSH was normalized. Four years later, she returned to us hypothyroid (TSH = 24.7 mU/L). The same dose of L-T4 was swallowed with a double espresso, and another cup was drunk 5–10 min later. Over the next 4 years, TSH was normal when she returned to swallow the same dose of L-T4 with water, 30 min prior to coffee. Finally, TSH increased again (4.7–6.9) when she swallowed L-T4 either with one cup of espresso or with water, but followed by one cup of espresso 1–5 min later.</td>
<td>0.9–1.9</td>
<td>24.7</td>
<td>1.3–2.8</td>
<td>4.7–6.9</td>
<td></td>
</tr>
<tr>
<td>2 (31 years)</td>
<td>A nurse who was thyroidectomized for euthyroid multinodular goiter (TSH = 1.4 mU/L). Over the next year, TSH was high (13.6–18.3) in spite of treatment with 100–150 μg/day L-T4 (2.1–3.2 μg/[kg BW·day]). She swallowed L-T4 with one full cup of coffee, and a second cup was drunk within 10 min later. She had breakfast 90 min after L-T4 ingestion. Over the next 15 months, TSH ranged from 0.03 to 0.1 mU/L when L-T4 [2.1 μg/(kg BW·day)] was swallowed with water 60 min prior to drinking one cup of coffee.</td>
<td>13.6–18.3</td>
<td>0.03–0.1</td>
<td>[2.1–3.2]</td>
<td>[2.1]</td>
<td></td>
</tr>
<tr>
<td>3 (43 years)</td>
<td>A sales associate who was thyroidectomized for toxic multinodular goiter (TSH &lt; 0.001). Serum TSH, however, remained inappropriately high at 10.3–36.1 mU/L, even though L-T4 was increased from 100 to 150 μg/day (1.85–2.8 μg/[kg BW·day]). She drank a full cup of coffee within 5 min after ingestion of L-T4 and had breakfast 80 min later. She was unwilling to perform the acute oral L-T4 loading test. She swallowed L-T4 (100 μg/day) with water at least 60 min prior to coffee during the next 2½ years, and her serum TSH was between 0.6 and 2.2 mU/L.</td>
<td>10.3–36.1</td>
<td>0.6–2.2</td>
<td>[1.8–2.8]</td>
<td>[1.8]</td>
<td></td>
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<tr>
<td>4 (40 years)</td>
<td>A teacher with subclinical hypothyroidism due to Hashimoto’s thyroiditis (TSH = 6.5–9.8 mU/L). Treated with L-T4 (125 μg/day; 1.8 μg/[kg BW·day]), which was taken with water 1 h prior to breakfast, TSH was normalized (1.3–2.7 mU/L). Five months after having changed her habits, for working reasons, serum TSH was 5.7–6.2 mU/L. She swallowed L-T4 with a full cup of coffee and had breakfast 60–90 min later. During the next 8 years, she postponed coffee 60 min after L-T4 (100 μg/day) swallowed with mineral water, and as a result her TSH never exceeded 2.6 mU/L.</td>
<td>1.3–2.7</td>
<td>5.7–6.2</td>
<td>0.7–2.6</td>
<td>[1.8]</td>
<td></td>
</tr>
<tr>
<td>5 (35 years)</td>
<td>A woman who had undergone hemithyroidectomy for a histologically benign nodule. Put on TSH-suppressive L-T4 therapy (132 μg/day or 2.4 μg/[kg BW]) her TSH was at &lt;0.001 to 0.03 mU/L. Seven months prior to our observation, TSH become nonsuppressed (1.2–2.9 mU/L). For working reasons she changed her habits: she took L-T4 with tap water but drank one full cup of coffee within 2–5 min later, and had breakfast about 120 min later. She was instructed to return to have breakfast 60 min after ingestion of 132 μg/day L-T4 and omitting drinking coffee shortly after. During the next 19 months, serum TSH never exceeded 0.02 mU/L.</td>
<td>&lt;0.001–0.03</td>
<td>1.2–2.9</td>
<td>&lt;0.001–0.02</td>
<td>[2.4]</td>
<td></td>
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</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Case no. (age\textsuperscript{a})</th>
<th>Relevant history</th>
<th>TSH (mU/L)\textsuperscript{b} when L-T4 swallowed with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Water</td>
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<tr>
<td>6 (38 years)</td>
<td>A housewife who had subclinical hypothyroidism due to the goitrous and nodular variant of Hashimoto’s thyroiditis (TSH = 12.5 mU/L). Treated for 15 months with L-T4 at TSH-suppressive doses (125–175 (\mu)g/day or 2.3–3.2 (\mu)g/kg BW), TSH never became suppressed (1.1 mU/L). This patient used to take L-T4 with tab water 10–15 min prior to breakfast. She declined the acute load of oral L-T4 to demonstrate delayed intestinal absorption. Over the next 16 months, while taking 125 (\mu)g/day L-T4 120 min prior to breakfast, TSH was 0.003–0.02 mU/L. We saw again the same patient almost 4 years later: in the two controls performed in the last 2 years, serum TSH had increased to 0.6 and 0.9 mU/L under the same dose of L-T4. The woman admitted to take one full cup of coffee immediately after swallowing the L-T4 tablet. She was instructed to postpone drinking coffee by 60 min after having swallowed L-T4. Nine months after, her serum TSH was &lt;0.001 mU/L.</td>
<td>0.003–0.02</td>
</tr>
<tr>
<td>7 (58 years)</td>
<td>A housewife hypothyroid for Hashimoto’s thyroiditis (TSH = 46–53 mU/L). Over the next 5 months, under L-T4 at doses of 100–200 (\mu)g/day (1.75–3.5 (\mu)g/kg BW), serum TSH dropped scantily (31–18 mU/L). Careful investigation disclosed that she used to swallow L-T4 with espresso; a second cup of espresso was drunk 2–10 min later, 60 min prior to breakfast. Over the next 2 years, TSH dropped between 2.3 and 0.7 mU/L when she swallowed L-T4 with water 1 h prior to coffee and breakfast.</td>
<td>31–18</td>
</tr>
<tr>
<td>8 (52 years)</td>
<td>A teacher with the atrophic variant of Hashimoto’s thyroiditis (TSH = 55 mU/L). An acute oral loading test performed demonstrated a quantitatively low-normal and delayed intestinal absorption of L-T4 (serum T4 peak = 44% of the dose ingested, at 240 min). She was instructed to postpone breakfast by 4 h after ingestion of 100 (\mu)g/day L-T4, and her serum TSH decreased without being fully normal (3.8–6.3 mU/L). She admitted to swallow L-T4 with water, and to drink a full cup of coffee or double espresso soon after. Over the next 5 years, she swallowed L-T4 (100 (\mu)g/day) with water 1 h prior to coffee and 4 h prior to breakfast; TSH never exceeded 2.4 mU/L. Finally, in the sixth year of follow-up, she returned to the old habit, and serum TSH increased between 3.5 and 5.7 mU/L.</td>
<td>6.3–3.8</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Age is at our observation.

\textsuperscript{b}For each patient, data are listed in chronological order (see the column “Relevant history” for more details). For instance, patient no. 1 began swallowing T4 with water; she next switched to swallowing L-T4 with espresso, to return later to water and, finally, back to espresso. The pretherapy value of patient no. 3 is suppressed because she had toxic multinodular goiter, for which she was thyroidectomized. Other patients who had been thyroidectomized prior to our observation were patients no. 2 and 5. Patients no. 1, 2, 4, 5, 7, and 8 performed the T4 absorption test in the absence or presence of espresso, while patients no. 3 and 6 refused the test.

\textsuperscript{c}Patients no. 1, 2, 3, and 7 used to drink another cup of coffee/espresso 2–10 minutes after the first one; for patient no. 1, the first drink was a double espresso (two shots of espresso in one cup). Note that the related serum TSH levels of these four women were higher than in woman no. 4, which, in turn, were greater than in women no. 5, 6, and 8 who drank the coffee/espresso from immediately (no. 8) to within 5 minutes after having swallowed the T4 tablet with water (no. 5 and 6); patient no. 8 drank a double espresso.

\textsuperscript{d}Patient no. 1 ingested L-T4 with espresso or with water but drank one cup of espresso 1–5 minutes later. Patient no. 8 returned precisely to the old habit of swallowing T4 with espresso.

L-T4: levothyroxine; TSH: thyroid-stimulating hormone; BW: body weight.
obtained when subjects ingested the 200 μg L-T4 with water and anything else thereafter.

Volunteers

While the patients with the delayed intestinal absorption of T4 we had observed (3) and continue to observe (unpublished data) belong to either gender, all eight patients reported here were women. Thus, we wished to ascertain that the interference of coffee was restricted to women. To this end, we looked for volunteers of either gender. Volunteers (four men and six women; age 24–52 years) were personnel of this Endocrine Division. Except one man, all five volunteers were euthyroid (TSH = 0.6–2.4 mU/L, normal value [n.v.] 0.4–4.0 mU/L; free triiodothyronine = 2.4–3.5 pg/mL, n.v. 1.8–4.2 pg/mL; free T4 = 12.3–16.7 pg/mL, n.v. 8.0–19.0 pg/mL) with undetectable thyroglobulin antibody and thyroid peroxidase antibody, as measured by immunoradiometric methods, and with normal sonography of the thyroid. The exception was a doctor who, after the cytological diagnosis of a colloid nodule, was under L-T4 at TSH-suppressive dose (2.4 μg/kg body weight); he used to ingest L-T4 60 minutes prior to coffee and breakfast, and serum TSH was stably <0.01 mU/L.

In vitro studies

Experiments were adapted from those reported to test in vitro the T4 adsorption property of antacids (6) and calcium carbonate (7), using a commercially available solid-phase RIA (DSL Laboratories). The performances of this kit are a sensitivity of 0.4 μg/dL, and an intraassay and interassay precision defined by CVs of 5.0% and 7.4%, respectively.

In brief, 100 μL taken from a known solution of 10.0 μg/dL L-T4 was mixed with 200 or 400 μL of freshly brewed espresso. In parallel experiments, 100 μL of the above solution of L-T4 (10.0 μg/dL) was mixed with 200 or 400 μL of the following: buffered saline, aluminium hydroxide plus magnesium hydroxide (Maalox), sucralfate (Antespine, 20% oral suspension), or dietary fibers from bran (10.2 g/200 mL water). The mixtures of standard T4 plus espresso or the control additions were allowed to incubate in a shaking bath for 2 hours at 37°C, and then centrifuged at 3000 rpm for 10 minutes. The supernatant was aspirated, and 100 μL of it was processed, in quadruplicate not differently from a serum sample.

Next, 25 μL of the supernatant (which is the volume specified in the package insert of the T4 RIA kit) was pipetted into the anti-T4-coated tubes. Soon after, 200 μL of the 125I-T4 (approximately 75,000 cpdm) was added. Tubes were quickly vortexed and incubated in a shaker for 60 minutes at room temperature. After aspiration and washings as recommended, tubes were counted for radioactivity in a gamma counter. This study of in vitro interference by coffee and, for comparison, aluminum hydroxide plus magnesium hydroxide, sucralfate, bran, or saline was conducted in a single run.

Statistics

Results are mean ± SD. Differences between means were analyzed by the Wilcoxon signed rank sum test because of their non-Gaussian distribution. A level of p < 0.05 was taken as statistically significant, while a level of p between 0.10 and 0.05 was taken as trendwise significant.

Results

In vivo studies (intestinal absorption of L-T4) in patients

Data are summarized in Table 2, and illustrative cases presented in Figure 1.

Figure 1 shows that the negative effect of espresso was variable, and present only if espresso was swallowed simultaneously with L-T4 (left panels), not 60 minutes later (right panels). In terms of AIRST4, espresso lowered this index by a minimum of 25% in patient no. 2 to a maximum of 57% in patient no. 8, as compared to water. Reduction of MIRST4 ranged from 14% (patient no. 1) to 49% (patient no. 2), while AUC reduction ranged from 23% (patient no. 2) to 55% (patient no. 8). Compared to water, espresso delayed TMRIST4 by 0 minute (patient no. 2) to 90 minutes (patient no. 4).

Upon pooling data of the 36 past-zero time points of the test in the absence of coffee and contrasting them with the pooled corresponding time points of the test in the presence of coffee in the same six patients, AIRST was 36.3 ± 16.7 and 23.0 ± 12.7 nmol/L, respectively, a 1.6-fold difference (p < 0.0001) (Table 2). When data are expressed in terms of AUC (in nmol/[L·4 hours]), the corresponding values were 8696 ± 1590 vs. 5592 ± 1452, a 1.6-fold difference (p < 0.05). Significant (p < 0.05) were also the 1.4-fold smaller MIRST4 and the retarded time to reach such a peak (50 minutes) (Table 2).

When the test was repeated allowing patients to drink one cup of espresso 60 minutes after having swallowed the T4 tablets with water, none of the four parameters showed any significant change from control (Table 2 and right panels of Fig. 1).

Figure 1 (left panels) and Table 2 also show that 10.2 g dietary fibers in one glass of water inhibited T4 absorption stronger than one cup of espresso did.

In vivo studies (intestinal absorption of L-T4) in healthy volunteers

Data are summarized in Table 2, and illustrative cases presented in Figure 1. Data of volunteer no. 5 deviated from data of the other volunteers. In three volunteers, the effect of espresso was compared with that of two known interferers of T4 intestinal absorption: dietary fibers (volunteers no. 1 and 2) and antacids (volunteer no. 5). Either compound inhibited T4 intestinal absorption more than espresso did.

As observed in patients (Fig. 1), the effect of espresso was variable. Table 2 shows that changes of the four parameters mimicked those described above for patients, but were of lower magnitude. Upon pooling data of the 54 past-zero time points of the test with water and contrasting them with the corresponding time points of the test with coffee in the same nine volunteers, the corresponding AIRST4 was 35.4 ± 14.9 and 25.1 ± 14.2 nmol/L, a 1.4-fold difference (p < 0.001). Swallowing L-T4 with espresso decreased AUC by 1.4-fold (p < 0.01), MIRST4 by 1.2-fold (p < 0.05), and TMIRST4 by 43 minutes, a trendwise significant difference (p = 0.068).

Again, similarly to patients, when the test was repeated allowing the nine volunteers to drink one cup of espresso 60 minutes after having swallowed T4 with water, none of the four parameters showed any significant or trendwise significant change (Table 2 and Fig. 1).
<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 6)</th>
<th>Volunteers no. 1–4, 6–10 (n = 9)</th>
<th>Volunteer no. 5 (n = 1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (nmol/L)</td>
<td>Peak (nmol/L)</td>
<td>Peak (minutes)</td>
<td>AUC (nmol/[L·4 hours])</td>
</tr>
<tr>
<td>Water alone</td>
<td>Mean 36.3</td>
<td>51.8</td>
<td>130</td>
<td>8696</td>
</tr>
<tr>
<td></td>
<td>± SD 16.7</td>
<td>± 11.9</td>
<td>± 41</td>
<td>± 1590</td>
</tr>
<tr>
<td>Espresso</td>
<td>Mean 23.0</td>
<td>36.0</td>
<td>180</td>
<td>5592</td>
</tr>
<tr>
<td></td>
<td>± SD 12.7</td>
<td>± 8.8</td>
<td>± 38</td>
<td>± 1452</td>
</tr>
<tr>
<td></td>
<td>p-value &lt; 0.0001</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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</tr>
<tr>
<td>Water (espresso 1 hour later)</td>
<td>Mean 36.2</td>
<td>52.0</td>
<td>125</td>
<td>8622</td>
</tr>
<tr>
<td></td>
<td>± SD 16.1</td>
<td>± 8.5</td>
<td>± 44</td>
<td>± 1481</td>
</tr>
<tr>
<td></td>
<td>p-value 0.86 (NS)</td>
<td>0.53 (NS)</td>
<td>0.56 (NS)</td>
<td>0.40 (NS)</td>
</tr>
<tr>
<td>Bran b</td>
<td>Mean 7.0</td>
<td>20; 7</td>
<td>180; 180</td>
<td>2715; 900</td>
</tr>
<tr>
<td></td>
<td>± SD 7.3</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td></td>
<td>p-value &lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
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<tr>
<td>Aluminum hydroxide</td>
<td>Mean Not</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td></td>
<td>± SD Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td></td>
<td>p-value Not done</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
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</table>

*aStatistical analysis (vs. water alone) is by Wilcoxon signed rank sum test for paired data.

bBran refers to patients no. 1 and 2, and volunteers no. 1 and 2. In the two patients, the four tabulated values for water alone were 32.7±11.8, 42 and 120, and 7350 and 8145. In the two volunteers, the four tabulated values for water alone were 32.8±9.8, 44 and 41, 120 and 120, and 7830 and 7535. In a comparison between bran and espresso, 7.0±7.3 was different from 232±12.9 (p<0.01) in patients no. 1 and 2, and 8.9±7.2 was different from 22.8±16.7 (p<0.01) in volunteers no. 1 and 2. Numbers in brackets are daily doses of L-T4 in μg/kg body weight.

T4: thyroxine; L-T4: levothyroxine; AUC: area under the curve; N/A: not applicable; NS: not significant.
In vitro

Volunteer no. 5 had a peculiar pattern, and consistently so. Not only was her T4 absorption clearly the lowest, but also her absorption was increased (rather than decreased) by espresso (Fig. 1 and right columns of Table 2). AIRST4 was increased by 1.9-fold, MIRST4 and AUC by 1.7-fold both, while TMIRST4 was apparently unaffected.

In vitro experiments

Dietary fibers from bran, sucralate, aluminum hydroxide, and magnesium hydroxide are nonabsorbable compounds that are known to impair the intestinal absorption of T4. Bran and antacids were compared with espresso both in vivo and in vitro. Confirming in vivo data on patients (Fig. 1) and volunteers (Fig. 1), the in vitro experiments summarized in Table 3 show that coffee was less potent in interacting with T4.

In vivo

The single subject who volunteered for the interference by antacids was an outlier in the in vivo coffee test. Thus, a correlation between in vivo and in vitro data given by the two compounds appears not homogeneous with respect to the equivalent correlation in the other four subjects, in whom coffee consistently behaved as an inhibitor (rather than facilitator) of T4 intestinal absorption.

Discussion

Herein we have presented evidence that coffee interferes with the intestinal absorption of T4.

First, the case histories show a highly consistent pattern across patients: whenever T4 was swallowed with coffee (or with water but followed by coffee soon after), serum TSH failed to be normalized or suppressed. Correction of this habit resulted in normalization (or suppression) of serum TSH, while resumption of the habit resulted again in inappropriately high or nonsuppressed serum TSH. Drinking coffee a minimum of 30 minutes after having swallowed T4 with water eliminated coffee’s interference, suggesting that such interference derives from the physical contact of coffee with T4.

Second, the kinetics of T4 intestinal absorption in patients and volunteers provided important results. When either patients or volunteers swallowed the 200 μg T4 with water
Coffee does not change the intragastric pH and times of gastric emptying and intestinal transit (12,13). Thus, it is more likely that coffee physically interacts with T4, rendering the hormone less available for intestinal absorption, and the following literature cited is consistent with this interpretation.

Coffee lowers the intestinal absorption of both inorganic and organic compounds. A cup of coffee reduced iron absorption from an hamburger meal by 39% as compared to a 60% decrease caused by tea (14). No decrease in iron absorption occurred when coffee was consumed 1 hour before a meal, but the same degree of inhibition as with simultaneous ingestion was seen when coffee was taken 1 hour later. Iron absorption from the breakfast with 100 g of white wheat flour decreased from 6% when the breakfast was given alone to less than 2% when it was given with coffee (15). Coffee decreases the efficiency of calcium (16) and zinc (17) absorption. In the Framingham cohort, women who consumed more than two cups of coffee daily had a risk of fracture over the next 12 years that was 69% higher than women who did not consume caffeinated beverages (16). Interestingly, coffee also decreases the absorption of the antosteoporosis drug alendronate (18).

A meta-analysis found that habitual coffee consumption is associated with a substantial lower risk of type 2 diabetes, consistent with previous studies in different nations showing that higher coffee consumption was associated with a lower prevalence of postprandial hyperglycemia (19). Finally, studies in rats showed that green tea and coffee both inhibited intestinal cholesterol absorption due to their content in epigallocatechin gallate and caffeine (20).

Although our case histories and our data refer to the Italian-style coffee and espresso, it is likely that the inhibitory effects exerted by coffee and tea on the intestinal absorption of cholesterol and iron, it will be of interest to ascertain whether tea might impair T4 intestinal absorption.

In conclusion, coffee should be added to the list of compounds that decrease T4 intestinal absorption. At the same time, T4 should be added to the list of compounds whose intestinal absorption is altered by coffee.

### References


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**Table 3. Test of Recovery of Thyroxine (T4) from a Solution Containing a Known Concentration of T4 (10.0 μg/dL)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>2:1</th>
<th>4:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (control)</td>
<td>10.12 ± 0.5 (101%)</td>
<td>9.88 ± 0.4 (99%)</td>
</tr>
<tr>
<td>Espresso</td>
<td>8.04 ± 0.3 (80%)</td>
<td>5.57 ± 0.1 (56%)</td>
</tr>
<tr>
<td>Aluminum hydroxide + magnesium hydroxide</td>
<td>4.75 ± 0.1 (47%)</td>
<td>2.10 ± 0.1 (21%)</td>
</tr>
<tr>
<td>Dietary fibers</td>
<td>4.51 ± 0.2 (45%)</td>
<td>2.20 ± 0.1 (22%)</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>3.85 ± 0.1 (38%)</td>
<td>1.69 ± 0.1 (17%)</td>
</tr>
</tbody>
</table>

*Note:* T4 was assayed in quadruplicate by radioimmunoassay. A solution with a known concentration of T4 (10 μg/dL) was mixed with two or four volumes of each of the five listed compounds separately. For further details, see “Materials and Methods” section. Results are corrected for the dilution with the interfering compound. The intra-assay coefficient of variation of the T4 kit is 5.0%.

### Notes

and, 60 minutes later, they drank coffee, the four indices of the intestinal absorption test were very similar to those obtained when the T4 tablets were swallowed with water alone. In contrast, when the 200 μg T4 were swallowed with coffee, all four outcome measures were more unfavorable compared with ingestion of T4 with water alone.

Third, we showed that liquid coffee is capable of sequestering T4 *in vitro*.

As ancillary findings of our *in vivo* and *in vitro* studies, we found that coffee ranks behind other known interferers of T4 absorption. By similarity with these compounds, it seems reasonable to infer that coffee acts by sequestering T4 and rendering less hormone available for uptake by the intestinal epithelium. In this respect, volunteer no. 5 is an exception, as the corresponding concentrations in the 4:1 mixture (final volume = 500 μL) were 26, 29.2, 40.8, and 160 mg/mL.

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