

13% in people who have diabetes. We also note that our model matches quite closely the progression of retinopathy seen in the UKPDS and other trials (5).

Concerning myocardial infarctions, the 12% and 50% values are measuring entirely different things and are not comparable. To evaluate the accuracy of our model for calculating cardiovascular events, we recommend looking at the rate actually seen in the Diabetes Prevention Program after 3 years, 7.3 events per 1000 person-years (6). We calculated 8.4 events per 1000 person-years. About 40% of people with diabetes die of ischemic heart disease (7). For the population from the Diabetes Prevention Program, we calculated 28%, which is right on target given the differences in populations and time horizons. Additional validations of myocardial infarction rates in 12 clinical trials, including UKPDS and a prospective prediction of CARDS (Collaborative Atorvastatin Diabetes Study) are described elsewhere (1, 5).

We can correct other misunderstandings. First, we did not assume that glycemic progression is a “linear process”; in our model, progression varies from person to person and is not linear even for any particular person. Second, we did not “constrain” diabetes progression nor did we fix HbA<sub>1c</sub> levels at 6.6%. The physicians in our simulation followed American Diabetes Association guidelines and treated people to achieve a target of 7% (making the average less than 7%). From that point on, we assumed the degree of control would gradually deteriorate as seen in the intensive care group of the UKPDS. Third, we used the same model that had been validated against 18 clinical trials (5); those validations *do* apply to this analysis. Fourth, we have validated the model for analyzing prediabetes; we did a blinded validation against the Diabetes Prevention Program itself (1, 5). Fifth, we have searched the literature again and still cannot find any validations of the model that Dr. Herman and his colleagues used. Specific references might help.

In addition to the issues that the authors raise in their letter, other aspects of their model may help explain why they achieved different results. Some examples from their paper and technical report (2) are as follows: HbA<sub>1c</sub> levels increase at a constant annual rate of 0.2% during clinical diabetes (technical report, page 22; note that the rate was 0.11% in the UKPDS); at the beginning of clinical diabetes, no one yet has any signs of retinopathy (technical report, page 88); the annual probability that a person with prediabetes progresses to diabetes does not depend on how long they have had impaired fasting glucose or impaired glucose tolerance (paper, page 324); lifestyle reduces the probability of progressing from prediabetes to diabetes by a fixed 58% (paper, page 324; note that for patients in the Diabetes Prevention Program, the effect declined steadily over time and was about 44% after 4 years of follow-up); costs are multiplicative (paper, page 326); retinopathy and neuropathy do not affect costs (paper, page 326); blood pressure and levels of total serum cholesterol and high-density lipoprotein can only be categorized as “normal” or “above normal” (technical report, pages 39 and 43); risk for coronary heart disease in people with early (preclinical) diabetes is calculated from the UKPDS risk engine (paper, page 325), which was designed to be used after a patient develops clinical diabetes; and the annual risk for end-stage kidney disease does not depend on how long someone has had diabetes, clinical nephropathy, or blood pressure levels (technical report, page 12). These and other assumptions, some of which are summarized in the appendix to our paper, may deserve reconsideration.

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## CLINICAL OBSERVATIONS

### Hepatotoxicity Associated with Supplements Containing Chinese Green Tea (*Camellia sinensis*)

**TO THE EDITOR:** *Background:* Recent reports have identified an association between hepatotoxicity and health supplements containing green tea extract (*Camellia sinensis*).

*Objective:* To present a new case study involving a patient who exhibited a positive response to a rechallenge and to summarize previous reports of *C. sinensis*-associated hepatotoxicity.

*Methods and Findings:* A 37-year-old Hispanic woman was evaluated for a 10-day history of diffuse abdominal pain, nausea, and jaundice. She had been using a weight-loss supplement called The Right Approach Complex (Pharmanex, Provo, Utah) for 4 months. She was afebrile. Her serum aspartate aminotransferase (AST) level was 1783 U/L (reference range, 17 to 39 U/L), her serum alanine aminotransferase (ALT) level was 1788 U/L (reference range, 8 to 39 U/L), her serum total bilirubin level was 200  $\mu$ mol/L (11.7 mg/dL) (reference range, 7 to 24  $\mu$ mol/L [0.4 to 1.4 mg/dL]), her serum

direct bilirubin level was 169  $\mu\text{mol/L}$  (9.9 mg/dL) (reference range, 0 to 3  $\mu\text{mol/L}$  [0 to 0.2 mg/dL]), her serum alkaline phosphatase level was 238 U/L (reference range, 39 to 113 U/L), and her serum albumin level was 650  $\mu\text{mol/L}$  (reference range, 580 to 800  $\mu\text{mol/L}$ ). Results of serologic tests for antibodies against hepatitis A IgM, hepatitis C, and hepatitis B surface antigen were negative. An anti-nuclear antibody titer was weakly positive (1:40, speckled); results of tests for antiliver–kidney microsomal, anti-dsDNA, anti-smooth muscle, and antimitochondrial antibodies were negative. Liver biopsy revealed marked interface necrosis and inflammation and mild lobular inflammation. Cholecystectomy and intraoperative cholangiography were performed; the gallbladder and bile ducts were normal, and there was no evidence of cholecystitis or stones. The patient was discharged on day 13. One month later, her serum AST level was 79 U/L, her serum ALT level was 92 U/L, and her serum total bilirubin level was 33  $\mu\text{mol/L}$  (1.9 mg/dL).

Approximately 1 year later, the patient was again admitted with a 1-week history of diffuse abdominal pain and jaundice. She reported loss of appetite, mild nausea, and pruritus. Approximately 1 month earlier, she had resumed taking The Right Approach Complex but stopped taking it 1 week before presentation because of dysphagia. On admission, her serum AST level was 977 U/L, her serum ALT level was 1131 U/L, her serum total bilirubin level was 200  $\mu\text{mol/L}$  (11.7 mg/dL), and her international normalized ratio was 1.3. Her serum acetaminophen level was less than 66  $\mu\text{mol/L}$  (reference range, 35 to 130  $\mu\text{mol/L}$ ). Results of repeated screens for infectious and autoimmune causes were negative. On day 8 of hospitalization, the patient's serum AST level was 816 U/L, her serum ALT level was 877 U/L, her serum total bilirubin level was 49  $\mu\text{mol/L}$  (2.9 mg/dL), and her serum alkaline phosphatase level was 165 U/L. The patient was discharged, and her physician stressed that she should not resume taking the weight-loss supplement or any others with similar ingredients. One month later, her serum AST and ALT levels were 80 and 69 U/L, respectively, and her serum total bilirubin level was 20.52  $\mu\text{mol/L}$  (1.2 mg/dL). Six months later, her serum AST level was 27 U/L, her serum ALT level was 25 U/L, her serum alkaline phosphatase level was 85 U/L, and her serum total bilirubin level was 17  $\mu\text{mol/L}$  (1.0 mg/dL).

**Conclusion:** The Table summarizes published studies that associate products containing *C. sinensis* with hepatotoxicity, usually with a mixed hepatocellular–cholestatic picture (1–5). Most patients were younger than 40 years of age and 7 of 9 were women, perhaps reflecting greater susceptibility or greater use of such supplements among women. All patients improved after stopping the products and had normal liver test results within 4 months after they stopped taking the supplement. Chronic, self-sustaining liver injury was not found. In view of the severity of injury, continuing or long-term use

in the setting of injury could lead to serious liver failure. Features to suggest an immunoallergic cause were absent in our case and in the other reports. The pathogenesis remains unknown.

It is difficult to establish a definitive causal relationship between extracts of *C. sinensis* and the reported cases of hepatotoxicity because of the multiplicity of ingredients and coingestants in many of the cases. In our patient, the temporal pattern of *C. sinensis* administration and liver enzyme abnormalities (with a positive rechallenge and exclusion of other possible causes) strongly suggested that the supplement was the inciting agent for both episodes of severe, symptomatic drug-induced liver injury. Extract of *C. sinensis* is the most probable cause of hepatotoxicity in this patient because 1) this extract is the major ingredient of the supplement by weight (383.3 mg per 3 capsules); 2) there are now several recent reports of similar symptomatic hepatotoxicity in patients using *C. sinensis* extracts; and 3) other ingredients of the supplement have not been reported to be hepatotoxic at levels found in 3 capsules (calcium, 167 mg; chromium, 67  $\mu\text{g}$ ; magnolia extract, 100 mg; aqueous epimedium extract, 100 mg;  $\beta$ -sitosterol, 40 mg; banaba leaf extract, 11 mg; and vanadium, 10  $\mu\text{g}$ ). Although Chinese green tea is widely touted as a cytoprotective antioxidant and panacea, we believe that large amounts (5) or concentrated preparations of *C. sinensis* are dangerous and should be avoided.

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**Table. Liver Injury Associated with Supplements Containing *Camellia sinensis*\***

Study, Year (Reference)	Age, y	Sex	Ethnicity	Substance Implicated	Approximate Duration of Exposure before Symptom Onset, d	Approximate Cumulative Dose of Extract Consumed, g†	Rechallenge Results	Peak Serum Alanine Aminotransferase Level, U/L	Peak Serum Alkaline Phosphatase Level, U/L
Bonkovsky, 2005‡	37	Female	Hispanic	The Right Approach (Pharmanex, Provo, Utah)	120	240	Positive	1788	238
Bonkovsky, 2005§	38	Female	Hispanic	The Right Approach (Pharmanex, Provo, Utah)	16	32	None	1166 (hospital day 2)	212
Stevens et al., 2005 (1)	27	Male	NR	Hydroxycut (MuscleTech, Mississauga, Ontario)	28	41	–	3962	171
Stevens et al., 2005 (1)	30	Male	NR	Hydroxycut (MuscleTech, Mississauga, Ontario)	5	5.9	–	45	530
Porcel et al., 2005 (2)	53	Female	NR	Fitofruit grasas acumuladas (Gerble, Barcelona, Spain)	16	27¶	–	1259	187
Pedros et al., 2003 (3)	35	Female	White	Exolise (Arkopharma, Carros, France)	35	26	–	1558	340
Pedros et al., 2003 (3)	29	Female	White	Exolise (Arkopharma, Carros, France)	45	68	–	1674	260
Garcia-Moran et al., 2004 (4)	25	Female	White	Camilina Akocapsulas (manufacturer not reported)	60	108	–	2398	164
Thiolet et al., 2002 (5)	39	Female	White	Oolong tea fine tonic (manufacturer not reported)	15	Not reported	Resumed supplement in 3 months; no increase in serum aminotransferase levels observed	45× normal	3× normal
Vial et al., 2003 (6)	46	Female	White	Exolise (Arkopharma, Carros, France)	75	Not reported	Serum alanine aminotransferase levels greater than 10× normal (rechallenge with Exolise and a second supplement)	>100× normal	2× normal

\* Additional case reports not referenced in text are available from Porcel et al. NR = not reported.

† On the basis of history and dose size stated on package.

‡ One case reported; these findings were observed during first episode.

§ One case reported; these findings were observed during second episode.

|| Uncertain because of vague labeling.

¶ According to authors, each capsule contains 651 mg of green tea extract.

Table—Continued

Peak Serum Total Bilirubin Level, $\mu\text{mol/L}$ (mg/dL)	Peak Serum Direct Bilirubin Level, $\mu\text{mol/L}$ (mg/dL)	Peak Prothrombin Time, s	Imaging Results	Biopsy Results	Duration of Injury	Outcome
11.7	9.9	12.5	Ultrasonogram: coarsened echotexture suggestive of fatty infiltration	Marked periportal piecemeal necrosis; periportal inflammation; mild lobular inflammation; no plasma cells; negative trichrome stain	>1 month	Recovery; serum alanine aminotransferase level of 31 U/L on 4 November 2004
9.0	7.3	13.2	Ultrasonogram: normal postcholecystectomy findings	—	<2 months	Recovery; serum alanine aminotransferase level of 69 U/L on 27 January 2005
133 (7.8)	—	16	—	—	4 weeks	Recovery
133 (7.8)	—	15	Computed tomogram and endoscopic retrograde cholangiopancreatogram: normal	Cholestasis and portal inflammation	<2 months	Recovery
92 (5.36)	—	12.7	Ultrasonogram: hepatomegaly	—	<5 weeks	Recovery
323 (18.9)	222 (13)	—	Ultrasonogram: normal	—	—	Recovery
308 (18)	246 (14.4)	—	—	—	—	Recovery
340 (19.9)	219 (12.8)	77% of normal	Ultrasonogram: normal	—	15 days	Recovery
—	—	Normal	Ultrasonogram: hepatomegaly, hyperechogenicity favoring steatosis	—	<2 months	Recovery
508 (29.7)	155 (9.1)	85% of normal	Normal	—	<4 months	Recovery