Financial Disclosures: Mr Steinglass is technical director of the IMMUNIZATIONbasics Project. He reports that he is a salaried full-time employee of JSI Research & Training Institute, which receives funding from the United States Agency for International Development for IMMUNIZATIONbasics to provide developing countries with technical support to strengthen immunization programs, including polio eradication. He states no conflict of interest or special financial interest.

1. Cochi SL, Kew O. Polio today: are we on the verge of global eradication? *JAMA*. 2008;300(7):839-841.
2. Centers for Disease Control and Prevention. Progress toward poliomyelitis eradication: Nigeria, January 2007-August 12, 2008. *MMWR Morb Mortal Wkly Rep*. 2008;57(34):942-946.
3. Ehrenfeld E, Glass RI, Agol VI, et al. Immunization against poliomyelitis: moving forward. *Lancet*. 2008;371(9621):1385-1387.
4. Progress towards polio eradication, Nigeria, 1996-1998. *Wkly Epidemiol Rec*. 1999;74(16):121-128.
5. Immunization surveillance, assessment and monitoring. World Health Organization Web site. http://www.who.int/immunization_monitoring/en. Accessed October 20, 2008.

In Reply: Mr Steinglass correctly points out that we could not explore the full complexity of global polio eradication in our article. Regular, detailed updates are available on the Internet[1] and from weekly publications.[2,3] The cause of all remaining poliovirus circulation worldwide is insufficient population immunity, usually the consequence of low rates of OPV coverage. In northern Nigeria, failure to vaccinate is the reason for continuing poliovirus circulation. Up to 60% of children in certain high-risk states (eg, Kano) have received 3 or fewer doses of OPV despite numerous opportunities either through routine immunization or the many rounds of supplemental immunization activities (SIAs).[2] This large-scale failure to vaccinate is unique among the remaining endemic areas of the world.

All 3 poliovirus serotypes are co-circulating, a situation that has not existed anywhere else in the world since 1999, when wild poliovirus type 2 was eradicated globally. The capacity for wide international spread has been demonstrated for the Nigerian wild poliovirus type 1[2,4] and on a more limited basis for the wild poliovirus type 3.[3] An outbreak of type 2 circulating vaccine-derived poliovirus (cVDPV) in the northern states of Nigeria has been ongoing since 2005.[2,5] Past experience in other countries with either type 2 wild poliovirus outbreaks or type 2 cVDPV outbreaks demonstrates uniformly that such outbreaks have been quickly controlled by increasing OPV coverage.[5]

Efficacy of the basic eradication strategies has been validated repeatedly by the eradication of the indigenous wild polioviruses in almost all countries, including areas of Pakistan, Afghanistan, and Nigeria where the communities are more accessible and the biological risks are at least as high as in the remaining endemic areas. However, low rates of OPV coverage in insecure areas of Pakistan and Afghanistan have resulted in persistent pockets of endemicity for wild poliovirus types 1 and 3.[3] While most of India has been able to stop transmission of wild poliovirus, the situation in northern parts of the country appears to be different than in the other endemic areas. Poliovirus circulation persists despite frequent high-quality SIAs that have increased OPV coverage rates to greater than 90% in the outbreak states of Uttar Pradesh and Bihar.[3] Improved routine immunization and the addition of inactivated poliovirus vaccine given in mass campaigns may help accelerate polio eradication in these states where the biological risks for poliovirus circulation (500 000 or more births per month, poor sanitation, subtropical climate) are very high.[3]

Steinglass also correctly points out the need to improve the quality of delivery of polio vaccines to all children of the world. Indeed, the success of polio eradication, which means the total cessation of all poliovirus circulation, rests on achieving that goal through a proper balance between routine immunization and supplemental mass immunization campaigns. Successful navigation[6] from the current polio-endemic phase, through the posteradication phase, and to the post-OPV phase requires the continued development of a comprehensive endgame strategy for maintaining high population immunity and sensitive polio surveillance.

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Financial Disclosures: None reported.

1. Global Polio Eradication Initiative Web site. http://www.polioeradication.org. Accessed October 14, 2008.
2. Centers for Disease Control and Prevention. Progress toward poliomyelitis eradication: Nigeria, January 2007-August 12, 2008. *MMWR Morb Mortal Wkly Rep*. 2008;57(34):942-946.
3. Progress towards interrupting of wild poliovirus transmission worldwide, January 2007-April 2008. *Wkly Epidemiol Rec*. 2008;83(19):170-176.
4. Centers for Disease Control and Prevention. Resurgence of wild poliovirus type 1 transmission and consequences of importation: 21 countries, 2002-2005. *MMWR Morb Mortal Wkly Rep*. 2006;55(6):145-150.
5. Centers for Disease Control and Prevention. Update on vaccine-derived polioviruses: worldwide, January 2006-August 2007. *MMWR Morb Mortal Wkly Rep*. 2007;56(38):996-1001.
6. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. *Annu Rev Microbiol*. 2005;59:587-635.

RESEARCH LETTER

Thyroid-Stimulating Hormone–Receptor Antibody and Thyroid Hormone Concentrations in Smokers vs Nonsmokers With Graves Disease Treated With Carbimazole

To the Editor: Cigarette smoking increases the risk of complications of Graves disease, such as ophthalmopathy and relapse after treatment with antithyroid drugs.[1] Anecdotally, patients with Graves disease who smoke appear to respond more slowly to treatment with carbimazole. We therefore retrospectively compared the decline in concentrations of thyroid-stimulating hormone (TSH)–receptor antibody and thyroid hormones in smokers and nonsmokers during carbimazole therapy.

Methods. We studied 59 consecutive patients (25 smokers and 34 nonsmokers) meeting inclusion criteria who attended the Endocrine Clinic, Royal Infirmary, Edinburgh, United Kingdom, between January and April 2007 during the first 12 months of carbimazole therapy for Graves disease (TABLE). Carbimazole was used in an initial maximum dose of 40 mg/d and at review reduced according to thyroid hormone and TSH concentrations. TSH-receptor antibody, free thyroxine (FT_4), and total triiodothyronine (T_3) concentrations were measured every 4 to 6 weeks. TSH-receptor antibodies were measured using the TRAK human luminescence immunoassay (Brahms, Hennigsdorf, Germany), which is a competitive-binding assay. Values greater than 1.5 IU/L were regarded as positive. Levels of TSH, FT_4, and T_3 were measured using an Architect automated immunoassay platform (Abbott Diagnostics, Dartford, United Kingdom). Patients who were pregnant, allergic to carbimazole, former smokers, irregular attenders, and those who reported poor medication adherence were excluded. The project was approved by the local ethics committee, and all patients provided oral consent.

Power calculations revealed that 16 participants were needed in each group to have a 90% chance of detecting at least a 25% difference in each outcome at a 2-sided α level of .05. Data collected over the 12 months of carbimazole therapy were analyzed by summary measure analysis[2] using the area under the curve (AUC) as calculated by the trapezoid rule. Groups were compared using the Mann-Whitney test. All statistical tests were performed using GraphPad Prism version 4 (GraphPad Software Inc, La Jolla, California).

Results. All 59 patients completed the study. Smokers and nonsmokers had similar concentrations of TSH-receptor antibodies and thyroid hormones at diagnosis (Table). With carbimazole treatment, smokers compared with nonsmokers showed a much slower reduction in concentrations of TSH-receptor antibody (AUC, 107.5 vs 59.0 IU/L; $P=.02$), FT_4 (AUC, 17.4 vs 12.5 ng/dL; $P=.01$), and T_3 (AUC, 2078 vs 1526 ng/dL; $P=.003$) (FIGURE and Table). After 12 months the concentrations of TSH-receptor antibody, FT_4, and T_3 were not significantly different between smokers and nonsmokers. Smokers required higher doses of carbimazole than nonsmokers (median, 17.8 mg/d vs 10.4 mg/d; $P=.04$) (Table).

Comment. These findings suggest an association between smoking and the rates of decline of TSH-receptor antibody and thyroid hormones with carbimazole use. The mechanism for such differences is unclear. There is no evidence that smokers were less adherent with carbimazole use than nonsmokers. Aside from inhibiting thyroid hormone synthesis, antithyroid drugs have immunomodulatory effects that attenuate TSH-receptor antibody concentrations, which may contribute to their efficacy[3]; cigarette smoking might inhibit this immunosuppressive action. The rate of decrease in TSH-receptor antibody concentrations during the early phase of antithyroid drug treatment may reliably predict remission of Graves hyperthyroidism.[4] Thus, protracted elevation of TSH-receptor antibody concentrations might explain why smoking increases the risk of treatment failure.[1]

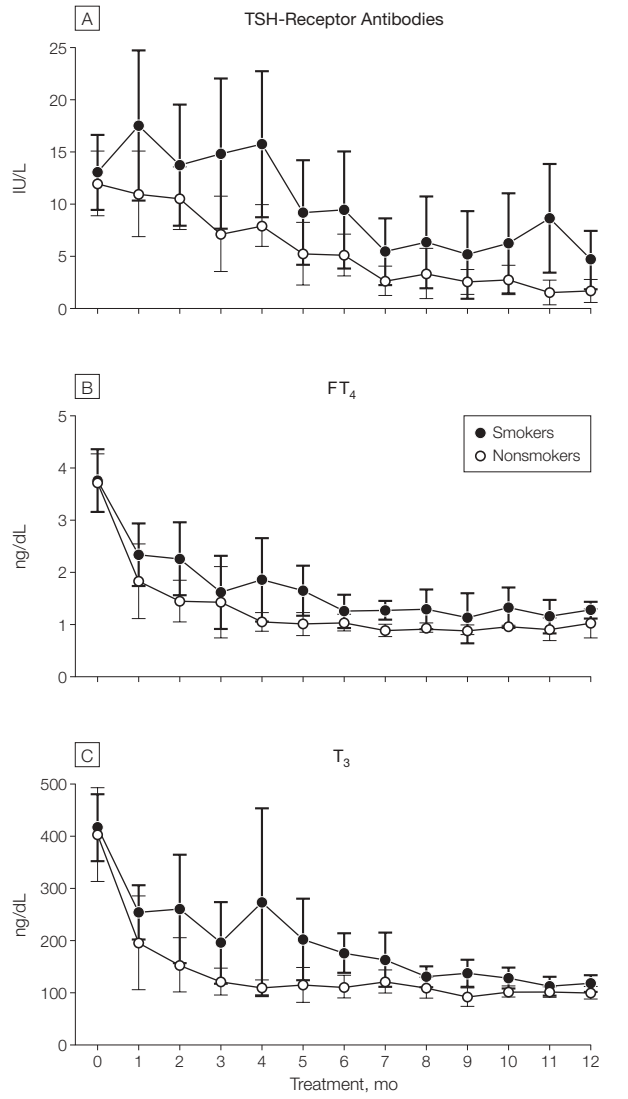
lnterindividual differences in the response to antithyroid therapy in patients with hyperthyroidism may reflect kinetic variability.[5] It is also possible that smoking affects

Table. Clinical Characteristics and Response of TSH-Receptor Antibodies and Thyroid Hormones During Treatment With Carbimazole for Graves Disease

	Median (IQR)		
	Smokers (n = 25)	Nonsmokers (n = 34)	*P* Value[a]
Age, y	40 (33-49)	39 (29-49)	
Women, No. (%)	24 (96)	33 (97)	
Cigarettes/d	15 (10-20)		
Pack-years of smoking	17.5 (9.9-38.1)		
Baseline thyroid tests			
TSH, mIU/L	<0.01	<0.01	
TSH-receptor antibody, IU/L	11.0 (6.0-18.2)	10.2 (6.3-16.3)	.42
FT_4, ng/dL	3.3 (2.4-4.4)	3.7 (2.6-4.2)	.43
T_3, ng/dL	389.6 (321.4-546.8)	344.2 (217.5-539.0)	.80
Area under the curve over 12 mo			
No. of serial measurements	9 (7.5-10)	9 (7-10)	.78
TSH-receptor antibody, IU/L	107.5 (45.5-200.5)	59.0 (31.0-101.0)	.02
FT_4, ng/dL	17.4 (14.8-24.2)	12.5 (11.3-17.0)	.01
T_3, ng/dL	2078 (1851-2305)	1526 (1266-1890)	.003
Carbimazole dose, mg/d	17.8 (13.3-22.9)	10.4 (7.8-18.5)	.04

Abbreviations: IQR, interquartile range; TSH, thyroid-stimulating hormone.
SI conversion factors: To convert free thyroxine (FT_4) to pmol/L, multiply by 12.871; to convert total triiodothyronine (T_3) to nmol/L, multiply by 0.0154.
[a] By Mann-Whitney test.

Figure. Thyroid-Stimulating Hormone (TSH)–Receptor Antibody and Thyroid Hormone Concentrations in Smokers and Nonsmokers With Graves Disease During Treatment With Carbimazole



Means at each time point are shown for serum concentrations of TSH-receptor antibodies (A), free thyroxine (FT_4) (B), and total triiodothyronine (T_3) (C) in smokers (n=25) and nonsmokers (n=34) during the first 12 months of carbimazole therapy. Area under the curve comparisons yielded $P=.02$ for TSH-receptor antibodies, $P=.01$ for FT_4, and $P=.003$ for T_3. Error bars represent 95% confidence intervals. To convert FT_4 to pmol/L, multiply by 12.871; to convert T_3 to nmol/L, multiply by 0.0154.

carbimazole absorption, concentration in the thyroid gland, or metabolism. Smoking is thought to affect expression of microsomal enzymes, which may influence the concentration of carbimazole or its metabolites.[6]

Study limitations include small patient sample size from a single site, retrospective data collection, and the possibility of confounders such as sex and drug interactions. These results require confirmation in a larger prospective study.

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Financial Disclosures: None reported.
Funding/Support: None.

1. Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *JAMA*. 1993; 269(4):479-482.
2. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ*. 1990;300(6719):230-235.
3. McGregor AM, Petersen MM, McLachlan SM, Rooke P, Smith BR, Hall R. Carbimazole and the autoimmune response in Graves' disease. *N Engl J Med*. 1980; 303(6):302-307.
4. Takasu N, Yamashiro K, Komiya I, Ochi Y, Sato Y, Nagata A. Remission of Graves' hyperthyroidism predicted by smooth decreases of thyroid-stimulating antibody and thyrotropin-binding inhibitor immunoglobulin during antithyroid drug treatment. *Thyroid*. 2000;10(10):891-896.
5. Skellern GG, Knight BI, Low CK, Alexander WD, McLarty DG, Kalk WJ. The pharmacokinetics of methimazole after oral administration of carbimazole and methimazole, in hyperthyroid patients. *Br J Clin Pharmacol*. 1980;9(2):137-143.
6. Hukkanen J, Dempsey D, Jacob P III, Benowitz NL. Effect of pregnancy on a measure of FMO3 activity. *Br J Clin Pharmacol*. 2005;60(2):224-226.