

## IMPAIRED ACTION OF THYROID HORMONE ASSOCIATED WITH SMOKING IN WOMEN WITH HYPOTHYROIDISM

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**Abstract** *Background.* The effect of smoking on thyroid function is controversial, and its effect on thyroid hormone action is unknown. We investigated the effects of cigarette smoking in women with various grades of hypothyroidism and in normal women.

*Methods.* We studied 138 normal women and 135 women with primary hypothyroidism, of whom 84 had subclinical hypothyroidism and 51 overt hypothyroidism. Sixty of the women with hypothyroidism were reevaluated during thyroxine therapy. The women were categorized as smokers or nonsmokers according to their responses to a questionnaire. Thyroid function was evaluated by measurements of serum thyrotropin, free thyroxine, and triiodothyronine. Peripheral thyroid hormone action was assessed by a clinical score and measurements of ankle-reflex time and serum lipids and creatine kinase.

*Results.* Among the women with subclinical hypothyroidism, the smokers had a higher mean ( $\pm$ SD) serum thyrotropin concentration ( $21.3 \pm 16.6$  vs.  $12.7 \pm 7.2$  mU per liter,  $P=0.004$ ) and a higher ratio of serum triiodothyronine to serum free thyroxine (by 30 percent,  $P=0.003$ ) than the nonsmokers. Their serum concentrations of total

cholesterol and low-density lipoprotein (LDL) cholesterol were higher (by 16 percent,  $P=0.013$ ; and 28 percent,  $P=0.003$ , respectively). Among the women with overt hypothyroidism, the serum concentrations of thyrotropin, free thyroxine, and triiodothyronine were similar in the smokers and nonsmokers. As compared with the nonsmokers, the smokers had a clinical score indicating a greater degree of hypothyroidism ( $P<0.001$ ), higher serum concentrations of total and LDL cholesterol (by 25 percent,  $P<0.001$ ; and 24 percent,  $P=0.002$ , respectively), longer ankle-reflex time (by 25 percent,  $P<0.001$ ), and higher serum concentrations of creatine kinase (by 236 percent,  $P<0.001$ ). There were dose-response relations between smoking and serum concentrations of total and LDL cholesterol, serum creatine kinase concentrations, and ankle-reflex time in the women with overt hypothyroidism, and between smoking and serum concentrations of total and LDL cholesterol in the women with subclinical hypothyroidism.

*Conclusions.* Smoking increases the metabolic effects of hypothyroidism in a dose-dependent way. This may be explained by alteration of both thyroid function and hormone action. (N Engl J Med 1995;333:964-9.)

**T**HYROID dysfunction and cigarette smoking are both common in the general population, with prevalences of about 10 percent<sup>1</sup> and 30 percent,<sup>2</sup> respectively. The influence of cigarette smoking on thyroid function is controversial. Both decreased and increased thyroid function<sup>3-6</sup> and a goitrogenic effect<sup>4,7</sup> have been described in smokers in some studies, but in others smoking has had no effect on thyroid function<sup>8</sup> or thyroid size.<sup>9</sup> These studies presumed a direct effect of constituents of cigarette smoke on the thyroid gland, since some components of tobacco smoke (e.g., nicotine, thiocyanate, hydroxypyridine metabolites, and benzopyrenes) have been reported to interfere with thyroid function.<sup>3,5,6,10,11</sup> Whether smoking has any effect on the peripheral actions of thyroid hormone is not known. We studied the effect of cigarette smoking on serum thyrotropin and thyroid hormone concentrations and on thyroid hormone action in large groups of women with various grades of hypothyroidism before and during thyroxine therapy and in normal women.

### METHODS

#### Study Subjects

We used a standardized protocol<sup>12</sup> to select the 273 study subjects from a larger group of 322 women studied prospectively in the endo-

crine outpatient clinic of the University Hospital of Basel, Switzerland. From this larger group we excluded 46 women (5 of them smokers and 41 nonsmokers) with mild subclinical hypothyroidism (basal serum thyrotropin concentration,  $\leq 6$  mU per liter), 2 receiving medications affecting thyroid function, and 1 with subacute thyroiditis. Only women were studied to exclude variations due to sex. All the hypothyroid women were ambulatory and in good general health. All the control subjects were normal women — mainly staff members, their relatives, or friends. After an overnight fast, all the women underwent full medical assessment and laboratory examinations (hematology and blood-chemistry tests and urinalysis) to rule out nonthyroidal illnesses.

We studied the following groups: 138 normal women, with a mean ( $\pm$ SD) age of  $47 \pm 13$  years, all of whom had serum concentrations of thyrotropin (both at base line and after receiving thyrotropin-releasing hormone), free thyroxine, and triiodothyronine within normal reference ranges; 84 women, with a mean age of  $52 \pm 13$ , who had subclinical hypothyroidism, defined as a basal serum thyrotropin concentration higher than 6.0 mU per liter with normal serum concentrations of free thyroxine and triiodothyronine<sup>12,13</sup>; and 51 women, with a mean age of  $57 \pm 12$ , who had overt hypothyroidism, defined as a basal serum thyrotropin concentration higher than 20 mU per liter and low serum free thyroxine concentrations ( $<0.6$  ng per deciliter [ $<8$  pmol per liter]). Among the 135 women with hypothyroidism, 62 had chronic autoimmune thyroiditis; 61 had Graves' hyperthyroidism treated with surgery or <sup>131</sup>I; and 12 had undergone thyroidectomy for simple goiter (11 women) or an autonomously functioning thyroid adenoma (1 woman). We also studied 60 of the 135 women with hypothyroidism (26 with subclinical and 34 with overt hypothyroidism) when they were euthyroid after treatment with thyroxine for at least three months, as confirmed by a normal serum thyrotropin response to thyrotropin-releasing hormone on two separate occasions.

For each woman, a standardized questionnaire — including questions about smoking habits, alcohol intake, menopausal status, and treatment with estrogen or other medications — was completed by a physician. The physicians did not know the results of the biochemical studies, which were available only after the clinical examination. Smoking habits were categorized in the following way: nonsmokers (women who had never smoked or had smoked previously but stopped before entering the study), one-pack-per-day smokers (those who smoked up to one pack of 20 cigarettes per day), two-packs-per-day smokers (up to two packs per day), and smokers of more than two

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packs per day. All the women reexamined later maintained their baseline smoking habits. The overall frequency of smokers among the 273 women was 23 percent, which is almost identical to the 22 percent frequency in the female population of Switzerland.<sup>2</sup> Thus, the smoking habits of our cohort are representative of the smoking habits of women in Switzerland. The study was approved by the Ethics Committee for Human Studies of the University Hospital of Basel, and informed consent was given by each woman.

### Serum Hormone Concentrations and Tests of Peripheral Action of Thyroid Hormone

Serum thyrotropin concentrations (reference range, 0.1 to 4.0 mU per liter) were measured in most women by immunoradiometric assay (TSH-RIA-gnost, Behring, Frankfurt, Germany); before its introduction we used a radioimmunoassay (correlation with the immunoradiometric assay:  $r=0.93$ ,  $P<0.001$ ,  $n=94$ ), as previously described.<sup>12</sup> Serum concentrations of triiodothyronine (reference range, 58 to 195 ng per deciliter [0.9 to 3.0 nmol per liter]) and free thyroxine (reference range, 0.6 to 2.1 ng per deciliter [8 to 27 pmol per liter]) were determined by radioimmunoassay (Clinical Assays, Baxter, Cambridge, Mass.). An oral thyrotropin-releasing hormone test was performed to verify the euthyroid status of the normal women and the thyroxine-treated women with hypothyroidism. In this test, we determined serum thyrotropin and triiodothyronine concentrations before and three hours after the oral administration of 40 mg of thyrotropin-releasing hormone (reference ranges, 7.5 to 37.3 mU per liter and 23 to 97 ng per deciliter [0.4 to 1.5 nmol per liter], respectively).<sup>13,14</sup> The increase in serum triiodothyronine after the administration of thyrotropin-releasing hormone, which we call the thyroid reserve, is a good marker of impending thyroid failure.<sup>12,13</sup> To estimate the proportion of active thyroid hormone (triiodothyronine) relative to its precursor (thyroxine), we divided the serum concentrations of triiodothyronine by those of free thyroxine.

We scored the degree of clinical hypothyroidism using the index of Billewicz et al.<sup>15</sup> This index is based on the quantitative scoring of 14 symptoms and signs of hypothyroidism (euthyroidism is indicated by a score of  $-30$  points or less; clinical hypothyroidism,  $+25$  points or more; and borderline hypothyroidism,  $-29$  to  $+24$  points). Serum

total cholesterol and triglycerides were measured enzymatically, and serum low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol by ultracentrifugation (Airfuge, Beckman, Fullerton, Calif.), as described previously.<sup>12,16</sup> Ankle-reflex time was measured by photomotography with an achillometer (Polymed, Glattbrugg, Switzerland; reference range, 290 to 410 msec); six tracings (three on each ankle) were recorded for each woman. The ankle-reflex time was the mean of the six readings. Serum creatine kinase was measured enzymatically by AutoAnalyzer (reference range, 40 to 160 U per liter).

### Statistical Analysis

Analysis of frequencies was performed with the use of contingency tables (chi-square). A two-way analysis of variance, including the factors smoking (yes or no) and severity of hypothyroidism, was performed for the peripheral tests of thyroid hormone action to evaluate the interaction between smoking and hypothyroidism. In addition, two group comparisons corrected for multiple testing (a one-way analysis of variance and a multiple-range test for least-square difference) between smokers and nonsmokers within the various groups were performed. Ordinal scaled data (the clinical scores) were verified by Wilcoxon's rank-sum test.<sup>17</sup> Finally, we categorized the number of packs of cigarettes smoked per day and computed the linear contrast for the measurements of peripheral thyroid hormone action to verify a dose-response relation within the groups.<sup>18</sup> All statistical tests were two-tailed.

## RESULTS

The effects of cigarette smoking on serum thyrotropin and thyroid hormone concentrations and on the tests of peripheral thyroid hormone action are summarized in Tables 1 and 2 and in Figure 1. The smokers and nonsmokers within the groups were well matched with respect to age, body-mass index, menopausal status, estrogen therapy, and incidence of treated Graves' hyperthyroidism. In all groups, more smokers than

Table 1. Characteristics and Thyroid Function of Women with Various Degrees of Hypothyroidism, According to Smoking Habits.\*

VARIABLE	NORMAL WOMEN			WOMEN WITH SUBCLINICAL HYPOTHYROIDISM†			WOMEN WITH OVERT HYPOTHYROIDISM‡			WOMEN RECEIVING THYROXINE THERAPY		
	NON-SMOKERS (N = 109)	SMOKERS (N = 29)	P VALUE	NON-SMOKERS (N = 65)	SMOKERS (N = 19)	P VALUE	NON-SMOKERS (N = 37)	SMOKERS (N = 14)	P VALUE	NON-SMOKERS (N = 45)	SMOKERS (N = 15)	P VALUE
Age (yr)	48±13	43±13	0.058	52±13	50±14	0.52	58±13	55±11	0.51	57±14	53±11	0.37
Postmenopausal (no.)	56	12	0.34	42	12	0.91	27	8	0.28	31	8	0.27
Estrogen therapy (no.)	10	3	0.57	6	2	0.84	4	1	0.87	4	1	0.98
Daily alcohol use (no.)	71	24	0.069	30	14	0.035	24	8	0.61	21	10	0.18
Dose of thyroxine (µg/day)	—	—	—	—	—	—	—	—	—	106±28	100±18	0.40
Thyroid function												
Serum thyrotropin (mU/liter)	1.5±0.8	1.4±0.5	0.96	12.7±7.2	21.3±16.6	0.004	51.1±22.8	45.1±33.2	0.088	2.1±1.5	1.8±1.7	0.95
Serum free thyroxine (ng/dl)‡	1.3±0.2	1.2±0.3	0.69	1.0±0.2	0.9±0.2	0.042	0.3±0.1	0.3±0.1	0.32	1.5±0.3	1.4±0.3	0.79
Serum triiodothyronine (ng/dl)§	117±31	114±16	0.63	116±25	130±39	0.058	66±22	56±29	0.30	102±22	115±40	0.12
Ratio of serum triiodothyronine to free thyroxine¶	97±30	94±19	0.77	123±32	159±56	0.003	221±96	217±71	0.80	73±23	80±23	0.64
Serum thyrotropin after thyrotropin-releasing hormone (mU/liter)	19.8±8.5	20.3±6.7	0.96	84.1±35.2	129.4±63.1	<0.001	117.3±83.0	92.5±63.2	0.058	18.7±11.5	12.8±10.8	0.62
Thyroid reserve (ng/dl)**	60±27	73±31	0.021	38±24	39±21	0.84	17±12	14±10	0.81	4±14	8±15	0.66

\*Plus-minus values are means ±SD. Analysis of frequencies was performed with the use of contingency tables (chi-square). Parametric data were tested by one-way analysis of variance (least-square difference).

†The distribution of women with a history of Graves' hyperthyroidism was as follows: subclinical hypothyroidism — nonsmokers, 36, and smokers, 7 ( $P=0.18$ ); overt hypothyroidism — nonsmokers, 14, and smokers, 4 ( $P=0.54$ ).

‡Measured in 328 women. To convert values for serum free thyroxine to picomoles per liter, multiply by 12.9.

§Measured in 294 women. To convert values for serum triiodothyronine to nanomoles per liter, multiply by 0.015.

¶Determined in 289 women.

||Serum thyrotropin concentration three hours after the oral administration of thyrotropin-releasing hormone (measured in 292 women).

\*\*Thyroid reserve is defined as the increase in serum triiodothyronine concentration three hours after the oral administration of thyrotropin-releasing hormone (measured in 284 women).

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Table 2. Peripheral Thyroid Hormone Action in Women with Various Degrees of Hypothyroidism, According to Smoking Habits.\*

VARIABLE	NO. OF WOMEN	NORMAL WOMEN			WOMEN WITH SUBCLINICAL HYPOTHYROIDISM			WOMEN WITH OVERT HYPOTHYROIDISM			WOMEN RECEIVING THYROXINE THERAPY		
		NONSMOKERS	SMOKERS	P VALUE	NONSMOKERS	SMOKERS	P VALUE	NONSMOKERS	SMOKERS	P VALUE	NONSMOKERS	SMOKERS	P VALUE
<b>Clinical score</b>													
Symptoms and signs (points)	328	-33±15	-33±14	0.94	-18±22	-13±23	0.29	+7±30	+35±28	<0.001	-27±15	-26±17	0.90
Body-mass index†	325	23.1±3.7	22.9±3.2	0.81	24.5±4.0	24.6±5.1	0.67	25.8±3.6	26.3±3.8	0.67	25.9±3.8	25.2±2.7	0.56
<b>Serum lipid profile‡</b>													
Total cholesterol (mg/dl)	317	236±49	229±56	0.55	236±43	274±73	0.013	292±75	365±94	<0.001	237±39	253±47	0.33
LDL cholesterol (mg/dl)	312	147±43	143±54	0.75	154±39	197±71	0.003	213±78	265±71	0.002	154±38	176±44	0.15
HDL cholesterol (mg/dl)	311	59±10	57±9	0.49	56±12	53±9	0.21	53±9	54±8	0.67	52±8	52±6	0.94
Total cholesterol:HDL cholesterol	311	4.1±1.0	4.1±1.2	0.92	4.3±1.0	5.3±1.4	0.01	5.8±2.2	6.9±2.3	0.019	4.7±1.2	4.9±1.0	0.65
Triglycerides (mg/dl)	316	95±47	89±37	0.69	112±103	126±68	0.48	145±75	173±76	0.25	130±70	135±107	0.81
<b>Muscle</b>													
Ankle-reflex time (msec)	273	356±40	345±30	0.48	380±44	382±36	0.89	468±121	584±109	<0.001	378±43	396±36	0.37
Serum creatine kinase (U/liter)	312	88±37	83±41	0.93	85±35	78±33	0.91	252±326	846±1125	<0.001	80±37	92±58	0.88

\*Plus-minus values are means  $\pm$ SD. Analysis of frequencies was performed with the use of contingency tables (chi-square). Parametric data were tested by one-way analysis of variance (least-square difference). The ordinal scaled data (the clinical scores) were verified by Wilcoxon's rank-sum test.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡To convert values for cholesterol to millimoles per liter, multiply by 0.026. To convert values for triglycerides to millimoles per liter, multiply by 0.011.

nonsmokers drank alcohol daily; the difference was statistically significant in the women with subclinical hypothyroidism.

### Normal Women

Among the normal women, there were no significant differences between smokers and nonsmokers in basal serum thyrotropin or thyroid hormone concentrations or in the measures of peripheral thyroid hormone action. The thyroid reserve was slightly higher among the smokers.

### Subclinical Hypothyroidism

As compared with the nonsmokers with subclinical hypothyroidism, the smokers with subclinical hypothyroidism had higher serum thyrotropin concentrations (by 68 percent,  $P=0.004$ ), slightly lower serum free thyroxine concentrations (by 10 percent,  $P=0.042$ ), and higher ratios of serum triiodothyronine to free thyroxine concentrations (by 29 percent,  $P=0.003$ ; independent of estrogen therapy). The thyroid reserves were similar. In the smokers, the serum total and LDL cholesterol concentrations were higher (by 16 percent,  $P=0.013$ ; and 28 percent,  $P=0.003$ , respectively), as were the ratios of serum cholesterol to HDL cholesterol concentrations (by 23 percent,  $P=0.01$ ). In contrast to the smokers, the nonsmokers with subclinical hypothyroidism had serum lipid values not significantly different from those in the normal women. The results of the symptom scoring and of the other tests of peripheral thyroid hormone action in the smokers and nonsmokers were similar.

### Overt Hypothyroidism

The serum thyrotropin and thyroid hormone concentrations were similar among the smokers and non-

smokers with overt hypothyroidism. In contrast, the mean ( $\pm$ SD) clinical score was higher in the smokers ( $+35\pm28$  vs.  $+7\pm30$  points,  $P<0.001$ ), indicating more severe tissue hypothyroidism. As compared with the nonsmokers, the smokers had higher serum total and LDL cholesterol concentrations (by 25 percent,  $P<0.001$ ; and 24 percent,  $P=0.002$ , respectively). Similarly, the smokers had longer ankle-reflex times (by 25 percent,  $P<0.001$ ) and higher serum creatine kinase concentrations (by 236 percent,  $P<0.001$ ).

The nonsmokers with overt hypothyroidism had serum lipid values similar to those of the women with subclinical hypothyroidism who smoked, despite the marked differences in serum thyrotropin and thyroid hormone concentrations.

### Thyroxine Therapy

The doses of thyroxine, the serum thyrotropin and thyroid hormone concentrations, and the results of the tests of peripheral thyroid hormone action were similar in the smokers and nonsmokers studied during treatment. The daily dose of thyroxine required did not correlate with the severity of hypothyroidism and did not differ between the subclinical and overt-hypothyroidism groups: the 26 women with subclinical hypothyroidism were taking a mean ( $\pm$ SD) of  $102\pm28$   $\mu$ g per day and the 34 women with overt hypothyroidism were taking  $106\pm25$   $\mu$ g per day ( $P=0.65$ ).

There was a dose-response relation between cigarette smoking and serum total and LDL cholesterol concentrations in the women with subclinical hypothyroidism and those with overt hypothyroidism (Fig. 2); in the women with overt hypothyroidism, there was also a dose-response relation between smoking and the ankle-reflex time ( $P=0.012$ ) and serum creatine kinase con-

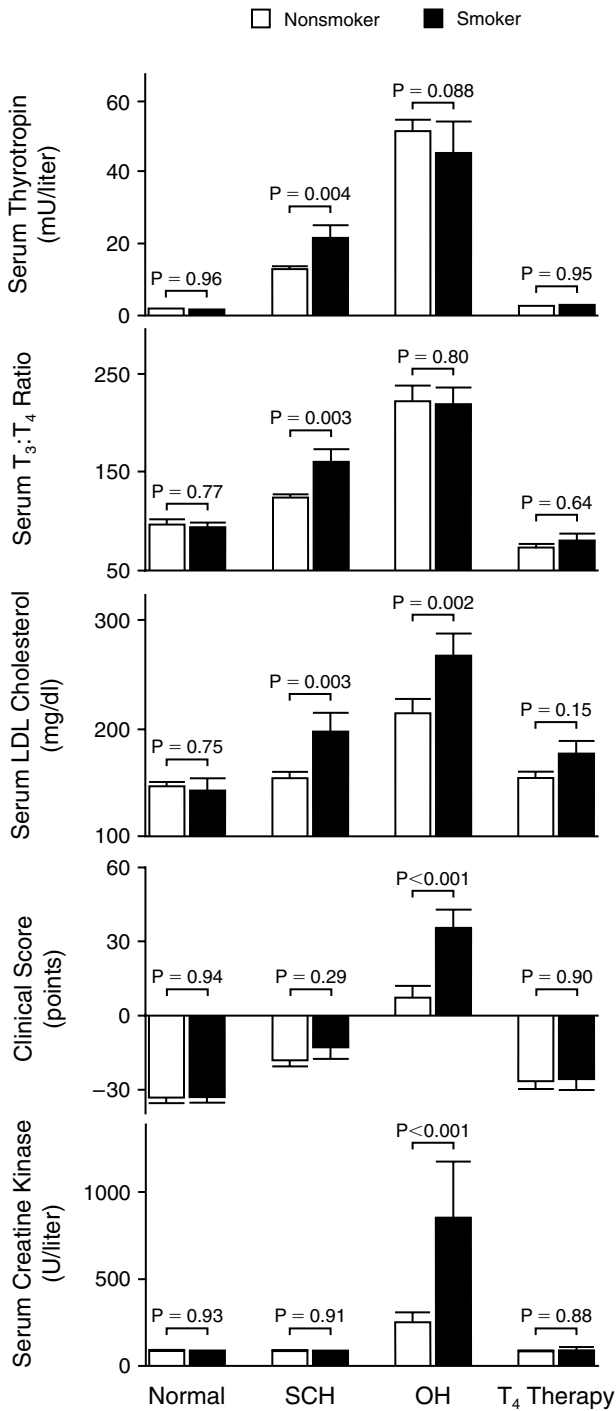


Figure 1. Influence of Cigarette Smoking on Thyroid Function and Results of Tests of Thyroid Hormone Action in Normal Women and Women with Subclinical or Overt Hypothyroidism. P values were derived by one-way analyses of variance. SCH denotes subclinical hypothyroidism, OH overt hypothyroidism, T<sub>3</sub> triiodothyronine, and T<sub>4</sub> free thyroxine. Boxes represent means, and bars standard errors. To convert values for serum LDL cholesterol to millimoles per liter, multiply by 0.026.

centration ( $P < 0.001$ ) (data not shown). For the clinical score, the level of significance was  $P = 0.094$ . There was no relation between smoking frequency and serum thyrotropin and thyroid hormone concentrations. The two-way analysis of variance revealed a significant contribu-

tion of smoking to the increased severity of peripheral manifestations of hypothyroidism, as reflected in the clinical score ( $P = 0.005$ ), the serum cholesterol concentration ( $P = 0.002$ ), and the ankle-reflex time and serum creatine kinase concentration (both  $P < 0.001$ ).

### DISCUSSION

Our findings of no differences in thyroid function among normal women who smoke (as compared with nonsmokers) and of higher serum thyrotropin and lower serum free thyroxine concentrations among women with subclinical hypothyroidism who smoke indicate that smoking has a noxious effect on the thyroid gland that becomes apparent when thyroid function is slightly compromised. The higher ratio of serum triiodothyronine to free thyroxine concentrations in this group reflects preferential secretion of triiodothyronine resulting from increased secretion of thyrotropin. In women with overt hypothyroidism, the harmful effect of smoking on the thyroid gland was no longer detectable, probably because of the overriding effect of the thyroid destruction itself. The discrepancies in the literature regarding the effect of smoking on thyroid function<sup>3-8</sup> could be explained by differences in general health or by the inclusion of subjects with subclinical hypothyroidism. The inhibition of thyroid function may reflect the higher serum thiocyanate concentrations in smokers. Thiocyanate is a goitrogenic agent that acts acutely by inhibiting transport of thyroid iodide and, at higher doses, by competing with iodide in the organification process.<sup>11</sup> Alternatively, pyridine or other components of cigarette smoke may have a mild antithyroid effect.<sup>3,6,10</sup>

We found evidence of impaired thyroid hormone action in both smokers with subclinical hypothyroidism and those with overt hypothyroidism. The women with subclinical hypothyroidism who smoked had higher serum total and LDL cholesterol values than those who did not, and the women with overt hypothyroidism who smoked had higher clinical scores, higher serum cholesterol concentrations, and more severe muscle dysfunction than those who did not. Some effects of cigarette smoking on lipid metabolism have been reported in normal subjects — namely, decreased serum HDL cholesterol and increased LDL cholesterol concentrations<sup>19,20</sup> — but we found no differences in these values between smokers and nonsmokers in the group of normal women or in the group of hypothyroid women treated with thyroxine. The observed effects of smoking in subclinical hypothyroidism could explain the conflicting findings on the changes in serum lipid concentrations in the literature.<sup>21</sup> According to our data, subclinical hypothyroidism is a risk factor for hypercholesterolemia only in smokers. The smokers with subclinical hypothyroidism had higher serum thyrotropin and lower free thyroxine concentrations than the nonsmokers, suggesting that their higher serum total and LDL cholesterol values resulted from their poorer thyroid function, even though the latter group did not have more symptoms or greater changes in ankle-reflex time or serum creatine kinase concentrations. However, the findings of higher serum total and LDL cholesterol values, as well as higher clinical-symptom scores and

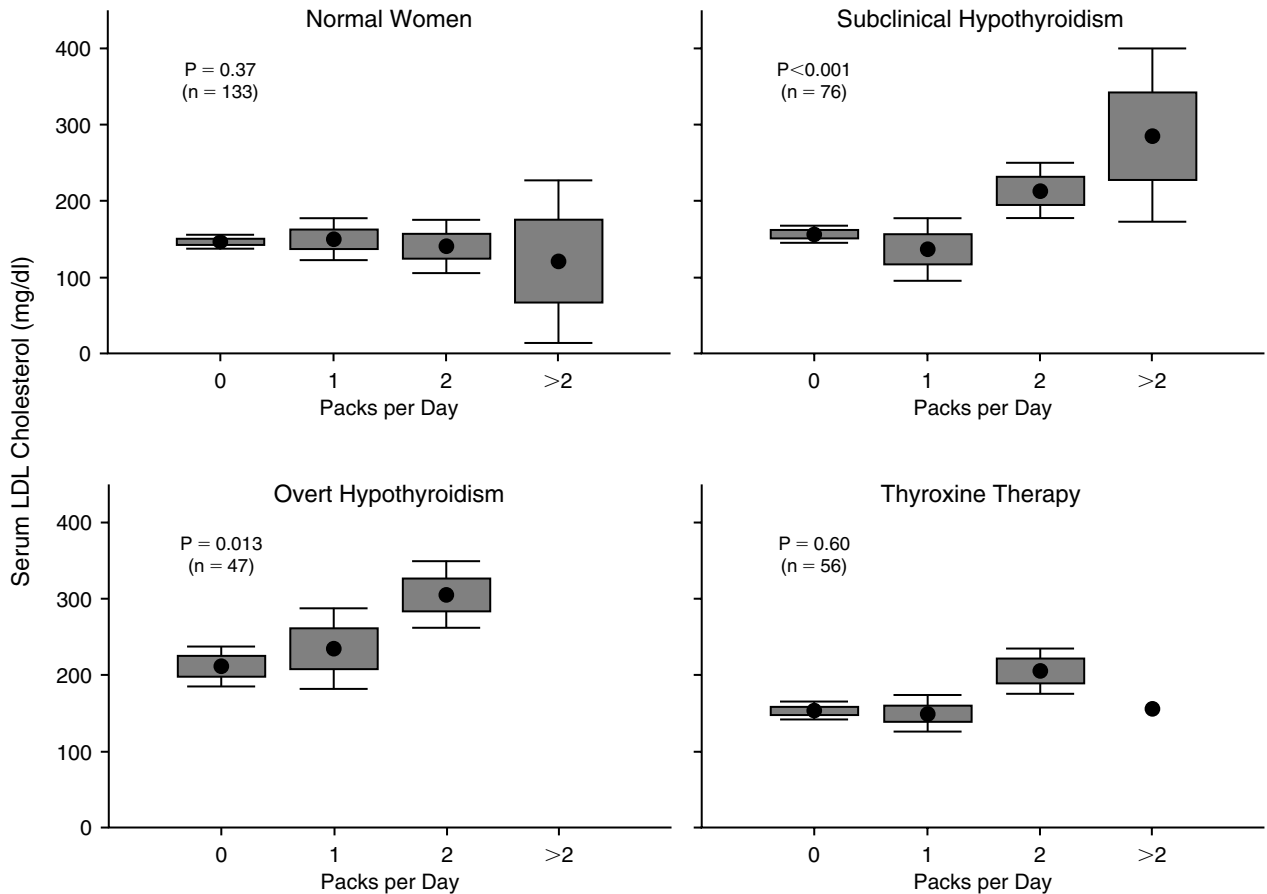


Figure 2. Dose–Response Relation between Smoking and Serum LDL Cholesterol Concentrations in Normal Women and Women with Subclinical or Overt Hypothyroidism.

P values denote the linear contrast. The categories (0, 1, 2, and >2 packs per day) are defined in the text. Dots indicate means, boxes standard errors, and bars 1.96 times the standard error. To convert values for serum LDL cholesterol to millimoles per liter, multiply by 0.026. Data are included for all women for whom complete information on LDL cholesterol concentrations and smoking habits was available.

serum creatine kinase values and longer ankle-reflex times in the smokers with overt hypothyroidism than in the nonsmokers, suggest that smoking impaired thyroid hormone action, because the serum thyrotropin and thyroid hormone concentrations in these two groups were similar.

One might argue that smokers tend to lead less healthy lives and to have higher serum lipid concentrations for that reason. All the women in the study came from the same small area of Switzerland, and their habits and lifestyles were similar, as were their body-mass indexes and serum triglyceride concentrations. As expected, more smokers than nonsmokers drank alcohol daily, with a significant difference among the women with subclinical hypothyroidism. Therefore, we calculated the results of all tests of peripheral thyroid hormone action in relation to the presence or absence of alcohol consumption in the hypothyroid and euthyroid women. There were no differences between the women who drank alcohol daily and those who did not. Furthermore, as noted above, the effect of smoking on thyroid hormone action was evident not only in differences in serum cholesterol concentrations but also in differences in symptoms and signs and in muscle function. Therefore,

we do not believe that differences in lifestyle, dietary habits, or alcohol consumption can explain our data.

The way in which the effects of smoking are mediated remains speculative at present, since the responses of tissues and organs to the more than 4000 constituents of tobacco smoke are multiple and complex.<sup>22</sup> Carbon monoxide is known to increase the blood carboxy-hemoglobin concentration, resulting in relative tissue hypoxia.<sup>23</sup> In hypothyroidism, however, oxygen consumption by peripheral tissue is reduced, and resistance to hypoxia is increased.<sup>24,25</sup> A more convincing hypothesis to explain our results is that constituents or metabolites of tobacco smoke impair thyroid hormone action more directly. Thyroid hormones (mainly triiodothyronine) exert their effects by interaction with nuclear receptors that bind to regulatory regions of genes and modify their expression.<sup>26</sup> We found a dose–response relation between smoking and serum total and LDL cholesterol concentrations and also muscle function, but not between smoking and the serum thyrotropin concentration. The heterogeneity of responses in different tissues could be explained by the tissue-specific expression of the different types of triiodothyronine receptors ( $\alpha 1$ ,  $\alpha 2$ ,  $\beta 1$ , and  $\beta 2$ ). Liver and skeletal mus-

cle contain mainly  $\beta 1$  and  $\alpha 1$  receptors, respectively. In contrast, the pituitary contains  $\beta 2$  receptors.<sup>27</sup> Smoking may exert tissue-specific effects on thyroid hormone action at both the pretranslational and posttranslational levels. Thus, the metabolic effects on smokers with hypothyroidism may be the net result of altered expression of several genes directly or indirectly regulated by triiodothyronine. In euthyroid patients, the pool of circulating thyroid hormones is adequate to compensate for this reversible defect of thyroid hormone action, but in patients with hypothyroidism it is not.

In summary, smoking impairs both thyroid hormone secretion and thyroid hormone action. Although the mechanisms of these effects are not known, the results have several clinical implications. First, smoking may contribute to the high incidence of subclinical hypothyroidism — 10 percent in some studies<sup>1,12</sup> — and may aggravate the peripheral biochemical effects even if it does not aggravate the clinical manifestations of subclinical hypothyroidism. Our finding that all metabolic effects are normalized in smokers treated with thyroxine is an argument for treating all smokers with subclinical hypothyroidism. Second, smoking may aggravate both the clinical manifestations and biochemical effects of overt hypothyroidism. Smoking status should be considered in the evaluation of patients in whom hypothyroidism is suspected.

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#### APPENDIX

The study team consisted of the following: *clinical research* (Division of Clinical Endocrinology, Medical Outpatient Clinic, Department of Medicine, Division of Nuclear Medicine, University Hospital of Basel): B. Althaus, P. Exer, R. Gräni, W. Häfeli, T. Heinemann, T. Kühne, K. Marquardt, C. Mitrache, J. Müller-Brand, B. Noelpp, P. Palacios, C.B. Roth, F. Roulet, A.S. Ryff, K. Scheidegger, F. Tortosa, P. Trabucco, T. Vogt, D. Weyermann, and A. von Weymarn; *hormone measurements* (Hormone Laboratories, University Hospital of Basel): J. Girard and S. Frei; *lipid analysis* (Lipid Laboratory, University of Basel): U. Keller, H.B. Stähelin, and A. Oberhänsli; and *ankle-reflex time* (Medical Outpatient Clinic, University Hospital of Basel): S. Alscher, E. Eckhoff, M. Kunz, and H. Neuenschwander.

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