Prospective study of factors predicting outcome of transdermal nicotine treatment in smoking cessation

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Abstract

***Objective*—To assess the factors associated with cessation of smoking with transdermal nicotine and brief behavioural counselling.**

***Design*—Interviews, treatment, and follow up for 26 weeks.**

***Subjects*—1481 subjects recruited by mass media publicity who smoked ≥15 cigarettes a day and were motivated to stop smoking.**

***Interventions*—Twelve weeks' treatment with transdermal nicotine and brief behavioural counselling at monthly visits.**

***Main outcome measure*—Sustained smoking cessation for the 28 days before the visit at week 26 verified by expired carbon monoxide concentrations. The logistic regression analysis included all subjects.**

***Results*—Most subjects were dependent on nicotine, and the mean (SD) number of cigarettes smoked a day was 32 (12). Overall, 316/1481 subjects (21·3%) stopped smoking. Factors associated with stopping were being male (adjusted odds ratio 2·0; 95% confidence interval 1·5 to 2·7), age ≥40 years (1·5; 1·1 to 2·0), living with a spouse or partner (1·5; 1·1 to 2·1), motivation ("want to quit" 1·7; 1·2 to 2·3), and concern about weight gain (1·7; 1·3 to 2·2). Negative associations were smoking marijuana (0·4; 0·2 to 0·8) and the presence of other smokers in the household (0·8; 0·6 to 0·9). Almost all subjects who smoked three or more cigarettes in the first four weeks of treatment resumed smoking in the long term (525/547, 96%).**

***Conclusions*—Age, sex, marital status (living with a spouse or partner), motivation, concern about weight gain, recent marijuana smoking, and other smokers in the household were baseline factors associated with differences in outcome of smoking cessation attempts. Smoking three or more cigarettes in the first few weeks after stopping strongly predicted long term relapse.**

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Introduction

Transdermal nicotine replacement treatment in general practice and other settings is now firmly established as an aid to stopping smoking[1-4] so repeated placebo controlled efficacy studies seem inappropriate. Success rates are about twofold higher with transdermal nicotine than with placebo, but factors associated with a better outcome in placebo controlled studies of adequate size have not yet been determined.

Observational studies of large populations have shown that heavier smokers and those reporting a shorter interval between waking and the first cigarette of the day are least likely to give up smoking.[5-10] Such smokers may particularly benefit from nicotine replacement treatment. Factors such as younger age, lower education level, and being black have also been associated with lower rates of stopping.

We conducted a large open study of treatment with transdermal nicotine in conjunction with brief behavioural counselling of the type likely to be used in a routine consultation with a general practitioner. The purpose of the first six months of this study was to determine the baseline factors associated with smoking cessation in moderate to heavy smokers by using transdermal nicotine treatment. Those relapsing were recruited into a double blind, randomised placebo controlled study of a repeat course of treatment.

Subjects and methods

The study of 1481 subjects aged 18-70 was conducted in metropolitan Melbourne, Australia. Smokers were included if they expressed a strong desire to stop smoking, had smoked 15 or more cigarettes daily for at least three years, and were willing to consider a second serious attempt to stop should the first be unsuccessful.

Behavioural treatment consisted of five to 10 minutes of counselling and a booklet containing advice and instructions for use of patches. Counselling concentrated on contingency management for smoking urges, advice about weight gain, and the need for no smoking at all after the date of stopping. The nicotine patches used were Nicotinell TTS (Ciba-Geigy, Pendle Hill, Australia) in a fixed regimen starting from a "quit day" within two weeks of the planning visit. A patch of 30 cm^2 (21 mg/24 hours) was used for the first four weeks, followed by one of 20 cm^2 (14 mg/24 hours) for four weeks and one of 10 cm^2 (7 mg/24 hours) for four weeks (see fig 1).

The study was approved by the ethics review committee of the Alfred Hospital and was conducted in accordance with guidelines issued by the Australian Department of Community Services and Health.[11]

RECRUITMENT

Subjects were recruited after a newspaper article about the study in a popular daily newspaper. After a screening interview by telephone 1618/1807 subjects (90%) were offered a planning appointment at the study centre. Of these subjects, 83 (5%) did not attend. At the appointment an additional 54/1535 smokers (4%) were ineligible.

EXCLUSION CRITERIA

The main exclusion criteria were drug treatments that might interfere with tobacco withdrawal symptoms (that is, regular use of other nicotine replacement products, β blockers, clonidine, α methyldopa, appetite suppressants, minor and major tranquillisers); pregnancy, lactation, or potential pregnancy; mental or psychiatric illness; symptomatic ischaemic heart disease or cerebrovascular disease within the past three months; alcohol misuse; active malignancy; major medical disorders; and extensive skin lesions precluding application of patches. Subjects were instructed not to use other nicotine products during the study.

FOLLOW UP

Each subject was scheduled for review at the study centre four, eight, 12, and 26 weeks after their chosen quit day and received five to 10 minutes of counselling in addition to the time spent collecting data and dispensing drugs. Those known to have resumed smoking 15 or more cigarettes a day between the 17th

and 30th weeks after the date of stopping were invited to take part in the second phase of the study.

MEASUREMENTS

Blood pressure, heart rate, weight, and carbon monoxide concentration in expired air were measured at each visit. The blood pressure and heart rate recorded were the average of two measurements taken five minutes apart with the appropriately sized cuff on the left arm of a seated subject. Korotkoff phase I and V sounds were used for the systolic and diastolic pressures respectively. Carbon monoxide concentration was measured after the subject held his or her breath for 15 seconds by using the Bedfont EC50 hand held monitor (Bedfont Technical Instruments, Kent). All instruments were checked and calibrated regularly according to the manufacturer's instructions. Nicotine dependence was assessed by the modified Fagerström tolerance questionnaire.[12]

TABLE I—*Characteristics of subjects undergoing treatment with nicotine patches to stop smoking. Values are numbers (percentages) of subjects unless stated otherwise*

Characteristic	All subjects (n=1481)	Men (n=658)	Women (n=823)
Mean (SD) age (years)	41·1 (10·8)	41·0 (10·8)	41·2 (10·8)
Mean (SD) No of cigarettes a day	32·3 (11·8)	34·5 (12·9)	30·6 (10·5)
Mean (SD) duration of smoking (years)	23·2 (10·7)	23·8 (11·2)	22·7 (10·2)
Nicotine dependence*:			
High	866 (58)	423 (64)	443 (54)
Moderate	474 (32)	187 (28)	287 (35)
Low	141 (10)	48 (8)	93 (11)
Motivation:			
"Want to stop"	1100 (74)	472 (72)	628 (76)
"Should stop"/other	381 (26)	186 (28)	195 (24)
Likelihood of stopping:			
Certain/very likely	1058 (71)	467 (71)	591 (72)
Less likely	423 (29)	191 (29)	232 (28)

*Modified Fagerström tolerance score[12]: high, ≥7; moderate, 5-6; low, ≤4.

TABLE II—*Crude rates of smoking cessation and adjusted odds ratios* for all subjects*

Variable	No of subjects	No (%) who stopped smoking	Adjusted odds ratio (95% confidence interval)	P value
All subjects	1481	316 (21)		
Age (years):				
<40	717	122 (17)		
≥40	764	194 (25)	1·5 (1·1 to 2·0)	0·004
Sex:				
Women	823	151 (18)		
Men	658	165 (25)	2·0 (1·5 to 2·7)	<0·001
Marital status:				
No spouse or partner	424	69 (16)		
Spouse or partner	1057	247 (23)	1·5 (1·1 to 2·1)	0·006
Education†:				
Primary or some secondary	677	130 (19)		
Completed trade	178	33 (19)	0·8 (0·5 to 1·3)	0·395
Completed secondary	316	74 (23)	1·3 (1·0 to 2·0)	0·083
University	310	79 (25)	1·4 (1·0 to 2·0)	0·058
Motivation to stop:				
"... Should..."/other	381	64 (17)		
"...Want to..."	1100	252 (23)	1·7 (1·2 to 2·3)	0·001
No of cigarettes a day‡:				
15-20	249	58 (23)		
21-30	699	145 (21)	0·8 (0·6 to 1·2)	0·278
≥31	533	113 (21)	0·8 (0·5 to 1·1)	0·202
Concern about weight gain:				
Not concerned	765	144 (19)		
Concerned	716	172 (24)	1·7 (1·3 to 2·2)	<0·001
Concern about withdrawal symptoms:				
Not concerned	323	68 (21)		
Concerned	1158	248 (21)	1·0 (0·7 to 1·4)	1·000
Presence of other smokers in household:				
None present	775	184 (24)		
Others present	706	132 (19)	0·8 (0·6 to 0·9)	0·014
Smoking related disease:				
Not present	1329	285 (21)		
Present	152	31 (20)	0·8 (0·5 to 1·3)	0·373
Depression:				
Never or past	1376	298 (22)		
Current (Beck score ≥16)	105	18 (17)	0·8 (0·5 to 1·3)	0·373
Marijuana smoking:				
Never or past	1339	301 (22)		
Recent	142	15 (11)	0·4 (0·2 to 0·8)	0·005
Alcohol consumption (No of drinks when drinking):				
≤4	1127	251 (22)		
>4	354	65 (18)	0·8 (0·6 to 1·1)	0·212

*Odds ratios adjusted for all other factors in table. Odds ratio above 1 indicates positive association with stopping smoking whereas odds ratio below 1 indicates negative association.
†P value for trend=0·023. ‡P value for trend=0·240.

The motivation of enrolled smokers was graded by asking them to choose the most appropriate of six statements about stopping smoking, ranging from "I very much want to stop" to "I want to keep on smoking." Perceived likelihood of stopping was assessed by asking the smokers to choose one of seven phrases ranging from "certain" to "definitely not."

ANALYSIS

All subjects were included in the logistic regression analysis. The outcome of interest was smoking cessation, defined as sustained self reported non-smoking for the 28 days before week 26 of follow up, provided that it was confirmed by a carbon monoxide reading of ≤8 ppm. Multiple logistic regression assessed the joint effects of sociodemographic factors and other factors of interest on stopping smoking. Possible interactions of factors were investigated by adding the appropriate interaction terms to the logistic model. Changes in weight, blood pressure, and heart rate from baseline were analysed by the use of paired *t* tests.

The baseline factors studied were age, sex, marital status (living with a spouse or partner), education, motivation, number of cigarettes a day, possible diagnoses related to smoking (for example, ischaemic heart disease, other vascular disease, emphysema, or chronic bronchitis), depression (Beck score ≥16[13,14]), recent marijuana smoking (any use in the past month), usual alcohol consumption (>4 standard drinks when drinking), the presence of other smokers in the household, concern about gaining weight, and concern about withdrawal symptoms. These were selected on the basis of other published work[5-10,15-20] and hypotheses stated in the study protocol. Age was divided into two equal groups. The categories for the number of cigarettes a day were previously recommended.[21] Additional variables added to the initial model to explore sex differences were country of birth (Australia/outside Australia), income per capita, carbon monoxide concentration, and highly dependent modified Fagerström tolerance score. Subjects lost to follow up (9%) or unavailable for measurement of carbon monoxide in expired air (0·3%) were assumed to be smoking.

Data were analysed with SAS-PC[22] and EGRET[23] software packages. Results are reported as means (SD) or as odds ratios and 95% confidence intervals.

Results

CHARACTERISTICS OF PATIENTS

In total 1481 subjects were recruited for the study. Tables I and II show their demographic characteristics. The mean (SD) age was 41·1 (10·8) years, and most smokers were moderately (474/1481, 32%) or highly (866/1481, 58%) dependent on nicotine. The mean (SD) number of cigarettes smoked a day was 32·3 (11·8), and subjects had smoked for an average of 23·2 (10·7) years.

COMPLIANCE

After the first four weeks of treatment with the patches of 30 cm² 1211 out of 1481 subjects (82%) continued treatment. After treatment with the patches of 20 cm² 994 out of 1481 subjects (67%) continued. The rate of permanent discontinuation of treatment because of adverse effects possibly or likely to be related to transdermal nicotine was 7·1%.

SMOKING CESSATION

Overall 316/1481 subjects (21·3%) had stopped smoking 26 weeks after the quit day (fig 1). Table II summarises the crude rates of cessation and lists the adjusted odds ratios for the factors possibly influencing

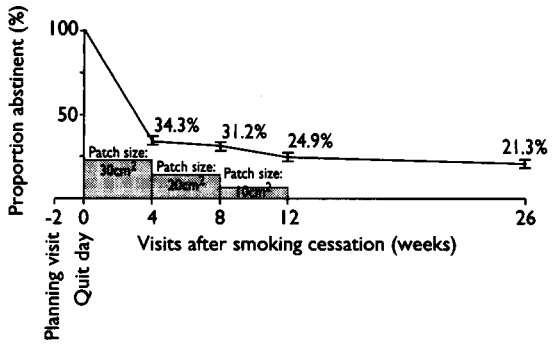

FIG 1—*Schedule of treatment and rates of abstinence at each visit (n=1481) with 95% confidence intervals. Abstinence defined as self reported sustained non-smoking for 28 days before follow up with expired carbon monoxide concentrations ≤8 ppm*

the outcome of attempts. There were no significant interactions between any factors.

Men were more likely than women to abstain successfully from smoking (adjusted odds ratio 2·0; 95% confidence interval 1·5 to 2·7), as were those smokers aged 40 or more (1·5; 1·1 to 2·0), subjects living with a spouse or partner (1·5; 1·1 to 2·1), and smokers who had responded that they very much wanted to stop smoking (1·7; 1·2 to 2·3). Those who at baseline expressed concern about possible weight gain were also more likely to be successful (1·7; 1·3 to 2·2). Anticipation of other problems, such as symptoms of nicotine withdrawal or failure to succeed, was not associated with differences in outcome. Depression, smoking related diseases, excessive use of alcohol and separate categories of level of education were not significant predictors, although there was a trend towards improved rates of stopping with higher levels of education (P value for trend=0·023).

Two factors predicted a lack of success in stopping smoking. A negative association was seen with recent marijuana smoking (0·4; 0·2 to 0·8) and if subjects lived with people who continued to smoke (0·8; 0·6 to 0·9).

When men and women were analysed separately the adjusted odds ratios were similar in most cases. The positive association between concern about weight gain and stopping smoking was more pronounced among men (1·9; 1·3 to 2·9) than among women (1·5; 1·0 to 2·2). Rates of cessation for women were the lowest in every category of predictive variable studied. In addition, rates for women who smoked more than 30 cigarettes a day were lower than for women who smoked 15 to 20 cigarettes a day (0·6; 0·3 to 0·9, P value for trend=0·026). No such relation with the number of cigarettes smoked a day was observed for men.

Additional baseline variables added to the initial logistic model were not significant. The principal conclusions of the analysis were unaffected when stepwise logistic regression was used instead of a model including all factors or when alternative definitions of smoking cessation were used. Specifically, with "continuous abstinence" as the end point (self reported and biochemically confirmed abstinence from smoking at every scheduled visit, n=198) all factors retained significance with similar odds ratios except for motivation grading (1·4; 1·0 to 2·1), marital status (1·3; 0·9 to 2·1), and the presence of other smokers in the household (0·9; 0·7 to 1·3).

EARLY RELAPSE

Smoking a total of three or more cigarettes in the first four weeks after the quit day was strongly associated with long term relapse (fig 2). Only 22/549 of such subjects (4%) were able to achieve abstinence by week 26 compared with 242/480 of subjects (51%) who had not smoked at all. The reported smoking of only one or two cigarettes during the first four weeks more than halved the likelihood of eventual success.

WEIGHT GAIN AND CHANGES IN BLOOD PRESSURE

There were no significant changes from baseline in mean systolic or diastolic blood pressures. Subjects who were not smoking at follow up at week 26 had gained an average of 4·2 (3·4) kg (n=316, P<0·001). Men gained an average of 4·5 (3·5) kg and women gained 3·8 (3·34) kg. For those subjects who relapsed to smoke 15 or more cigarettes a day the average weight gain was 0·7 (2·7) kg (n=629, P<0·001).

Heart rate in subjects who were not smoking at week 26 had decreased by an average of 3·2 (9·9) beats a minute (n=316, P<0·001), but if subjects relapsed to regular smoking it returned to baseline.

Abstinent subjects who expressed concern about weight gain before stopping smoking (716/1481, 48·3%) weighed more at baseline than those who were unconcerned (mean baseline differences: men 9·5 kg, women 6·8 kg). Smokers concerned about their weight gained the same amount of weight as other abstinent smokers and were also more likely to stop smoking successfully. The mean age and the history of smoking, as measured by the number of previous attempts to stop, daily urges to smoke, years of smoking, and earlier abstinence time, did not differ between the two groups.

Discussion

This open study was the first large scale investigation of factors associated with the outcome of attempts to stop smoking using transdermal nicotine replacement treatment. Such treatment for motivated subjects should minimise the importance of nicotine dependence as a predictor and facilitate the identification of other variables associated with success or failure. An earlier study of transdermal nicotine found no consistent relations between baseline factors and stopping smoking but was too small to form definite conclusions.[24] The advantages of our study were its prospective design, the large size of the cohort, biochemical verification of abstinence, and the return of a substantial proportion of unsuccessful smokers for follow up.

Other large prospective studies of predictors of giving up smoking have not focused on the type of smoker likely to present to a general practice for help. Doctors may tend to see the "harder cases" who have tried other methods and who are likely to be more dependent on nicotine.

The nature of our sample and the simple, brief style of behavioural counselling make the results generalis-

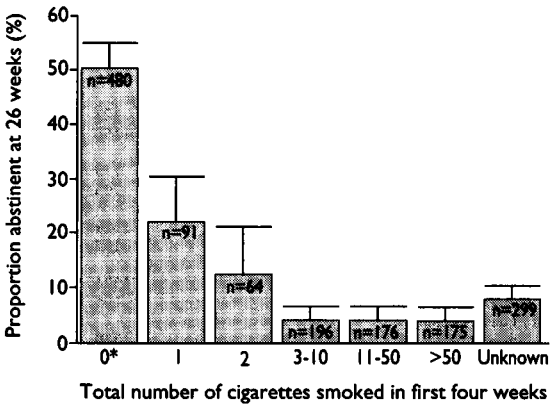

FIG 2—*Long term rates of abstinence (with upper limit of 95% confidence interval) according to reported total cigarette consumption during first four weeks after date of stopping. *Includes 12 subjects with carbon monoxide concentration >8 ppm*

able to clinical settings in which motivated, nicotine dependent smokers request help. Our subjects were similar to the population of a randomised study of transdermal nicotine in British general practices.[4] Smokers of 15 or more cigarettes a day were accepted into this study because the nicotine replacement treatment was expected to benefit mainly nicotine dependent smokers.[25,26]

FACTORS PREDICTING OUTCOME

We found that as the number of cigarettes a day increased, the rates of smoking cessation in women (but not in men) decreased. Higher motivation has previously been associated with men,[27] but moderate to high baseline motivation was a prerequisite for our study, limiting its discriminant value in this case. Other studies have reported similar sex differences in outcome,[15] and the Framingham study found a strikingly lower rate of cessation in women who smoked two packets a day compared with men and women who smoked half a packet a day.[7] Our results support the notion that women smoking heavily have particular difficulty stopping, even with the help of nicotine replacement treatment. This adds weight to recent concerns that increased smoking among women in many countries because of higher rates of uptake[28] may possibly be due to lower rates of cessation as well.[29]

We found relatively modest associations between stopping smoking and the baseline factors of older age, current marital status, and education level (table II). Several large observational studies have reported similar findings.[6-8,10,30]

A surprising finding was that concern about weight gain predicted success rather than failure. The difference in outcome was not explained by measured baseline characteristics or differences in weight gain, although concerned subjects weighed more at the outset. Most women anticipated the problem whereas only a minority of men expressed concern. This minority (195/658) had the highest rate of stopping of any subgroup of subjects (34%). Concern about weight gain might represent a marker of knowledge about stopping smoking or greater preparedness. As the issue of weight gain was included in the counselling given at each visit the findings suggest practitioners should not avoid a discussion of the problem for fear of dissuading patients from a serious attempt at stopping.

Recent marijuana smoking was reported by around 10% of our subjects at baseline. Rates of cessation were 50% lower for marijuana smokers than never or past users—an effect which persisted after other variables were controlled for. No data were collected about smoking marijuana during the study because the responses were expected to be unreliable and such follow up may have adversely affected the main aims of the study. Many marijuana smokers, however, probably continued to smoke the drug after the quit day. The possible reasons for a negative effect on stopping smoking are worthy of further study. They include the maintenance of smoking behaviour, continued nicotine addiction (in this region marijuana is nearly always combined with tobacco), and a social environment conducive to smoking. As smokers are primarily concerned about health when planning to stop,[8] perhaps giving up both drugs simultaneously should be recommended.

IMPORTANCE OF REVIEWING PROGRESS

These results suggest that it is important to review the progress of each patient before continuing transdermal nicotine treatment beyond four weeks. If a person has smoked more than one or two cigarettes over this time the probability of success is low (fig 2).[24,31] In this study continuation of transdermal nicotine treatment with brief counselling was unrewarding for this subgroup. After reviewing the smoker's commitment to behaviour change perhaps more intensive interventions focusing on behavioural aspects of stopping smoking, may be of more help than simply continuing an unsuccessful method. If underdosing during nicotine replacement is suspected, higher doses might be expected to help such smokers.[32] More rapid delivery of nicotine from nicotine gum may help some smokers more than the patches.[3] Whether or not transdermal nicotine is useful for a second serious attempt to stop is the subject of the second phase of this study.

Clinical implications

- Transdermal nicotine treatment is now commonly used to help patients give up smoking
- Success rates are twice as high in treated subjects than in those with placebo, but predictors of outcome are not yet established
- Treated subjects are unlikely to give up if they smoke three or more cigarettes in the first four weeks after starting treatment
- Factors associated with higher success rates were being male, age over 40, being married or living with a partner, high motivation, and concern about weight gain
- Recent marijuana smoking was strongly associated with lower success rates
- Intervention for modifiable negative factors might improve a smoker's chance of success

CONCLUSION

In conclusion, we identified several factors associated with the outcome of smoking cessation with transdermal nicotine and brief behavioural counselling. We identified significant associations between age, sex, marital status, motivation, concern about weight gain, marijuana smoking, and presence of other smokers in the household and outcome. Consideration of these factors may be useful when counselling smokers and developing strategies to improve the efficacy of transdermal nicotine treatment.

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High prevalence of serum antibodies to hepatitis C virus in patients with Hashimoto's thyroiditis

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Given the reports of thyroid dysfunction and various autoimmune disorders such as Sjögren's syndrome in patients infected with hepatitis C virus,[1,2] we hypothesised a link between autoimmune thyroid disease, mainly Hashimoto's thyroiditis, and such infection. We looked for antibodies to hepatitis C virus in the serum of patients with thyroid disease.

Subjects, methods, and results

We studied stored serum samples from 200 patients (190 women) with thyroid disease (simple goitre (n=50), Graves' disease (n=50), and Hashimoto's thyroiditis (n=50)) randomly selected from all patients seen at five centres between 1987 and 1992.

Thyroid function was assessed by standard radioimmunoassays for serum thyroxine, triiodothyronine, and thyroid stimulating hormone. Receptor antibodies for thyroid stimulating hormone were detected with radioreceptor assay (Trak-asay, Henning Laboratories, Berlin). Serum antibodies to thyroid microsome and thyroperoxidase were used to diagnose Hashimoto's thyroiditis, depending on the centre. Serum antibodies to thyroid microsome were detected with indirect immunoinflorescence assay by using cryostat sections of human thyroid or by passive haemagglutination with a commercial kit (Thymune-M, Wellcome Laboratories, Beckenham). Serum antibodies to thyroperoxidase were assessed by radioimmunoassay (Dynotest anti-TPO, Henning Laboratories, Berlin) and antibodies to thyroglobulin by passive haemagglutination (Thymune-T, Wellcome Laboratories, Beckenham).

A second generation enzyme linked immunosorbent assay (ELISA) (Diagnostics Pasteur, Marnes la Coquette, France) was used to detect antibodies to hepatitis C virus. Samples yielding positive results were retested with a second generation recombinant immunoblot assay (RIBA, Ortho Diagnostic Systems, Raritan, New Jersey). Serum concentrations of immunoglobulin G were assayed by laser nephelometry in the serum of patients with Hashimoto's thyroiditis.

Fisher's exact test and the Mann-Whitney U test were used for statistical analysis. Results are expressed as means (SD).

The table summarises the results of the assays. No significant difference was noted for age or serum concentration of immunoglobulin G in patients with Hashimoto's thyroiditis with or without hepatitis C virus antibodies.

Comment

We found a higher prevalence of serum hepatitis C virus antibodies in patients with Hashimoto's thyroiditis than in those with any other thyroid disease. Among patients with Hashimoto's thyroiditis those with a positive result on ELISA and a negative result on immunoblot assay had lower serum concentrations of immunoglobulin G than those with positive results in both tests, though this result was not significant. This suggests that false positive reactions because of high serum concentrations of immunoglobulin G are unlikely.

The disappearance of hepatitis C virus is followed by decreasing titres of serum hepatitis C virus antibodies, which become undetectable after several months or years of follow up,[3] though those patients with negative results in both assays may have low titres of antibodies not recognised by the highly specific but less sensitive immunoblot assay. If the result of the immunoblot assay becomes negative before the ELISA result, a few of these patients may be in fact infected with hepatitis C virus. The high prevalence of such antibodies in patients with Hashimoto's thyroiditis compared with other groups of thyroid disease and with the normal population[4] suggests that hepatitis C virus may be responsible for triggering Hashimoto's thyroiditis.