The supplementation of levothyroxine among indigenous people in endemic goitre areas: The impact of therapy

MI Zaleha,[1] A Osman,[1] ZA Iskandar,[1] S Sazali,[1] M Muhammad Ali,[2] I Roslan[2] and BAK Khalid[1]

[1]*Department of Community Health & Department of Medicine, Medical Faculty, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*
[2]*Department of Aboriginal Affairs, Gombak Hospital, Gombak, Selangor, Malaysia*

In order to study the effect of levothyroxine in the treatment of endemic goitre, a longitudinal study was conducted among the Aborigines in Lanai Post and Sinderut Post, situated in an iodine-deficient area located in the district of Kuala Lipis, Pahang. All subjects in the treatment group (Lanai Post) were given 100 μg of levothyroxine per day and were followed for 1½ years. A total of 311 subjects were examined at baseline, 323 on the first, 256 on the second, 239 on the third and 184 on the fourth visit following levothyroxine supplementation. Goitre prevalence, thyroid hormones, thyroid volume, nutritional status, urinary iodine levels, arterial blood pressure and mental performance were determined. Following the intervention, goitre prevalence was significantly reduced in the treatment group (baseline 42.8% *vs* final visit 13.0%, $P < 0.0001$); however, no significant difference was noted in the control group. Total T4 levels were increased in the treatment group ($P < 0.0001$), while a significant reduction was noted in the control group ($P < 0.0001$). Thyroid-stimulating hormone levels increased significantly in the treatment group following 1 year of intervention, while no significant changes were observed in the control group. As for the thyroid volume, both groups showed a significant increment following the intervention ($P < 0.0001$). With respect to the nutritional status, the treatment group showed a significant increase in body weight following the intervention ($P < 0.05$). In addition, the mid-arm circumference and body mass index also increased after 1 year of intervention. However, the control group showed a reduction in the waist–hip ratio ($P < 0.0001$). Although there was no statistical difference in the waist–hip ratio in the treatment group, there has been a significant reduction observed after 1 year of intervention. At 1 year, a reduction in skinfold thickness was noted in the treatment group while only the triceps and subscapular were increased in the control group. The body fat was decreased in the treatment group following 1 year of intervention ($P < 0.0001$). No particular trend was noted in the urinary iodine excretion in the treatment group, but surprisingly, the levels were increased in the control group ($P < 0.0001$). A significant increase in both systolic and diastolic blood pressures was observed in the treatment group following 1 year of intervention, but the controls showed a reduction in the systolic blood pressure ($P < 0.0001$). Both groups showed a remarkable increase in mental performance, with a more pronounced effect in the treatment group ($P < 0.05$). The correction of iodine deficiency by levothyroxine supplementation has a short-term beneficial effect in reducing the prevalence of goitre and improving the mental ability among the Aborigines in endemic areas; however, proper monitoring and close supervision are needed to maintain compliance.

Key words: levothyroxine, goitre, Malaysia, Aborigines, indigenous people, iodine deficiency.

Introduction

The use of levothyroxine in the treatment of endemic goitre offers a promising therapeutic approach by influencing the thyroid-stimulating hormone (TSH) secretion.[1] The increase in T4 levels under levothyroxine therapy is a well-established phenomenon and an important factor for the suppression of TSH secretion. Thyroid-stimulating hormone is known to be a stimulus for goitre growth by initiating cellular hypertrophy.[2] In Sweden, a country of approximately 8 million inhabitants, about 100 000 patients (i.e. 1.2% of the entire population) are receiving synthetic levothyroxine.[3] The preventive effect of levothyroxine on thyroid growth has also been studied in Germany,[1] where the effect of a combined administration of levothyroxine and iodine was able to reduce TSH secretion as well as cellular hypertrophy and hyperplasia. In euthyroid goitrous children, Einenkel *et al.* observed a significant reduction in the thyroid volume following three treatment regimens: levothyroxine, iodide and a combination of both.[4] However, no significant changes were found in urinary iodine excretion. Anderson *et al.* also found a significant effect of treatment with levothyroxine in the prevention of multinodular goitre.[5] Petersen *et al.* studied 29 women treated with levothyroxine for 1 to 28 years and concluded that the treatment caused no increase in morbidity, mortality, or side effects.[3]

Apart from improving the thyroid status of the goitrous patients, levothyroxine also caused a positive impact on nutritional status. Miura *et al.* concluded that levothyroxine

Correspondence address: Professor Dr Osman Ali, Department of Community Health, Medical Faculty, Hospital Universiti Kebangsaan Malaysia, Jalan Tenteram, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia.
Tel.: 603 9733333 ext. 2546; Fax: 603 9737825

treatment appears to prevent the disturbance in lipid metabolism that is seen in patients with subclinical hypothyroidism, especially in those patients with higher serum TSH levels (> 10 mIU/L).[6] The study by Arem and Patsch suggested that long-term levothyroxine therapy in patients with subclinical hypothyroidism is associated with a decrease in low-density lipoprotein cholesterol (LDLC) and apolipoprotein B levels, reflected in a trend of decreases in cholesterol/high-density lipoprotein cholesterol (HDLC) and LDLC/HDLC ratios which are related to coronary artery disease.[7]

Many studies have shown an association between endemic goitre and the psychological and intellectual outcome. Iodine deficiency is a well-known cause of disorders such as endemic goitre and cretinism, and a factor in the development of a wide spectrum of psychoneurological development disorders such as endemic mental deficiency and endemic cognitive deficiency, which are generally correlated with damage to the fetus.[8] Such damage is, by inference, deemed to be a direct consequence of iodine deficiency or of insufficient availability of thyroxine at the feto-placental unit. Therefore, in this study, we assessed whether treatment of hypothyroid children and adolescents with levothyroxine caused an improvement in their intellectual status.

Many previous studies indicate that thyroid hormones exert many effects on the heart by acting on myocardial growth as well as on systolic and diastolic function.[9] For example, Fazio *et al.* concluded that long-term levothyroxine therapy increases myocardial mass and causes diastolic dysfunction.[10] Due to this data, we also measured systolic and diastolic blood pressures of the patients receiving short-term levothyroxine supplementation.

In Malaysia, the problem of endemic goitre attracts less attention nowadays because it is no longer a public health problem. However, endemic goitre has been reported to be prevalent in many remote areas in the eastern part of the country, particularly Sarawak.[11] In 1976, Maberly *et al.* reported a goitre prevalence of 99.5% among members of the Iban community aged 11 years and above in the Ai river region of Lubok Antu district.[12] A recent study by Foo *et al.* in 1994 in the same area showed a goitre prevalence of 36.9% following 14 years of iodized salt distribution, indicating that endemic goitre continues to be an important public health problem in this area despite many efforts to control them.[13] In West Malaysia, endemic goitre is more prevalent among the Aborigines that occupy the remote iodide-deficient areas, located along the stretch of the Titiwangsa Divider Range. Lanai Post is one of the iodide-deficient areas and has been selected in this study to determine the ability of short-term levothyroxine therapy as an alternative strategy to improve the thyroid status. Because iodized salt was unsuccessful in iodine-deficiency disorder (IDD) prevention in Sarawak, the aim of this study was to evaluate the impact of using levothyroxine as a tool to eradicate IDD among Aborigines in iodide-deficient areas.

Methods

Study area

Lanai Post is an Aboriginal settlement located approximately 30 km from the town of Kuala Lipis, Pahang and 200 km from Kuala Lumpur. The area is located at the edge of Telom River, which is about a 2 h journey by boat from the jetty of Kuala Medang, Kuala Lipis (Fig. 1). It is comprised of villages lead by ‘Batin’ and consists of approximately 500 villagers. These Aborigines originate from the Semai (Senoi) ethnic group and most of them can speak Malay (the national language) in addition to their own distinct language. Their main activities are farming, such as planting cassava, hill rice, millet and maize; and collecting jungle products such as rattan, rattan seeds, banana leaves, medicinal herbs, etc. They also hunt with blow-pipes, using poisoned darts and also catch animals in traps. Once a week, the products are brought to Kuala Medang and sold to a ‘middle-man’. The profit they obtain from the sales is spent on food and daily needs. Most earn less than RM 250 per month. Only 44.1% have been to school and 34.2% have completed primary school. Most of them are animists by religion. Their houses are made of bamboo and wood with roofs made of rumbia or bertam leaves. They use the public water supply (gravity feed system) taken from the hills and nearby river. Due to limited water supply, the villagers are solely dependent on the river which was recently polluted due to timber activity in the upstream area. There is no electricity in this area and communication is by means of the wireless. A study done by Osman *et al.* revealed that adults in Lanai Post have the highest goitre prevalence (67.3%) when compared with other locations.[14]

Study population

The study was approved by the Universiti Kebangsaan Malaysia ethics committee. The programme on iodine deficiency eradication using levothyroxine supplementation was started in early January 1994. Subjects aged 4 years and above were used as participants in the study and another group of subjects in Sinderut Post (located nearby) were used as controls.

Intervention method

The study population was selected using a cluster sampling procedure. Subjects in the treatment group were given 100 µg of thyroxine sodium (Wellcome Australia Ltd, Cabarita,

Figure 1. Study area.

NSW, Australia) per day for a period of 18 months. The controls were not given any medication. A total of five visits in the treatment group and two visits in the control group were conducted (i.e. one baseline and four follow-ups and one pre- and post-evaluation, respectively).

In the treatment group, follow-up visits were performed at 4-monthly intervals during the first year and the impact evaluation was done 6 months later (during the second year). In each visit, villagers who attended our clinic were taken as subjects. Those who were too young or too old and those who suffered from cardiovascular diseases such as heart failure or arrythmias were excluded from the study. A total of 311 subjects were examined at baseline (before levothyroxine supplementation), 256 on the second (8 months of supplementation), 239 on the third (12 months) and 184 on the fourth visit (18 months). A total of seven Aboriginal adults were hired to ensure proper dose intake among the subjects. As for the control group, a total of 196 subjects during the pre-evaluation and 212 subjects during the post-evaluation were examined.

Food frequency

Food frequency data was obtained during the baseline study to assess the pattern of food intake. Types of food eaten were determined during the pilot study and parents from each family were interviewed regarding the food consumed by every member of the family. The foods were classified into two groups according to their iodine and goitrogen contents.

Clinical evaluation

All subjects were examined clinically at baseline and subsequent visits. Total serum thyroxine (normal range 40–140 nmol/L) and TSH (normal range 0.3–4.0 mIU/L) were measured by radioimmunoassay and immunoradiometricassay, respectively. Goitre stage was assessed by palpation according to the WHO classification,[15] while thyroid volume was determined by portable ultrasound (Toshiba Sonolayer, Model Sal-32B, Toshiba Corporation, Japan) with a 5.0 MHz transducer. Thyroid volume was calculated according to Brunn's formula:[16]

$$\text{volume} = \text{width} \times \text{thickness} \times \text{length } \$, 0.479^*$$

* being the correction factor.

Body weight was measured to the nearest 0.5 kg by a SECA balance scale and height without shoes was measured by the Microtoise tool (Depose, France) to the nearest 0.1 cm. Harpenden skinfold callipers (British Indicators Ltd, John Bull, England) were used to measure skinfold thicknesses to the nearest 0.1 cm. Waist and hip circumferences were measured to determine waist–hip ratio. Urinary iodine excretion was determined according to Sandell-Kolthoff reaction method.[17] Blood pressure was measured using a digital blood pressure/pulse monitor set (model HEM-400C, Omron Corporation, Japan) which was taken three times repeatedly and the mean were taken. Using WHO criteria, a systolic blood pressure (SBP) of 140 mmHg or more and a diastolic blood pressure (DBP) of 90 mmHg or more were classified as hypertension.[18]

Mental evaluation

Subjects aged 25 years and below were assessed for their intellectual outcome. The assessment of mental performance was conducted using Raven's Progressive Matrices (available from Oxford Psychologists Press). The test consists of 60 questions representing non-verbal figurative problems in the form of objects or designs which must be correctly aligned or rearranged to complete a prescribed pattern. Most subjects were helped by trained examiners particularly on how to mark the answers on the answer sheets. The mental evaluation score was stated in percentiles and a median score was used as the cut-off point. The results are shown by the number of subjects who scored above the median score.

Statistical analysis

The software for statistical analysis was the SAS package (System for Elementary Statistical Analysis, Propietary Software Release 6.04, SAS Institue Inc., Cary, NC, USA). All values were given as mean ± SD, unless otherwise stated. For statistical evaluation, analysis of variance (ANOVA), *t*-test and chi-square were used to observe the difference between groups or variables. A probability of 5% or less was considered significant.

Results

Demographics

The baseline demographic characteristics of the treatment and control groups are listed in Table 1. Both groups were

Table 1. Baseline clinical characteristics of study subjects

Clinical characteristics	Lanai Post (treatment group) $n = 311$	Sinderut Post (control group) $n = 196$
Proportion		
Male	169	101
Female	142	95
Age (year)	22.88 ± 16.94	21.17 ± 13.85
Weight (kg)	33.92 ± 14.23	31.92 ± 13.04
Height (cm)	134.38 ± 22.01	131.04 ± 17.65
Goitre prevalence (%)[a]	42.8 (133/311)	26.5 (52/196)
Thyroid hormone levels		
T4 (nmol/L)[a]	88.12 ± 24.55	75.38 ± 19.26
TSH (mIU/L)[a]	2.44 ± 2.58	4.89 ± 3.23
Thyroid volume (ml)	19.52 ± 14.84	21.40 ± 19.08
Mid-arm circumference (cm)	20.82 ± 4.18	20.50 ± 3.54
Waist–hip ratio	0.91 ± 0.13	0.93 ± 0.08
Body mass index (kg/m^2)	17.59 ± 3.00	17.39 ± 3.84
Skinfold thicknesses (cm)		
Biceps[a]	3.67 ± 1.44	4.57 ± 3.06
Triceps[a]	6.11 ± 2.56	7.18 ± 2.78
Suprailiac[a]	4.71 ± 2.54	6.35 ± 4.02
Subscapular[a]	6.89 ± 2.91	7.94 ± 3.97
Body fat (%)[a]	12.15 ± 5.88	14.57 ± 7.02
Urinary iodine levels (µg/dL)	1.70 ± 1.14	1.66 ± 1.00
Arterial blood pressure		
Systolic (mmHg)	114 ± 15	114 ± 15
Diastolic (mmHg)	69 ± 11	67 ± 13
Mental performance		
Frequency of subjects who scored above 5.0 percentile (%)	14.1 (29/206)	10.6 (14/132)

Data are mean values ± SD.
[a] Significant difference between the treatment and the control group, $P < 0.0001$.

similar with respect to sex, age, height, weight, thyroid volume, urinary iodine levels, arterial blood pressure, and mental performance except as noted in Table 1.

Food frequency

The food frequency of the treatment and control groups are shown in Table 2. Table 2 shows that high iodine food is rarely consumed by the Aborigines in Lanai Post, except for spinach which they grow themselves, and sea-fish and egg which they buy once a week from the market in Kuala Medang. Their staple food mainly consists of cassava leaves and roots (tapiocas), which have become the traditional food for generations. Besides these foods, cabbage is also eaten, at least once a week. These are the foods that contain a high concentration of goitrogens. The food intake in the control group showed a smaller variation. Among high iodine foods, only egg, meat and spinach are consumed by a minority in the community and it is obvious that cassava leaves and tapioca are the predominant goitrogenic agents in their diet. The prevalence of goitre during the food frequency evaluation was 42.8% in Lanai Post and 26.5% in Sinderut Post (see Table 1).

Table 2. The frequency of food intake among Aborigines in Lanai Post (treatment group) and Sinderut Post (control group)

	Treatment group (Lanai Post)						Control group (Sinderut Post)					
Types of food	a	b	c	d	e	f	a	b	c	d	e	f
High iodine food												
Crab	0.3	0.3	1.0	0.0	9.6	88.8	0.0	0.0	0.0	0.0	20.4	79.6
Shellfish	0.0	0.6	1.3	0.0	2.2	95.8	0.0	0.0	0.0	0.0	0.5	99.5
Cockle	0.0	0.3	2.2	2.6	14.5	80.4	0.0	0.0	0.0	0.0	2.0	98.0
Squid	0.0	0.3	2.9	0.6	12.5	83.6	0.0	0.0	0.0	0.0	1.5	98.5
Prawn	0.0	3.5	12.2	2.9	14.8	66.6	0.0	0.0	0.0	0.0	36.7	63.3
Sea fish	0.6	3.5	25.4	4.8	19.6	46.0	0.0	0.0	0.0	0.0	1.5	98.5
Egg	2.6	1.0	25.4	3.2	25.1	33.8	0.0	4.1	9.7	1.5	75.0	9.7
Meat	1.0	0.6	11.6	1.9	37.6	47.3	0.0	0.0	3.6	2.5	70.9	23.0
Spinach	8.4	24.4	25.7	2.2	19.0	20.3	0.5	1.5	1.5	2.0	11.7	82.6
High goitrogen food												
Mustard seeds	0.0	1.6	0.3	0.0	1.3	96.8	0.0	0.0	0.0	0.0	0.0	100.0
Ground nut	0.3	4.5	3.2	3.2	11.9	76.8	0.0	0.0	0.0	0.0	1.5	98.5
Soya bean	0.0	0.6	3.2	1.0	4.8	90.4	0.0	0.0	0.0	0.0	0.5	99 5
Carrot	0.0	1.3	1.6	0.6	3.2	93.2	0.0	0.0	0.0	0.0	0.0	100.0
Cassava leaves	35.1	20.3	23.2	3.9	7.1	10.6	81.1	7.6	4.6	0.5	5.1	1.0
Tapioca	39.6	19.6	24.8	3.5	10.0	2.6	99.5	0.0	0.5	0.0	0.0	0.0
Bamboo shoots	1.9	1.9	6.1	2.2	10.9	76.8	0.5	0.0	0.0	0.0	15.3	84.2
Cabbage	0.3	1.9	30.6	3.2	19.9	44.1	0.0	0.0	0.0	0.0	1.5	98.5
Potato	0.0	1.3	5.8	1.3	13.5	78.1	0.0	0.0	0.0	0.0	0.5	99.5
Sweet corn	0.0	1.6	5.8	1.3	13.5	78.1	0.0	0.0	0.0	0.0	18.9	81.1

a, every day; b, 2–3 times a week; c, once a week; d, < 3 times per month; e, once a month; f, none.

Table 3. Prevalence of goitre following levothyroxine supplementation

Factors	Levothyroxine supplementation						
Goitre prevalence (%)	Baseline	4 months	8 months	12 months	18 months	Statistical test	*P*
Overall							
Treatment	42.8[a]	22.3	31.2	18.0	130[a]	χ^2 trend	< 0.0001
Control	26.5	—	—	—	34.7	χ^2	NS
Gender							
Treatment							
Male	29.0[a,b]	15.2[a]	20.2[b]	7.9[b]	7.1[b]	χ^2 trend	< 0.0001
Female	59.2[a]	30.8	42.5	29.5	20.0[a]	χ^2 trend	< 0.0001
Control							
Male	17 2[b]	—	—	—	17.5[b]	χ^2	NS
Female	38.0	—	—	—	50.8	χ^2	NS
Age (year)							
Treatment							
< 12	11 8[c]	1 0[c]	17 6[c]	0.0[c]	0.0[a,c]	χ^2 trend	< 0.0001
12–18	51.8[a]	12.9	30.8	22.9	18.5	χ^2 trend	< 0.0001
> 18	60.1[a]	39.4	41.3	26.9	19 2[a]	χ^2 trend	< 0.0001
Control							
< 12	13.4[c]	—	—	—	13.6[c]	χ^2	NS
12–18	6.4	—	—	—	26.3	χ^2	NS
> 18	44.1	—	—	—	54.6	χ^2	NS

[a] Significant difference between treatment and control; [b] significant difference between male and female; [c] significant difference between age groups.

Prevalence of goitre

There was a significant decrease in goitre prevalence in both males and females following the intervention ($P < 0.0001$). The prevalence was also reduced in all age groups (Table 3). In both treatment and control groups, females showed a higher goitre prevalence compared with the males. No child less than 12 years of age developed goitre after 1 year of intervention, but among the adolescents and adults, more than a 20 and 10% reduction in goitre frequency, respectively, was observed as early as 4 months of intervention. When looking into the stages of goitre (Table 4), no male developed stage three goitre after 4 months of intervention; and as for the females, stage three goitre started to cease following 8 months of intervention. In both groups, higher stages of goitre were more common among the females compared with the males.

T4 and TSH levels

Total T4 levels were significantly increased in all age groups and in both sexes after 4 and 8 months of intervention (Table 5 and Fig. 2). However, the levels were found to be reduced after 1 year. In the control group, total T4 levels were decreased following the intervention. In the first 4 months of intervention, a decrease in TSH levels was observed in both children and adolescent groups but not in the adult group (Fig. 3). After 4 months, TSH levels started to increase rapidly in all age groups with a sharp increase noted in the adolescent females (except for the adult males) up to 1 year of intervention ($P < 0.05$). However, 6 months after, the levels were found to be decreased again. Comparison between visits showed a significant difference in TSH levels ($P < 0.05$) following the intervention. Meanwhile, in the control group, no significant difference was observed (Table 5).

Thyroid volume

Thyroid volumes following intervention are listed in Table 6. A reduction in thyroid volume was observed in all age groups during the first 4 months of intervention. Despite the ongoing treatment with levothyroxine, thyroid volume continued to increase during the subsequent follow ups. However,

Table 4. Stages of goitre following levothyroxine supplementation

Factors	Levothyroxine supplementation						
Goitre prevalence (%)	Baseline	4 months	8 months	12 months	18 months	Statistical test	*P*
Treatment							
Male							
0	71.0[a,b]	84.8[b]	79.8[b]	92.1[b]	92.9[b]	χ^2 trend	< 0.0001
2	21.3	12.4	19.4[b]	6.3[b]	40[a]	χ^2 trend	< 0.0001
2	6.5[b]	2.8[b]	0.8[b]	1.6[b]	3.0[b]	χ^2 trend	< 0.05
3	1.2[b]	0.0	0.0	0.0	0.0	χ^2 trend	NS
Female							
0	40.8[a]	69.2	57.5	70.5	80.0[a]	χ^2 trend	< 0.0001
1	26.1	17.1	32.3	19.6	8.2[a]	χ^2 trend	< 0.0001
2	26.1[a]	11.6	10.2	8.9	11.8	χ^2 trend	< 0.0001
3	7.0	2.1	0.0	0.9	0.0	χ^2 trend	< 0.0001
Control							
Male							
0	82.8[b]	—	—	—	82.5[b]	χ^2	NS
1	12.1	—	—	—	15 8[b]	χ^2	NS
2	5.0	—	—	—	1.8	χ^2	NS
3	0.0[b]	—	—	—	0.0	χ^2	—
Female							
0	62.0	—	—	—	49.2	χ^2	NS
1	19.6	—	—	—	37.7	χ^2	< 0.05
2	9.8	—	—	—	9.8	χ^2	NS
3	8.7	—	—	—	3.3	χ^2	NS

[a] Significant difference between case and control; [b] significant difference between male and female.

Table 5. Thyroid (T4) and TSH levels following levothyroxine supplementation

Visits	Treatment group (Lanai Post)		Control group (Sinderut Post)	
	T4 levels (nmol/L)	TSH levels (mIU/L)	T4 levels (nmol/L)	TSH levels (mIU/L)
Baseline	88.12 ± 24.55	2.44 ± 2.58	75.38 ± 19.26	4.89 ± 3.23
1	109.86 ± 39.99	2.42 ± 6.42	67.86 ± 23.84	4.19 ± 6.03
2	125.35 ± 45.81	2.85 ± 3.13		
3	103.82 ± 36.10	3.35 ± 2.62		
4	100.40 ± 34.06	2.89 ± 2.78		
	ANOVA	ANOVA	*t*-test	*t*-test
	$F = 37.80$	$F = 2.42$	$t = 3.451$	$t = 1.426$
	$P < 0.0001$	$P < 0.05$	$P < 0.0001$	NS

$P < 0.05$ is considered significant; NS, not significant.

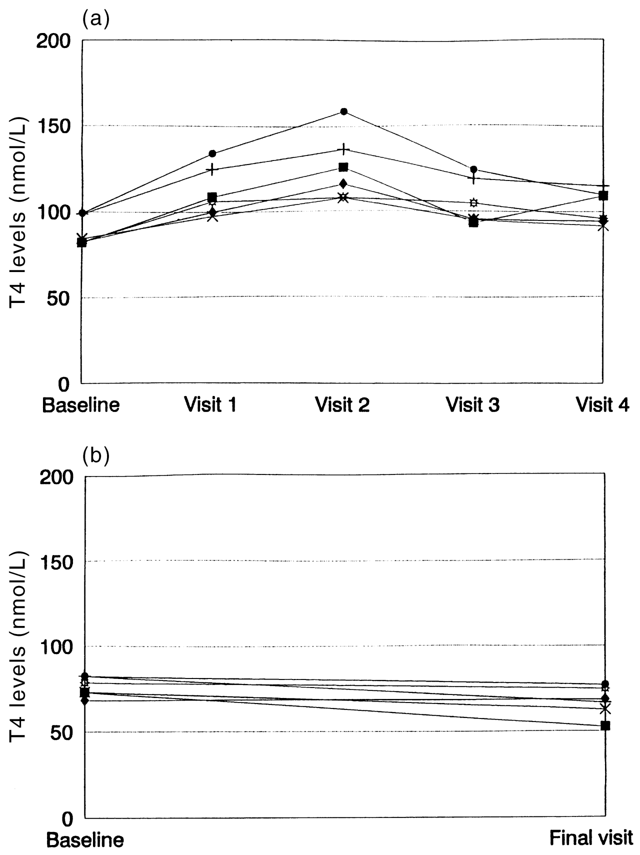


Figure 2. Thyroxine levels (T4) (nmol/L) following levothyroxine supplementation by age groups and gender. (a) Treatment group (Lanai Post); (b) control group (Sinderut Post); M, male; F, female; (●) < 12 years old (M); (+) < 12 years old (F); (□) 12–18 years old (M); (■) 12–18 years old (F); (×) > 18 years old (M); (◆) > 18 years old (F).

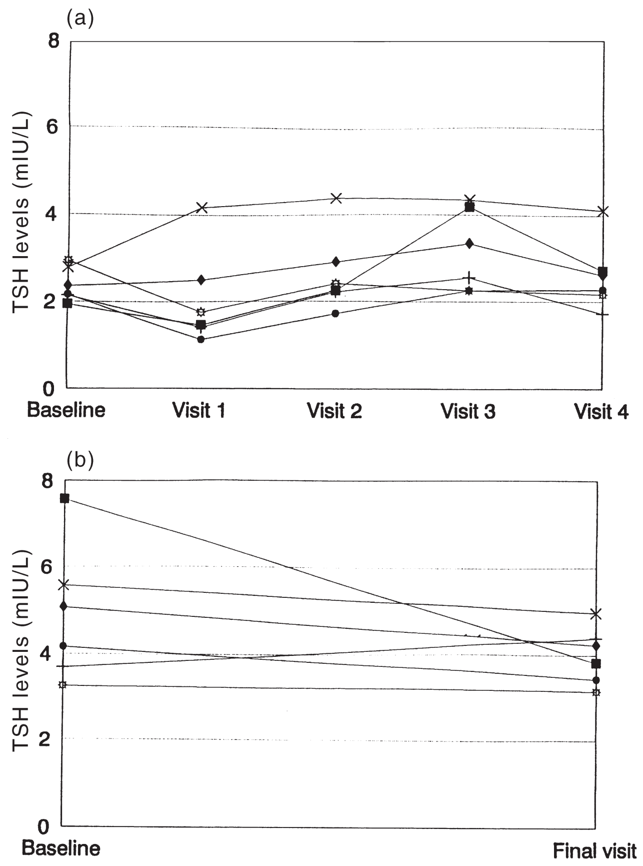


Figure 3. Thyroid-stimulating hormone levels (mIU/L) following levothyroxine supplementation by age groups and gender. (a) Treatment group (Lanai Post); (b) control group (Sinderut Post); M, male; F, female; (●) < 12 years old (M); (+) < 12 years old (F); (□) 12–18 years old (M); (■) 12–18 years old (F); (×) > 18 years old (M); (◆) > 18 years old (F).

during the last 6 months of intervention, there was again a reduction in the thyroid volume. Comparison between visits showed a significant increase in thyroid volume in both treatment and control groups following the intervention.

Nutritional status

Significant changes were noted in body weight, mid-arm circumference and body mass index following levothyroxine supplementation (Table 7) with a significant increase in the mid-arm circumference and body mass index following 1 year of intervention. Although there was no statistical difference in the waist–hip ratio, there was a significant reduction up to 1 year of intervention. The control group, however, showed no difference in body weight, mid-arm circumference and body mass index but a reduction in the waist–hip ratio occurred following the intervention. Skinfold evaluation showed a mark decrease in thickness over the biceps, triceps, suprailiac and subscapular areas following 1 year of intervention before it was significantly increased 6 months later ($P < 0.0001$). In the control group, skinfold thicknesses remained unchanged except for the triceps and subscapular areas which were increased significantly ($P < 0.0001$). Similar to the skinfold thicknesses, there was also a decrease in the percentage of body fat up to 1 year of intervention before it increased again in the last 6 months ($P < 0.0001$) (Table 7). The control group however, showed a significant increase in the body fat following the intervention ($P < 0.01$).

The nutritional status of the Aborigines is shown by the BMI (Table 7). More than two-thirds of the subjects of both sexes were underweight (BMI < 20), while another one-third of the subjects showed a normal BMI (20 < BMI < 25). Overweight subjects were seldom seen in this community, but a small percentage were overweight and this predominantly involved females. Although insignificant, the prevalence of overweight showed a slight tendency to increase following levothyroxine supplementation, particularly in females.

Table 6. Thyroid volume following levothyroxine supplementation

Visits	Thyroid volume (mL)	
	Treatment group (Lanai Post)	Control group (Sinderut Post)
Baseline	19.52 ± 14.84	21.40 ± 19.08
1	17.27 ± 17.70	31.43 ± 19.62
2	17.34 ± 11.92	
3	26.98 ± 12.70	
4	23.11 ± 8.65	
	ANOVA	*t*-test
	$F = 17.35$	$t = -4.835$
	$P < 0.0001$	$P < 0.0001$

$P < 0.05$ is considered significant.

Table 7. Nutritional indices/status following levothyroxine supplementation

Factors	Levothyroxine supplementation						
	Baseline	4 months	8 months	12 months	18 months	Statistical test	*P*
Weight (kg)							
Treatment	33.92 ± 14.23	34.06 ± 14.19	33.62 ± 13.62	36.56 ± 14.00	36.82 ± 12.44	ANOVA	< 0.05
Control	31.92 ± 13.04	—	—	—	32.42 ± 12.49	*t*-test	NS
Mid-arm circumference (cm)							
Treatment	20.82 ± 4.18	20.98 ± 5.30	20.52 ± 4.07	21.63 ± 4.16	20.11 ± 3.84	ANOVA	< 0.05
Control	20.50 ± 3.54	—	—	—	21.08 ± 3.77	*t*-test	NS
Waist–hip ratio							
Treatment	0.91 ± 0.13	0.96 ± 0.16	0.91 ± 0.08	0.87 ± O.07	1.09 ± 3.38	ANOVA	NS
Control	0.93 ± 0.08	—	—	—	0.86 ± 0.07	*t*-test	< 0.0001
Body mass index (kg/m^2)							
Treatment	17.59 ± 3.00	17.08 ± 3.78	17.25 ± 2.94	18.35 ± 2.83	18.08 ± 3.06	ANOVA	< 0.0001
Control	17.39 ± 3.84	—	—	—	18.00 ± 2.99	*t*-test	NS
Skinfold thicknesses (cm)							
Biceps							
Treatment	3.67 ± 1.44	3.52 ± 1.39	2.90 ± 0.94	2.35 ± 0.63	4.98 ± 5.81	ANOVA	< 0 0001
Control	4.57 ± 3.06	—	—	—	4.74 ± 1.48	*t*-test	NS
Triceps							
Treatment	6.11 ± 2.56	6.53 ± 2.91	5.20 ± 1.90	4.21 ± 2.04	7.00 ± 3.59	ANOVA	< 0 0001
Control	7.18 ± 2.78	—	—	—	8.61 ± 2.78	*t*-test	< 0.0001
Suprailiac							
Treatment	4.71 ± 2.54	5.35 ± 3.07	4.34 ± 1.52	3.68 ± 1.06	6 61 ± 3 39	ANOVA	< 0 0001
Control	6.35 ± 4.02	—	—	—	6 54 ± 3.23	*t*-test	NS
Subscapular							
Treatment	6.89 ± 2.91	6.75 ± 2.68	6.09 ± 2.34	5.62 ± 2.13	7 82 ± 3 21	ANOVA	< 0.0001
Control	7.94 ± 3.97	—	—	—	10.28 ± 5.21	*t*-test	< 0.0001
Body fat (%)							
Treatment	12.15 ± 5.88	12.59 ± 6.02	10.66 ± 5.01	8.99 ± 7.05	14.52 ± 6.92	ANOVA	< 0.0001
Control	14.57 ± 7.02	—	—	—	16.52 ± 6.76	*t*-test	< 0.01
Nutritional status shown by BMI (%)							
Treatment							
Male							
BMI < 20.0	66.3	73.4	77.9	58.9	71.7	χ^2 trend	< 0.01
20.0 ≤ BMI ≤ 25.0	33.7	26.0	22.1	41.1	27.2	χ^2 trend	<0.01
BMI > 25.0	0.0	0.6	0.0	0.0	1.1	χ^2 trend	NS
Female							
BMI < 20.0	77.5	80.0	83.8	77.4	66.3	χ^2 trend	< 0.05
20.0 ≤ BMI ≤ 25.0	21.1	20.0	15.4	20.9	30.1	χ^2 trend	NS
BMI >25.0	1.4	0.0	0.8	1.7	3.6	χ^2 trend	NS
Control							
Male							
BMI < 20.0	71.3	—	—	—	67.0	χ^2	NS
20.0 ≤ BMI ≤ 25.0	27.7	—	—	—	32.1	χ^2	NS
BMI > 25.0	1.0	—	—	—	0.9	χ^2	NS
Female							
BMI < 20.0	66.3	—	—	—	70.7	χ^2	NS
20.0 ≤ BMI ≤ 25.0	29 5	—	—	—	29.3	χ^2	NS
BMI > 25.0	4.2	—	—	—	0.0	χ^2	NS

BMI < 20.0, under weight; 20.0 ≤ BMI < 25.0, normal; BMI > 25.0, over weight.

Urinary iodine levels

Significant changes were observed in urinary iodine levels following 1½ years of intervention (Table 8). Although there were large variations in the treatment group, no specific trend was observed following the intervention. Surprisingly, the control group showed a significant increase in urinary iodine excretion ($P < 0.0001$).

Arterial blood pressure

Blood pressure evaluation showed an increase in systolic and diastolic blood pressures in the treatment group following 1 year of intervention before they were reduced during the last visit (Table 9). The control group, however, showed a reduction particularly in the systolic blood pressure ($P < 0.0001$). In the treatment group, both sexes showed a significant reduction in blood pressures except for the diastolic blood pressure in females. In terms of hypertension, the prevalence of hypertensives remain constant throughout the intervention, and no hypertensive subjects was noted in the control group following the pre- and post-evaluation.

Mental performance

Mental performance was evaluated based upon the proportion of subjects who scored above the 5.0 percentile, which is the median score of every visit. In the treatment group, there was a significant increase in mental performance following 1½ years of intervention (Table 10). In addition, mental performance was also found to be increased in the control group. When the subjects were stratified according to age groups, young children of 4–6 years old and school children of 7–12 years old showed a significant increase in the prevalence following intervention (Fig. 4). In younger children, the performances were quite good where none scored below 5.0 percentile after 8 months of levothyroxine supplementation (represented by a flat line in Fig. 4). However, the prevalence of mental performance remains constant in adolescents of 13–20 years of age; while no adult of 21–25 years old scored above 5.0 percentile following the entire intervention. Since both the treatment and control groups showed a significant increase in prevalence, mental performance outcome was compared statistically to eliminate confounders. The confounders thought to bring about mental improvement are firstly, growth and brain maturation and secondly, the ability to learn from repetitive measures. Even though both groups showed significant results, the effect was more pronounced in the treatment group ($P < 0.05$) in the sense that it shows larger difference from the baseline observation compared to the control group (Fig. 5).

Discussion

Although iodine prophylaxis is the oldest method of goitre prevention, its efficacy depends on several factors.[19] For example, the iodine concentration should be adjusted according to the people's consumption and the presence of goitrogenic agents in the area. Earlier studies have shown that iodine is potentially dangerous when given to established sporadic goitre (the Jod-Basedow effect).[20] Among the indigenous people who depend mostly on cassava or tapioca, which contain goitrogens, it may not be appropriate to provide them with iodine, perhaps because thiocyanate (particularly in cassava) will block thyroidal iodine uptake,[21] and subsequently interfere with the synthesis and secretion of thyroid hormones. Although giving iodine is usually sufficient to overcome the block, the effects of some goitrogenic agents are not prevented. Therefore, it is hoped that goitre intervention by means of levothyroxine will be able to eliminate IDD in endemic areas, which consume large amounts of cassava.

Table 8. Urinary iodine levels following levothyroxine supplementation

Visits	Treatment group (Lanai Post)		Control group (Sinderut Post)	
	n	Iodine levels (μg/dl)	*n*	Iodine levels (μg/dl)
Baseline	277	1.70 ± 1.14	174	1.66 ± 1.00
1	272	2.21 ± 2.37	50	2.62 ± 2.52
2	255	2.08 ± 2.54		
3	233	1.21 ± 1.19		
4	153	1.52 ± 1.38		
	ANOVA	$F = 11.53$ $P < 0.0001$	*t*-test	$t = 6.37$ < 0.0001

$P < 0.05$ is considered significant.

Table 9. Arterial blood pressure following levothyroxine supplementation

Factors	Levothyroxine supplementation						
	Baseline	4 months	8 months	12 months	18 months	Statistical test	*P*
Arterial blood pressure (mmHg)							
Treatment							
Systolic	114 ± 15	116 ± 14	111 ± 22	121 ± 20	112 ± 18	ANOVA	< 0.0001
Diastolic	69 ± 11	78 ± 10	78 ± 15	81 ± 14	69 ± 11	ANOVA	< 0.0001
Control							
Systolic	114 ± 15	—	—	—	106 ± 14	*t*-test	< 0.0001
Diastolic	67 ± 13	—	—	—	64 ± 16	*t*-test	NS
Gender							
Treatment							
Male							
Systolic	117 ± 16	116 ± 14	114 ± 21	123 ± 16	112 ± 17	ANOVA	< 0.0001
Diastolic	69 ± 11	78 ± 9	76 ± 14	81 ± 15	70 ± 11	ANOVA	< 0.0001
Female							
Systolic	112 ± 13	116 ± 14	107 ± 24	113 ± 24	112 ± 19	ANOVA	< 0.0001
Diastolic	65 ± 13	77 ± 11	81 ± 16	80 ± 11	68 ± 11	ANOVA	< 0.0001
Control							
Male							
Systolic	117 ± 16	—	—	—	108 ± 14	*t*-test	< 0.0001
Diastolic	69 ± 12	—	—	—	64 ± 12	*t*-test	< 0.05
Female							
Systolic	112 ± 13	—	—	—	104 ± 14	*t*-test	< 0.0001
Diastolic	65 ± 13	—	—	—	63 ± 19	*t*-test	NS
Prevalence of hypertension (%)							
Treatment	6.9	6.9	4.7	7.2	3 4	χ^2 trend	NS
Control	0.0	—	—	—	0.0	—	—

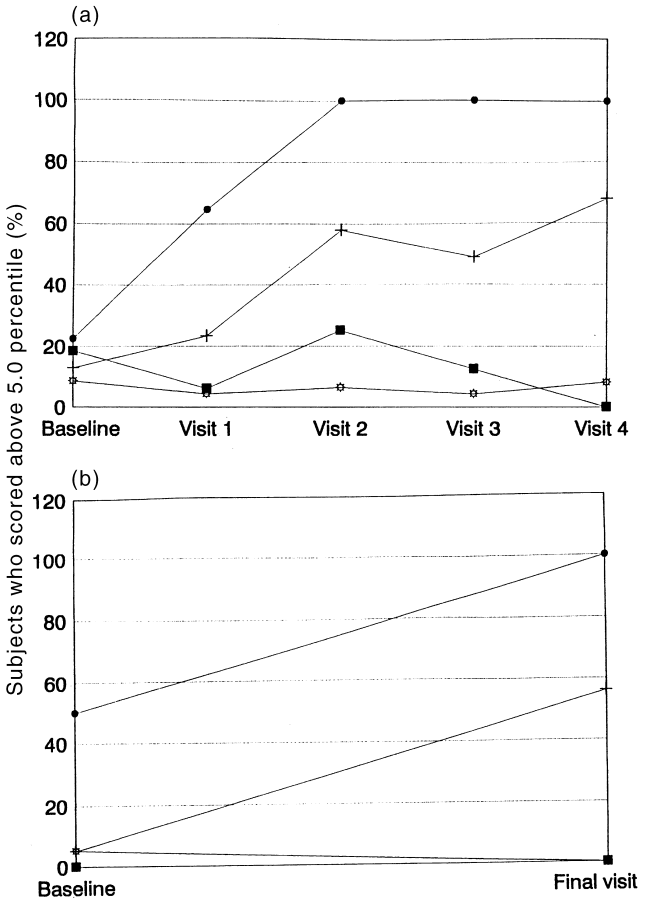


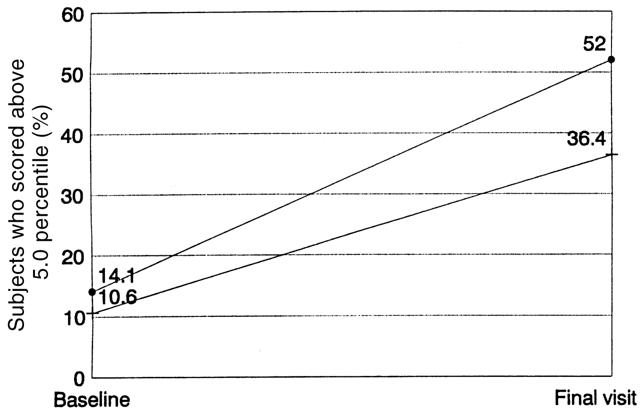
Figure 4. Mental performance. Percentage of subjects who scored above the median (5.0 percentile) following levothyroxine supplementation. (a) Treatment group (Lanai Post); (b) control group (Sinderut Post); (●) 4–6 years old; (+) 7–12 years old; (□) 13–20 years old; (■) 21–25 years old.

Table 10. Mental performance: percentage of subjects who scored above the median (5.0 percentile) following levothyroxine supplementation (Age ≤ 25 years)

	Treatment group (Lanai Post)		Control group (Sinderut Post)	
Visits	*n*	%	*n*	%
Baseline	29/206	14.1	14/132	10.6
1	42/169	24.8	40/110	36.4
2	75/162	46.3		
3	50/138	36.2		
4	40/77	52.0		
	χ^2 trend	65.357	χ^2	21.502
	P	< 0.0001	*P*	< 0.0001

P < 0.05 is considered significant.

Levothyroxine sodium is the most commonly used thyroid hormone preparation for treating hypothyroidism[22] and has also been widely used to prevent recurrent goitre after thyroid surgery.[23] This study demonstrates the effect of 1½ years of levothyroxine supplementation on the prevalence of goitre, T4 and TSH levels, thyroid volume, nutritional status, urinary iodine levels, arterial blood pressure and mental performance among the Aborigines of Lanai Post, Pahang compared with a control group in Sinderut Post. The present data shows that levothyroxine supplementation is associated with



Visits	Treatment group (Lanai Post)	Control group (Sinderut Post)	Probability
Baseline	14.1	10.6	X^2 = 0.589; p = 0.443
Final	52.0	36.4	X^2 = 3.880; p = 0.049
Probability	X^2 = 41.570 p = 0.000	X^2 = 21.502 p = 0.000	

Figure 5. Mental performance. Comparison between the (●) treatment (Lanai Post) and the (+) control group (Sinderut Post).

a 30% reduction in goitre prevalence, as the prevalence was 42.8% at baseline and 13% after intervention. The prevalence was considerably greater in females and increased with age, as found in other studies.[24] The intervention also led to a reduction in goitre stages in all age groups compared with the controls.

In theory, patients receiving exogenous levothyroxine for primary hypothyroidism should have suppressed TSH if physiological needs are constantly met.[25] Greer and Astwood suggested that levothyroxine will suppress TSH and reduce thyroid growth and functions.[26] In our study, T4 levels increased in response to levothyroxine supplementation in all age groups at the initial stage (the first 4 months). However, the levels were significantly reduced at the following visits. In addition, a reduction in serum TSH was only found during the first 4 months of intervention, while in the subsequent follow ups, the levels were increased rather than suppressed. Poor compliance with the medication could be one of the reasons for the reduction in T4 and the rise in TSH. The initial increase in T4 has never been documented previously perhaps because only in this study was the monitoring done more closely. The initial rise in T4 with the decrease in TSH indicates an actual increase in free T4 with suppressive effects on hypothalamopituitary axis. The increase was seen mainly in those less than 12-years-old and was transient implying a possible initial excess before the body achieves homeostasis. The final T4 and TSH levels remained significantly different from the control group, although still within the normal range. Thus the control group was in a persistently lower T4 and higher TSH states.

In controlled clinical trials, the largest reduction in thyroid volume usually occurs during the first months of treatment.[4] There is also evidence that levothyroxine causes a more pronounced reduction in thyroid size than does iodine.[27] In this study, thyroid volume did not correlate well with the changes in goitre stages and the changes were only observed among the females during the first 4 months of intervention. The increase in thyroid volume in all age groups after the first visit implies thyroid tissue growth despite lower TSH and this could be due to metabolic effect of sufficient thyroxine stimulating growth. Although there has been a remarkable reduction in goitre size during the last 6 months of intervention, it was still significantly larger than the baseline.

With regards to an effect of thyroid supplementation on nutritional status, evidence is still being sought to document an association between levothyroxine supplementation, anthropometry and body composition. Many previous studies on anthropometry and body composition were cross-sectional and not longitudinal observations and therefore the results are not clear. There have only been a few longitudinal studies performed but these have not included body composition studies from a random population sample. A longitudinal study performed in adult females showed that body weight, triceps and subscapular skinfold thicknesses, overarm circumference and waist circumference, increased with age.[28] In our study, we showed that body weight increased following the intervention. It was doubted that this is more likely due to increasing age rather than the intervention itself. Therefore, considering that the last visit was contaminated with poor compliance, an increase in the mid-arm circumference and body mass index up to 12 months of intervention was expected. Although there was an increase in the skinfold thicknesses with increasing age (as referred to in the previous study and shown in the control group), a reduction in all skinfold thicknesses was found following 12 months of intervention. This result was also supported by the reduction in body fat. There could be a number of explanations for this, but in this particular study, there is a possibility that it might be due to levothyroxine treatment. The reduction of waist–hip ratio in the treatment group could also be due to the intervention, but the significant reduction seen in the control group cannot be explained.

In this study, we also examined the urinary iodine excretion and its association with levothyroxine supplementation. The daily urinary excretion of iodine in a representative population sample is a good indication of the iodine available in a locality.[29] In the treatment group, no specific pattern was observed in the urinary iodine levels, indicating no particular association between levothyroxine supplementation and the iodine content in the human body. The increase in the urinary iodine excretion among controls could be due to random variation.

Thyroid hormones exert many relevant effects on the heart by acting on myocardial growth as well as on systolic and diastolic function.[30] One previous study has demonstrated that a number of cardiac effects frequently occur as a consequence of long-term therapy with suppressive doses of levothyroxine.[31] Such effects consist of increased heart rate, increased incidence of atrial arrythmias, enhanced left ventricular systolic function, and increased left ventricular mass. The current study has shown an increase in both systolic and diastolic blood pressures in both males and females following the first 12 months of intervention, a result that agrees well with the previous study. Although the blood pressure tended to rise, the prevalence of hypertension remained constant throughout the intervention, indicating that levothyroxine therapy was appropriate and harmless. Although it was safe, patients receiving levothyroxine treatment still should be carefully monitored in the long term because uncontrolled supplementation will dangerously increase blood pressure levels.

It is known that elemental iodine, either directly or via thyroid hormone, influences intrauterine fetal brain development[32] and it has been reported that early treatment of hypothyroidism is associated with an improved psychological outcome.[33] In this study, we evaluated the mental performance of young children, school children, adolescents and young adults who received levothyroxine supplementation. It was noted that there was a significant increase in proportion of subjects with mental performance above the 5th percentile using Raven's Progressive Matrices. It was also found that performance was inversely correlated with age. Major improvement in performance was particularly observed among young children and none of them scored below the 5th percentile at the end of intervention. Although both treatment and control groups showed significant increases in mental performance, a more significant effect was observed in the treatment group.

In this study, there was a significant early reduction of goitre prevalence and body fat content was also reduced following 1 year of intervention. However, during the last 6 months of intervention, the results were opposite, possibly due to poor compliance among the subjects. There was an increase in mental performance following the intervention which is the key reason for immediate policy action. Therefore, the correction of iodine deficiency by levothyroxine supplementation is of obvious benefit in reducing the prevalence of goitre and improving the mental ability of Aborigines in endemic goitre areas. However, proper monitoring and close supervision are needed to maintain compliance.

Acknowledgements. The authors would like to thank the Department of Aboriginal Affairs of Gombak and Kuala Lipis for their cooperation. Gratitude is also expressed to UKM's endocrine technologists for their technical assistance. This study was funded by IRPA Research Code 093 without which this study would not have been possible.

The supplementation of levothyroxine among indigenous people in endemic goitre areas: The impact of therapy
MI Zaleha, A Osman, ZA Iskandar, S Sazali, M Muhammad Ali, I Roslan and BAK Khalid
Asia Pacific Journal of Clinical Nutrition (1998) Volume 7, Number 2: 138–150

地方性甲狀腺腫區內本土居民左旋甲狀腺素的治療：治療效果的評估

摘 要

爲了研究左旋甲狀腺素治療地方性甲狀腺腫的效果，作者選擇了 Pahang 、Kuala Lipis 碘缺乏地區的 Lanai Post 和 Sinderut Post 的土著爲對象，進行了縱向的研究。所有治療對象(Lanai Post)每日給予左旋甲狀腺素 100 微克，連續一年半。測試了 311 位對象的基值作爲對照，補充左旋甲狀腺素後，第一次隨訪 323 人，第二次 256 人，第三次 239 人和第四次 184 人。測試了對象的甲狀腺腫發病率，甲狀腺素含量，甲狀腺体積，營養狀況，尿碘排量，血壓和智力表現，治療後甲狀腺腫發病率明顯減少（基值爲 42.8%，最後一次隨訪測定值爲 13%，$p < 0.0001$) 但對照組沒有顯示明顯不同。治療組 T4 水平增高（ $p < 0.0001$)，但對照組則明顯減少（ $p < 0.0001$)，治療一年後 TSH 水平明顯增加，而對照組則無明顯改變。治療組甲狀腺体積明顯增大（ $p < 0.0001$)，有關營養狀況，治療組體重明顯增加（ $p < 0.05$)，此外，治療一年後，中臂圍和體重指數（ BMI ）也增加，但對照組腰臀比值下降（ $p < 0.0001$)，雖然治療組腰臀比值沒有統計學上的差異，但治療一年後也明顯減少。一年後治療組皮褶厚度減少，而對照組僅三頭肌和鎖骨下皮褶厚度增加。治療組在一年後体脂明顯減少（ $p < 0.0001$)，治療組尿碘排量沒有多大改變，但奇怪的是對照組明顯增加（ $p < 0.0001$)，治療一年後的收縮壓和舒張壓均明顯增高，但對照組收縮壓下降（ $p < 0.0001$)，兩組均顯示智能明顯增高，尤以治療組爲甚（ $p < 0.05$)。最後作者認爲：用左旋甲狀腺素治療碘缺乏有短期良效，可減少甲狀腺腫流行區內土著的發病率和改善智力，但是要維持良好療效，適當的監控和指導是需要的。

The supplementation of levothyroxine among indigenous people in endemic goitre areas: The impact of therapy

MI Zaleha, A Osman, ZA Iskandar, S Sazali, M Muhammad Ali, I Roslan and BAK Khalid

Asia Pacific Journal of Clinical Nutrition (1998) Volume 7, Number 2: 138–150

Dalam usaha untuk mengkaji kesan levotiroksin di dalam rawatan goiter endemik, suatu kajian longitud telah dijalankan di kalangan orang Asli di Pos Lanai dan Pos Sinderut yang terletak di dalam kawasan kekurangan iodin di daerah Kuala Lipis, Pahang. Kesemua subjek di dalam kumpulan rawatan (Pos Lanai) diberikan 100 mikrogram levotiroksin per hari dan kesan rawatan ini diperhatikan selama satu setengah tahun. Sejumlah 311 subjek diperiksa pada lawatan asas, 323 subjek pada lawatan pertama, 256 subjek pada lawatan kedua, 239 subjek pada lawatan ketiga dan 184 subjek pada lawatan keempat berikutan pemberian levotiroksin. Prevalens goiter, hormon tiroid, isipadu tiroid, status pemakanan, paras iodin urin, tekanan darah arteri dan mental performans telah diperhatikan. Berikutan intervensi, prevalens goiter menurun secara bererti di dalam kumpulan rawatan (Lawatan asas, 42.8% vs. Lawatan akhir, 13.0%, $p<0.0001$); walau bagaimanapun, tidak terdapat perbezaan yang bererti di dalam kumpulan kawalan. Paras T4 jumlah meningkat di dalam kumpulan rawatan ($p<0.0001$), sementara kumpulan kawalan menunjukkan penurunan yang bererti ($p<0.0001$). Paras TSH meningkat secara bererti di dalam kumpulan rawatan berikutan satu tahun intervensi manakala tidak terdapat sebarang perubahan yang bererti di dalam kumpulan kawalan. Di dalam isipadu tiroid, kedua-dua kumpulan menunjukkan peningkatan yang bererti berikutan intervensi ($p<0.0001$). Dari segi status pemakanan, kumpulan rawatan menunjukkan peningkatan berat badan yang bererti berikutan intervensi ($p<0.05$). Ukurlilit lengan tengah dan indeks jisim tubuh juga meningkat selepas satu tahun intervensi Walau bagaimanapun, kumpulan kawalan menunjukkan penurunan di dalam nisbah pinggang-pinggul ($p<0.0001$). Walaupun tidak terdapat perbezaan yang bererti di dalam nisbah pinggang-pinggul pada kumpulan rawatan, terdapat penurunan yang bererti sehingga satu tahun intervensi. Selepas satu tahun, penurunan ketebalan lipatan kulit dapat dilihat di dalam kumpulan rawatan manakala hanya lipatan kulit trisep dan subskapular sahaja yang meningkat di dalam kumpulan kawalan. Lemak tubuh didapati berkurangan di dalam kumpulan rawatan berikutan satu tahun intervensi ($p<0.0001$). Tidak terdapat corak tertentu yang ditunjukkan oleh rembesan iodin urin di dalam kumpulan rawatan, tetapi apa yang menghairankan, parasnya meningkat di dalam kumpulan kawalan ($p<0.0001$). Peningkatan yang bererti di dalam tekanan darah sistolik dan diastolik telah diperhatikan di dalam kumpulan rawatan berikutan satu tahun intervensi, tetapi kumpulan kawalan menunjukkan penurunan di dalam tekanan darah sistolik ($p<0.0001$). Kedua-dua kumpulan menunjukkan peningkatan yang besar di dalam perFormans mental, dengan kesan yang lebih ketara pada kumpulan rawatan ($p<0.05$). Pembetulan kekurangan iodin melalui pemberian levotiroksin mempunyai kesan jangkamasa pendek yang berfaedah di dalam menurunkan prevalens goiter dan meningkatkan keupayaan mental di kalangan orang Asli di kawasan endemik; walau bagaimanapun, pemonitoran yang sesuai dan penyeliaan yang teliti diperlukan untuk mengekalkan komplians.

References

1. Saller B, Hoermann R, Ritter MM, Morell R, Kreisig T, Mann K. Course of thyroid iodine concentration during treatment of endemic goitre with iodine and a combination of iodine and levothyroxine. Acta Endocrinologica (Copenh) 1991; 125**:** 662–667.
2. Westermark B, Karlsson FA, Walinder O. Thyrotropin is not a growth factor for human thyroid cells in primary culture. Biochem Biophys Res Commun 1987; 149: 707–711.
3. Petersen K, Bengtsson C, Lapidus L, Lindstedt G, Nystrom E. Morbidity, mortality, and quality of life for patients treated with levothyroxine. Arch Intern Med 1990; 50: 2077–2081.
4. Einenkel D, Bauch KH, Benker G. Treatment of juvenile goitre with levothyroxine, iodide or a combination of both: the value of ultrasound grey-scale analysis. Acta Endocrinologica 1992; 127: 301–306.
5. Anderson PE, Hurley PR, Rosswick P. Conservative treatment and long term prophylactic thyroxine in the prevention of recurrence of multinodular goitre. Surg Gynecol and Obstet 1990; 171: 309–314.
6. Miura S, Iitaka M, Yoshimura H *et al.* Disturbed lipid metabolism in patients with subclinical hypothyroidism: effect of L-thyroxine therapy. Internal Medicine 1994; 33: 413–417.
7. Arem R, Patsch W. Lipoprotein and apolipoprotein levels in subclinical hypothyroidism: Effect of levothyroxine therapy. Arch Intern Med 1990; 150: 2097–2100.
8. Vermiglio F, Lo Presti VP, Scaffidi Argentina G *et al.* Maternal hypothyroxinaemia during the first half of gestation in an iodine deficient area with endemic cretinism and related disorders. Clin Endocrinol 1995; 42: 409–415.
9. Buccino RA, Spann JF, Pool PE, Sonnenblick EH, Braunwald E. Influence of thyroid state on intrinsic contractile properties and energy stores of myocardium. J Clin Invest 1967; 46: 1669–1682.
10. Fazio S, Biondi B, Carella C *et al.* Diastolic dysfunction in patients on thyroid-stimulating hormone suppressive with levothyroxine: Beneficial effect of β-blockade. J Clin Endocrinol Metab 1995; 80: 2222–2226.
11. Chen PCY, Yap SB. The prevalence of endemic goitre among Penans of the Baram. Med J Malaysia 1988; 2: 159–161.
12. Maberly GF, Eastman CJ. Endemic goitre in Sarawak, Malaysia: I. Somatic growth and aetiology. Southeast Asian J Trop Med Public Health 1976; 7: 434–442.
13. Foo LC, Zainab T, Letchuman GR *et al.* Endemic goitre in the Lemanak and Ai River villages of Sarawak. Southeast Asian J Trop Med Public Health 1994; 25: 575–578.
14. Osman A, Khalid BAK, Tan TT, Sakinah O, Wu LL, Ng ML. Endemic goiter and hypothyroidism in orang Asli and Malays in Peninsular Malaysia. Med J Islamic Rep Iran 1995; 9 (1) Spring 1374: 19–25.
15. Delange F, Dunn JT. The definition of goitre stages. International Council for the Control of Iodine Deficiency Disorder. IDD Newsletter, 1987: 3–5.
16. Brunn J, Block U, Ruf I, Kunze WP, Scriba PC. Volumetrie der Schilddrusenlappen mittles Real-time Sonographie. Dtsch Med Wochenschr 1981; 106: 1338–1340.
17. Sandell E, Kolthoff IM. Chronometric catalytic method for the determination of microquantities of iodine. Am J Chem Soc 1934; 56: 1426–1430.
18. Guidelines for the management of mild hypertension: memorandum from a World Health Organization/International Society of Hypertension. J Hypertension 1993; 11: 905–918.
19. Lamberg BA. Endemic goitre – iodine deficiency disorders. Ann Medicine 1991; 23: 367–72.
20. Edmonds C. Treatment of sporadic goitre with thyroxine. Clin Endocrinol 1992; 36: 21–23.
21. Delange F, Bourdoux P, Colinet E *et al.* Nutritional factors involved in the goitrogenic action of cassava. Ottawa: International Development Research Centre, 1982: 17–26.

22. Ain KB, Refetoff S, Fein HG, Weintraub BD. Pseudomalabsorption of levothyroxine. JAMA 1991; 266: 2118–2120.
23. Berghout A, Wiersinga WM, Drexhage HA, Smits NJ, Touber JL Comparison of placebo with L-thyroxine alone or with carbimazole for treatment of sporadic non-toxic goitre. Lancet 1990; 336: 193–199.
24. Rojeski MT, Gharib H. Nodular thyroid disease. N Engl J Med 1985; 313: 428–436.
25. Igoe D, Duffy MJ, McKenna TJ. TSH as an index of L-thyroxine replacement and suppression therapy. IJM S 1992; 161: 684–686.
26. Greer MA, Astwood EB. Treatment of simple goitre with thyroid. J Clin Endocrinol Metab 1953; 13: 1312–1331.
27. Wilders-Truschnig MM, Warnkroß H, Leb G *et al* The effect of treatment with levothyroxine or iodine on thyroid size and thyroid growth stimulating immunoglobulins in endemic goitre patients. Clin Endocrinol 1993; 39: 281–286.
28. Noppa H, Andersson M, Bengtsson C, Bruce A, Isaksson B. Longitudinal studies of anthropometric data and body composition. Am J Clin Nutr 1980; 33: 155–162.
29. Wayne EJ, Koutras DA, Alexander WD. Clinical aspects of iodine metabolism. Oxford: Blackwell Scientific Publications, 1964.
30. Klein I. Thyroid hormone and the cardiovascular system. Am J Med 1990; 88: 631–637.
31. Biondi B, Fazio S, Carella C *et al.* Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. J Clin Endocrinol Metab 1993; 77: 334–338.
32. Delange F, Bourdoux P, Chanoine JP, Ermans AM. Physiopathology of iodine nutrition during pregnancy, lactation, and early postnatal life. In: Vitamins and Minerals in Pregnancy and Lactation (ed. H. Berger). New York: Raven Press, 1988; 205–214.
33. Tillotson SL, Fuggle PW, Smith I, Ades AE, Grant DB. Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. BMJ 1994; 309: 440–445.