

Retrospective Analysis of a Long Term Iodine Intervention Program in Rural Iran

Salarkia N^a, Hedayati M^b, Azizi F^b

^aNational Nutrition and Food Technology Research Institute; ^bEndocrine Research Center, Shaheed Beheshti Medical University, Tehran, Iran

This investigation aimed at evaluating the effect of iodine supplementation on the IDD impact indicators in a group of 571 hypothyroid iodine deficient schoolchildren.

Materials and Methods: Values of levels obtained were compared with data from our previous 1989 study in these villages and results of the comparison showed that total goiter rate decreased by 42% in 1999.

Results: A significant decrease in grade 2 goiter concomitant with an increase in grade 1 goiter was seen, $P < 0.001$. Serum T4, T3, TSH concentrations, urinary iodine level and IQ were normal in all children. Mean IQ was higher in children aged 6-10 years as compared to other age groups, $P < 0.05$.

Conclusion: Study shows that euthyroidism induced by administration of iodized oil in hypothyroid iodine deficient schoolchildren can be maintained following iodized salt consumption.

Key Words: Iodine Supplementation, Schoolchildren, Rural area, Iran

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Introduction

Iodine deficiency disorders had been recognized as a major health issue in Iran.¹ Pre-

vious studies had suggested inadequate intake of iodine to be the main cause of endemic goiter in the nation.² Iodine deficiency is one of the most important causes of mental impairment and has serious effects on the physical development of children, infant mortality and on the reproductive performance of women as indicated by increased rates of abortion, stillbirth and congenital abnormalities.³ Iodized oil administration is recommended for prevention of IDD in severe endemic areas when iodized salt is not available.⁴

In order to take preventive measures against iodine deficiency disorders (IDD) in Iran, the National IDD Council was formed in 1988 and subsequently a national plan of action was prepared with the main aim of preventing and controlling IDD in the country. The main objective was to reduce the prevalence of goiter to below 5%, in children aged 8-10 years by the year 2000.⁵

Northern rural areas of Tehran, situated in mountainous regions in our previous studies have been shown to have severe iodine deficiency.^{1,6,7} In 1989, the populations these villages received iodized oil injection (one ml of intramuscular iodized oil, Lipiodol, containing 480 mg iodine). In addition iodized salt, as the main strategy of the national plan for IDD control was distributed after four

Correspondence: Nahid Salarkia, National Nutrition and Food Technology Research Institute, Shaheed Beheshti University of Medical Services, Tehran, I.R. Iran; *E-mail:* n_salarkia@hotmail.com

years (1993) in the country. This study aims at evaluating the impact of intervention program on iodine and health status of school aged children in these villages, ten years after iodine supplementation.

Materials & Methods

Subjects: The villages of Kiga, Keshar, Randan, Sangan, Zagoon and Ahar are situated in a mountainous region, at an altitude of approximately 2000 meters above sea level and are located about 35 km north of Tehran, the capital of Iran. Kiga and Randan were known for severe endemic goiter, and Keshar, Sangan, Zagoon and Ahar had a high rate of endemic goiter.^{6,7} These areas have similar ecological, socio-economic and cultural conditions. The numbers of households in these villages range between 170-270 and the average family size is around four members. The main occupation of the men in these areas is farming and animal husbandry, some also being welders and grocers. Most men and women have primary education while some of them are illiterate.

In the 1999 study, all schoolchildren, age 6 to 15 years, from the above villages were examined in three subgroups; subgroup I (n=228), 6-10 years (mothers received iodized oil+iodized salt 1-4 yr pre-conception); subgroup II (n=71): 10-11 years old (mothers received iodized oil during pregnancy + child received iodized salt at the age of 4); and subgroup III (n=272), 11-15 years old (child received iodized oil below 4 yr + iodized salt from 4 years onwards).

Methodology and study design: A descriptive epidemiological study using an evaluation research approach was designed to evaluate the impact of iodine supplementation program on the indicators of iodine deficiency disorder status using clinical, biochemical and anthropometrics measurements, intelligence quotient (IQ) and psychomotor evaluation. Tests were those chosen for which there were norms for Iran. The plan was to compare the indicators of IDD status such as thyroid size, thyroid hormone con-

centration, urinary iodine excretion, IQ, and physical growth in children, aged 6-15 years, residing in these villages with values obtained for those studied in 1989.

Baseline data: In 1989, the inhabitants of the above villages received iodized oil injection followed by iodized salt distribution in 1993. Prior to iodized oil injection in 1989, all of pupils aged 6-15 years (n=525) from these areas were studied in order to determine the goiter prevalence, thyroid hormone assays, IQ, anthropometric indices and urinary iodine excretion. Again in 1999, the same studies were performed in all 571 schoolchildren of these villages.

Anthropometric measurements: Anthropometric measurements for weight and height were obtained according to the Gibson recommendations, 1990.⁸ Weight was measured using electronic scales (SECA, Hamburg, Germany), which had been calibrated for accuracy. Height was measured bare foot with minimum clothing, to the nearest 0.1 cm using a microtoise (UNICEF, Copenhagen, Denmark); the microtoise was hung on the way in such a way as to ensure a vertical position.⁸ The weight was measured to the nearest 0.1 kg. Anthropometric data was presented as indices of Z scores of height for age and weight for age. These indices were compared with reference data of the National Center of Health Statistics (NCHS).⁹ The cut off point of below 5th and between the 5th and 50th percentiles of NCHS was used to determine underweight children.

Clinical examination: Goiter grade was examined by palpation by two endocrinologists and classified as grade 0, 1 or 2 according to WHO classification.¹⁰

Biochemical assessments: Measurement of urinary iodine was based on the iodine concentration in urine samples that were collected randomly in 10% of subjects. Casual samples taken from each child were stored in a clean containers at -20°C until analysis. All urine samples were sent to and analyzed in the urinary iodine laboratory of the Endocrine Research Center; acid digestion method

was used for urinary iodine analysis.¹¹ Venous blood samples were obtained from all subjects, centrifuged and serum were separated and stored at -20°C , until analysis. Serum T4, T3 and TSH concentrations were determined by radioimmunoassay using commercial kits from Fenzia, Finland. Free T4 index (FT4I) and free T3 index (FT3I) were calculated.¹² The reference ranges of serum parameters for assays were: T4: 4.5-12.5 $\mu\text{g/dL}$, T3: 80-210 ng/dl and TSH :< 0.3-4.5 $\mu\text{U/mL}$ and urinary iodine 10-30 $\mu\text{g/dL}$.¹³

Intelligence quotient (IQ) & psychomotor evaluation: The Raven test was used as a measure of cognitive functioning; this test gives a fair estimation of the intellectual quotient.^{10,14} The Bender Gestalt (BG) test was administered to all subjects. This test consists of copying a number of geometrical figures and can be applied to both children and adults, those who are literate or illiterate and to subjects with language problems. The BG test explores visual perception and neuromotor ability and is affected by specific portions of intellectually function, i.e. memory, spatial concepts, and ability to organize and make representations. Individual scores from the BG test were evaluated and the number of errors in copying figures was determined. The psychomotor ages were ascertained.¹⁵

Statistical analysis: Data of the present

study were compared to those obtained before iodine intervention in all villages. A comparison of results between the 3 subgroups was also made. Student's t test was employed for quantitative variables. Chi-Square and Fisher exact tests were employed for nominal and ordinal variables. The correlation among variables was performed by Spearman test. All P values were obtained from two-tailed tests, and only values below 0.05 were considered significant. This study was approved by appropriate Research Ethics Committee and informed consents were obtained from school officials and parents.

Results

Anthropometric results show that 25.4 and 25.1% of students were below 5th percentiles of height for age and weight for age, respectively; 49.3 and 56% were in the 5th-50th and 25.3 and 18.9% were in 50th-95th percentiles of height for age and weight for age respectively. As shown in Fig.1, medians of height and weight of all schoolchildren in six villages were below NCHS, in 1999.

Table 1 shows findings of clinical and biochemical parameters and IQ in all schoolchildren of the six villages in 1999 and 1989. Total goiter rate decreased by 42% in 1999, as compared to that in 1989.

Table 1. Urinary iodine, serum T4, T3 and TSH concentrations and IQ in schoolchildren, before and 10 years after iodine supplementation

Variable	Year	
	1989	1999
Total goiter rate (%)	100(419)*	58 (567)†
Median urinary iodine ($\mu\text{g/dL}$)	1.6 (111)	19.4 (313)†
Serum T4 ($\mu\text{g/dL}$)	6.5 \pm 2.0 (436)	8.4 \pm 1.6 (520)†
Serum T3 (ng/dL)	177 \pm 38 (436)	145 \pm 29 (520)†
Serum TSH ($\mu\text{U/mL}$)	10.8 \pm 15.1 (436)	1.8 \pm 0.8 (520)†
TSH above 5 $\mu\text{U/mL}$ (%)	40(436)	0(520)
Intelligent quotient (IQ)	89 \pm 13 (208)	97 \pm 10 (106)‡
IQ below 70 (%)	12 (208)	0 (106)

*The number in parentheses indicates the number of subjects; † P < 0.001; ‡ P < 0.01, as compared to 1989

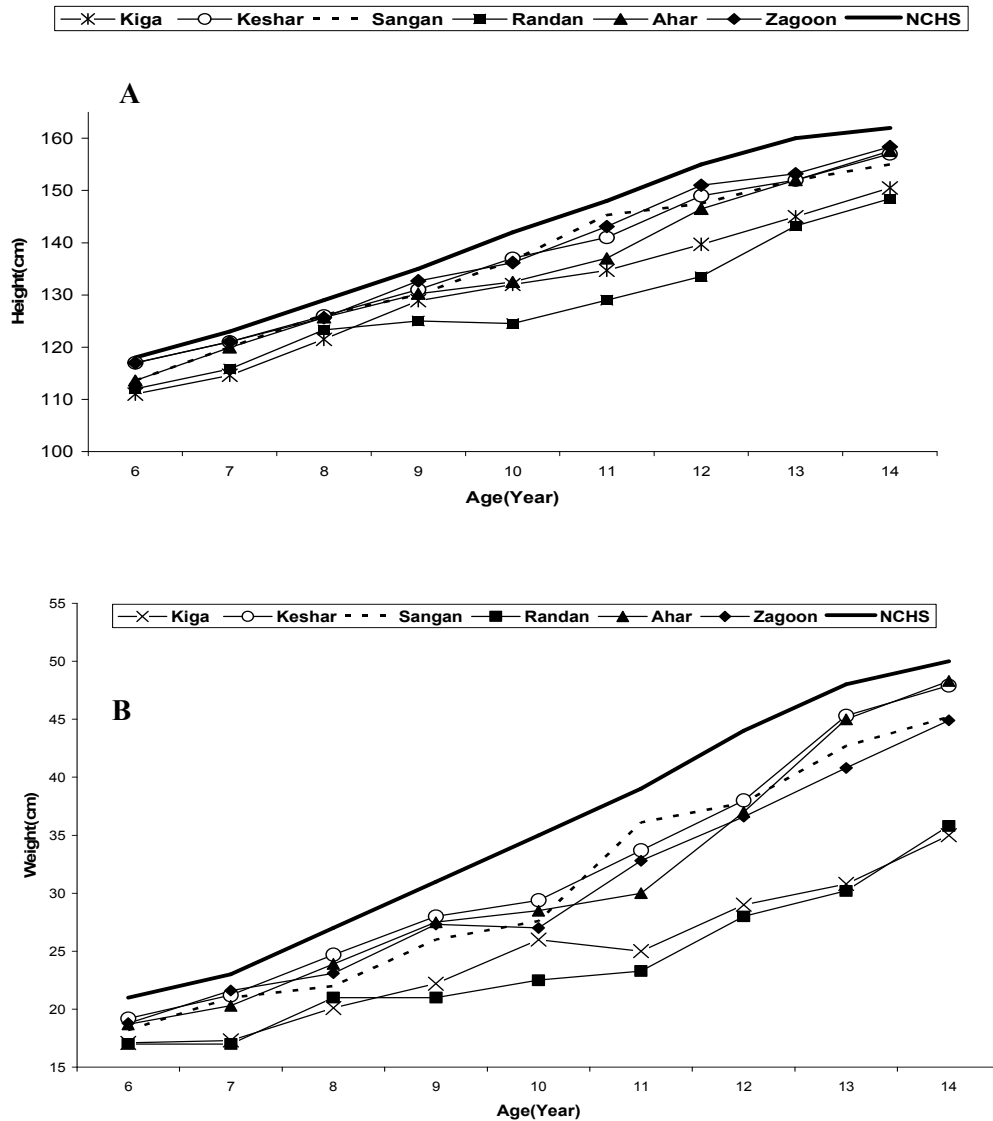


Fig.1. Median height and weight of schoolchildren in six villages compared with NCHS

Median urinary iodine concentration was above $17\mu\text{g}/\text{dL}$. In 1999, individual values for urinary iodine and serum T4, T3 and TSH concentrations in each child were within the normal range; none had TSH above $5\mu\text{U}/\text{mL}$. Mean IQ in children was 97 ± 10 and all children had IQ values above 70. Before

intervention, 40% had serum TSH above $5\mu\text{U}/\text{mL}$ and 12% had IQ below 70.

In each village, significant decrease in grade 2 goiter (Fig 2) concomitant with an increase in grade 1 goiter was seen, $P<0.001$. As shown in Fig.2, a significant decrease in grade 2 goiter was observed, $p<0.001$.

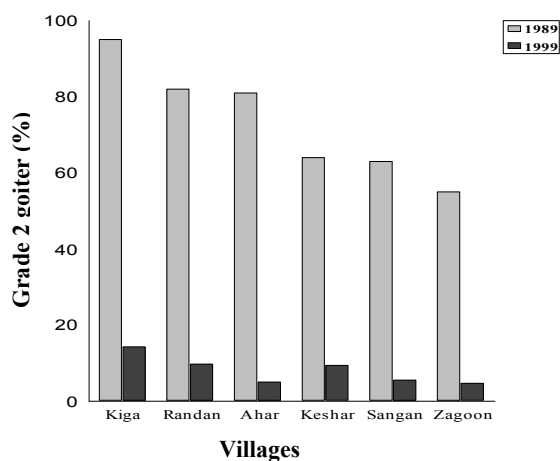


Fig.2. Prevalence of grade 2 goiter in schoolchildren of six villages in 1989(n=525) □ and 1999(n=571) ■. The changes in goiter prevalence and severity were statistically significant in all villages ($p<0.001$)

Table 2 shows median urinary iodine in villages in 1989 and 1999. In 1989, all villages had median urinary iodine concentration below $2 \mu\text{g/dL}$, while in 1999 the median urinary iodine in all villages was above $17 \mu\text{g/dL}$,

$P<0.001$. In 1999, 96% of the subjects had values above $10 \mu\text{g/dL}$ with none being below $5 \mu\text{g/dL}$.

Table 3 compares the mean hormone levels of each village in 1989 and 1999. In 1989, many of the school children were hypothyroid; serum TSH levels above $10 \mu\text{U/ml}$ in Kiga and Keshar were 40% and 24% respectively. TSH values between 5 and $10 \mu\text{U/ml}$ were 30% in Kiga and 22% in Randan. Serum T₄, T₃, and TSH concentrations, FT₄ I and resin T₃ uptake levels were normal in all schoolchildren in 1999. No correlation was established between thyroid hormones, urinary iodine and grades of goiter.

In 1999, in subgroups I, II and III, there were 228, 71 and 272 schoolchildren, mean age 8.8 ± 1.9 , 9.9 ± 1.6 and 12.1 ± 1.3 years; mean height: 123.0 ± 7.9 , 133.5 ± 6.2 & 146.0 ± 8.1 cm and mean weight: 22.0 ± 4.5 , 26.5 ± 3.9 & 36.9 ± 3.6 kg, respectively. There was no significant difference in urinary iodine levels, T₄, T₃ and TSH concentrations between the 3 subgroups.

Table 2. Median urinary iodine in schoolchildren of 4 villages, before and 10 years after iodine supplementation

Village	Median urinary iodine excretion ($\mu\text{g/dL}$)	
	1989 (111)	1999 (313)
Kiga	1.9 (49)*	20.1 (61)†
Keshar	1.8 (15)	20.1 (135)†
Randan	1.2 (25)	17.3 (28)†
Zagoon	1.8 (22)	20.1 (89)†

*The number in parentheses indicates number of subjects; † $P<0.001$, as compared to 1989

Table 3. Serum T4, T3, TSH in schoolchildren of rural areas of Tehran before and ten years after iodine supplementation

Village	Serum concentration (mean±SD)				
	T ₄ (µg/dL)	T ₃ (ng/dL)	TSH (µU/mL)	RT3Up (%)	FT4I
Kiga					
1989(n=95)	5.1±2.0	162±38	19.7±29.7	28±1.7	1.4±0.6
1999(n=66)	8.8±1.8*	149±27†	1.9±0.7*	27±1.9	2.4±0.6
Keshar					
1989(n=103)	8.4±2.1	179±39	3.3±4.2	27±2.1	2.3±0.6
1999(n=138)	8.9±1.7	152±31†	1.7±8.8*	27±2.7	2.4±0.5
Sangan					
1989(n=84)	8.1±2.2	136±24	3.4±6.7	28±3.0	2.3±0.6
1999(n=87)	7.6±1.4	140±30	1.9±1.3*	26.5±1.7	2.0±0.4
Randan					
1989(n=54)	6.0±1.8	189±37	9.4±11.6	25±2.0	1.5±0.5
1999(n=28)	7.6±1.4*	134±20*	1.7±0.8*	27±1.3	2.0±0.5
Ahar					
1989(n=80)	NA	160±41	4.7±1.9	30±4	NA
1999(n=104)	8.8±1.7	151±26	1.3±0.7*	28±2.5	2.5±0.6
Zagoon					
1989(n=20)	7.5±1.6	168±30	3.5±0.9	27±2.0	2.0±0.5
1999(n=99)	9.0±2.0†	158±23	1.5±0.8*	27±1.8	2.8±0.6
Total					
1989(n=436)	6.5±2.0	177±38	10.8±15.1	26±2.3	1.9±0.6
1999(n=520)	8.4±1.6*	145±29*	1.8±0.8*	27±1.8	2.2±0.5

* P<0.001, †P<0.05 as compared to 1989; NA= Not available

As shown in Fig.3, mean IQ was 102±7, 93±10 and 95±10 in sub-groups I, II and III, respectively. Children in sub-group I, had significantly higher IQ values than the other two sub-groups (P<0.002 and <0.05, compared to groups I and II, respectively). Of children in sub-group I, 67% had IQ values above 100, while only 33% and 37% of children in sub-groups II and III had IQ values exceeding 100. The numbers of errors in the BG test was almost similar in the 3 groups of children. Mean differences between chronological and psychomotor ages were 1.5±1.4, 2.1±1.0 and 1.8±1.2 years in groups I, II and III, respectively, not statistically significant.

Discussion

The present study demonstrates that iodine intervention in areas of severe iodine defi-

ciency restored euthyroidism in those subjects who were hypothyroid, caused a rise in urinary iodine, as well as, an increase in IQ. These changes occurred in all children, irrespective of the time of iodine supplementation, except for IQ, which showed greater improvement in the group in which iodine supplementation to their mothers had been initiated 1 to 4 years before conception.

Between 1962 and 1965, groups of researchers drew attention to the high incidence of endemic cretinism in regions of severe iodine deficiency.^{16,17} Since then, numerous clinical observations have established an association between severe iodine deficiency and endemic cretinism.¹⁸ The mechanism presumed to be responsible is a combination of maternal and fetal hypothyroidism at a critical stage in the maturation of the central

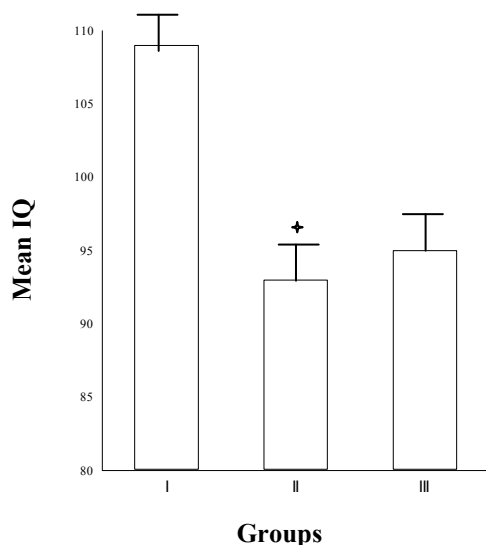


Fig.3. Mean \pm standard error (SEM) of (IQ) in schoolchildren (n=106) ten years following iodine supplementation in 1999. * $P < 0.002$; + $P < 0.05$ compared to group I

nervous system.^{19,20} It has been shown that areas of iodine deficiency are not limited to the two discrete populations of “cretins” and “normal”, but instead contain a continuum from frank cretinism through varying degrees of neurologic, auditory, physical and mental impairment and other stigmata of cretinism to apparent normality.^{7,21}

Iodized salt is the method of choice for prevention of iodine deficiency disorders.¹⁰ Iodized vegetable oil offers a temporary alternative to salt iodization. The major application for iodized oil is in areas of severe iodine deficiency where iodized salt is unavailable. Numerous studies have established that a single intramuscular injection of iodized oil provides sufficient iodine for up to three years. Iodized oil may have several disadvantages when compared to iodized salt, particularly the supra physiologic bolus dose that may cause a sudden increase in serum thyroid hormone concentration and occasional induction of hypo- or hyperthyroidism. It has however been used in many iodine deficient regions, when iodized salt is not available.²²

In the present study, 4 years following iodized oil administration, the effect of which was diminishing, distribution and consumption of iodized salt was implemented, which had a complementary effect on the control of iodine deficiency. The decrease seen in goiter prevalence 10 years after iodine prophylaxis, was appreciable; both prevalence and severity of goiter decreased. Similar results have been obtained in other countries.^{23,24} Median urinary iodine levels of 17.3-20.1 $\mu\text{g/dL}$ in the villages studied shows adequate iodine intake¹⁰ and propriety of 40 ppm iodized salt program in Iran, as shown in our previous report.²⁵

It has been shown that in euthyroid goitrous subjects with iodine deficiency, iodine supplementation results in an elevated thyroid iodine concentration²⁶, as well as a decrease in goiter prevalence and severity.²⁷ The effects of iodine supplementation on the thyroid status of hypothyroid subjects with endemic goiter have also been reported. Percutaneous application of iodine to iodine-deficient newborns increases serum TSH and borderline low serum T4 levels and normalized both values.²⁸ Iodized oil injection in children with endemic cretinism in Zaire resulted in decreased TSH and increased T4, concentrations in children.²⁹ Greater changes were however, observed in children below four years of age, who attained normal TSH and T4, five months following injection. In 14 children, aged 4 to 15 years, only partial response was seen. Administration of iodized oil did not reverse thyroid hormone deficiency in adolescents and adults with endemic myxedematous cretinism in western China.³⁰ We have reported that both in boys¹³ and girls³¹ residing in Kiga, the injection of iodized oil restores euthyroidism within 4 months following injection, perhaps due to lesser severity of the lesion, since all children in Kiga had goiterous hypothyroidism and none had an atrophic gland. Iodine supplementation has been recognized to increase the incidence of hyperthyroidism in iodine

deficient areas.³² Increases in T4 and T3 and decreases in TSH were observed in Kiga in the first year of iodized oil administration.³¹

Thyroid function, in our study, returned to normal, however, within a year and has remained so after 10 years. No untoward effects with respect to possible hyperthyroidism occurred. It has to be taken into consideration, however, that the population studied was the young schoolchildren and 10 years had passed since the initiation of iodine supplementation. Iodine induced thyrotoxicosis is seen mainly in adults, in elders, in particular usually one to two years following intervention³² with thyroid hormone.

A number of studies have demonstrated the effectiveness of iodine supplementation programs in the prevention and treatment of sporadic congenital hypothyroidism beginning in the neonatal period permits normal mental and neurologic development,³³ however, iodine or thyroxine treatment at birth does not prevent endemic cretinism.³⁴ Both animal and human studies have shown that up to the end of the second trimester, iodine treatment of the mother protects the fetal brain from the effects of iodine deficiency.^{19,20,35} Although treatment after the beginning of the third trimester showed some improvement in development quotients, it could not, improve the neurological status.³⁵

In the present study, the effects of iodine supplementation in preventing developmental injury were compared in 3 groups of schoolchildren, with differing timings of iodine supplementation, viz to the mother before conception, during pregnancy and to the child after birth. The results showed that children whose mothers received iodide supplementation before conception had normal IQ, ranging between 92 and 109; the range of

IQ of this group is almost comparable to the range of 91-130, obtained in normal Tehranian schoolchildren, using the Raven test, conducted by the same psychologist.^{6,7} The outcome of IQs in the other two groups was not optimal; however, both groups showed some improvement of IQ, as compared to schoolchildren of the same villages before intervention. In children who received supplementation after birth, partial improvement in IQ may have resulted from various additional factors that affect IQ measurement, such as improved eating habits, socio-economic changes in the area surveyed and a rise in educational level. However, it has been shown that improvement in IQ score in similar conditions has a significant association with goiter reduction after iodized oil administration to schoolchildren of an endemic region.³⁶ Improvement in development quotient has also been reported in children whose mothers were treated with iodine in the third trimester of pregnancy.³⁵

In conclusion, this study demonstrates that iodized oil administration followed by iodized salt consumption in children and adolescents with depressed thyroid function due to iodine deficiency is capable of restoring euthyroidism, and that normal thyroid function is sustained following consumption of iodized salt. In addition, the results confirm that iodine supplementation, given before conception, effectively prevents impairment of IQ development. Lesser beneficial effects in IQ scoring along with complete restoration of normal thyroid function in children who receive iodine supplementation after birth, suggest that in areas of severe iodine deficiency, iodine supplementation should be mandatory even for children who have suffered from iodine deficiency during intrauterine life.

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