USE OF ORAL IODIZED OIL TO CONTROL IODINE DEFICIENCY IN INDONESIA

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Proefschrift

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Stellingen (Propositions)

1. The efficacy of iodized peanut oil is greater than that of iodized poppyseed oil in combating iodine deficiency (this thesis).

2. Although many indicators have been used to assess whether and to what extent a population is iodine deficient and to monitor the effectiveness of iodine deficiency control programs, urinary iodine concentration and thyroid volume measured by ultrasound are the most suitable (this thesis).

3. Iodine deficiency disorders are recognized not only as a public health nutrition issue, but also as an obstacle to human development (this thesis).

4. The development of cognitive performance of stunted school children is less than that of their non-stunted counterparts (this thesis).

5. Non-iodized salt available in the market which is cheaper than iodized salt, may subvert the effectiveness of iodized salt in combating iodine deficiency (this thesis).

6. Simple goiter is the easiest of all known diseases to prevent. It may be excluded from the list of human diseases as soon as society determines to make the effort *(D Marine. Prevention and treatment of simple goiter, Atl. Med. J. 1923; 26: 437-443).*

7. When the twentieth century ends, it would be satisfying to be able to look back and say: "That was the century when iodine deficiency was eliminated from the face of our planet".

8. Selling iodized salt to a population with endemic iodine deficiency is not like marketing 'Coca-Cola'.

9. *Cybernet* enables people to contact others all over the world within seconds, but reduces meaningful contact between people.

10. Significant is not always relevant.

11. Learning does not end with the completion of formal education. Learning is a lifelong experience for those with an appetite for knowledge.

12. There is nothing wrong with having different opinions, but it's absolutely wrong to enforce one's opinion, no matter what the reason.

13. There is only one way to fight violence with nonviolence: education (*Dalai Lama*).

14. For everything we have missed, we have gained something else; and for everything we gain, we lose something else (*Ralph W Emerson. Nature, Addresses and Lectures. Harvard Divinity School, 1849*).

Proefschrift Juliawati Untoro
Use of oral iodized oil to control iodine deficiency in Indonesia
Landbouwuniversiteit Wageningen, 17 February 1999

For everyone who works towards
the eradication of iodine deficiency disorders

Abstract

Use of oral iodized oil to control iodine deficiency in Indonesia

PhD thesis by Juliawati Untoro, Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, the Netherlands.

Iodine deficiency is a leading cause of preventable mental retardation and universal salt iodization has been adopted as the main strategy for its control. However additional strategies are required where iodized salt cannot be made available in the short term or only with difficulty in the long term. Oral iodized oil supplementation is useful for this purpose. The aim of the work described in this thesis was to compare the efficacy of different preparations of oral iodized oil for controlling iodine deficiency. In addition, the performance of different outcome indicators of iodine deficiency, the impact of nutritional status and iodine supplementation on cognitive performance, as well as the effectiveness of salt iodization in the population were investigated. The studies were carried out in school children aged 8-10 y living in an endemic iodine deficient area in Indonesia.

A single oral dose of iodized oil prepared from peanut oil which is rich in oleic acid resulted in three times higher retention of iodine and twice the length of protection than iodized oil prepared from poppyseed oil which has less oleic acid and more linoleic acid. Thus iodized oils based on oleic acid rich oils should be given preference to iodized poppyseed oil in programs to control iodine deficiency.

Urinary iodine concentration and thyroid volume measured by ultrasound were found to be the most useful indicators for assessing iodine status and measuring the impact of iodized oil supplementation among iodine deficient school children. However thyroid palpation still has a useful place in assessing iodine status because no sophisticated equipment is required. Iodine status as measured by urinary iodine concentration at baseline and stunting were found to be related to the improvement of cognitive performance when children were dosed with iodized oil. The use of iodized salt, which was correlated with urinary iodine concentration and thyroid volume, resulted in improvement of the iodine status of the population studied. Apart from promulgation enabling legislation, much effort needs to be expended to increase the success of salt iodization for controlling iodine deficiency.

Contents

Chapter 1

General introduction

IODINE DEFICIENCY: MAGNITUDE OF THE PROBLEM AND ITS CONSEQUENCES

Iodine deficiency is the world's leading cause of preventable mental retardation. Up until the begin of the 1990s, it was regarded as being a significant public health problem in 118 countries with 1600 million people at risk (1). In 1990 the World Summit for Children, at United Nations Headquarters in New York, set the goal for the elimination of iodine deficiency disorders (IDD) by the year 2000. Since then, reduction in iodine deficiency is a global success story by any standard. This achievement involved a coordinated international effort to change diets in a subtle but important way by the introduction of iodized salt (2). UNICEF estimates that nearly 60 per cent of all edible salt in the world is now iodized. Of the countries that had iodine deficiency at the beginning of the decade, 26 now iodize over 90 per cent of their edible salt or import that proportion if they are not salt producers. Another 14 countries iodize between 75 per cent and 90 per cent of their salt. As late as 1994, 48 countries with established iodine deficiency still had no programs at all. Of these, 14 now iodize more than half of their salt (2). Although iodization of salt has been successful in reducing the prevalence of iodine deficiency, additional strategies are required to eradicate iodine deficiency. Probably the best alternative is oral dosing with iodized oil which is the subject of this thesis.

Although goiter is the most manifest sign, iodine deficiency results in irreversible brain damage in the fetus and infant, retarded mental and psycho-motor development in the child, and also impaired reproductive function (3-11). In the most severe cases, it leads to cretinism. The cumulative consequences in iodine deficient populations spell diminished performance for the entire economy. In Indonesia, IDD comprise one of the most important malnutrition problems with high rates of goiter prevalence being reported (Table 1).

The main cause of IDD is inadequacy of iodine intake due to environmental deficiency of this essential element. This interacts with poverty and remoteness when there is little contribution of food from outside an iodine deficient area to the diet, as is the case with much subsistence agriculture. Poverty, with poor sanitation and general malnutrition, may worsen the effects of iodine deficiency. Inadequacy of iodine intake is the major but not the sole factor responsible for IDD. The importance of other factors in causing iodine deficiency including goitrogenic substances, protein energy malnutrition (PEM), vitamin A and selenium deficiencies, has been revealed by several studies.

Table 1. General overview of iodine status in Indonesia

Period of investigation	Indicator
1980-1982 (12)	Prevalence of goiter, 11.3-74.7 % People at risk, 30 million Estimated number of cretins, 750,000
1987-1990 (12)	Prevalence of goiter, 2.8-62.2%
1983-1984 (13)	Adequately iodized salt (≥ 30 ppm), 33.0%
1995 (14)	Adequately iodized salt (≥ 30 ppm), 49.8%

Goitrogenic substances play a role in the etiology of IDD in humans (15-17). Natural goitrogens were first found in vegetables of the genus *Brassica* (the *Cruciferae* family). Their anti-thyroid action is related to the presence of thioglucosides, which after digestion release thiocyanate (SCN^-) and isothiocyanate (18). These compounds are powerful goitrogenic agents that act by inhibiting thyroid iodide transport and at high doses, compete with iodide in the organification process (15). Another important group of natural goitrogens is the cyanoglycosides, which are found in several staples (cassava, maize, bamboo shoots, sweet potatoes) (19). After ingestion, these glycosides release cyanide (CN^-) which is detoxified by conversion to thiocyanate. A cassava-based diet combined with a low iodine supply produces marked differences in the prevalence of goiter, such differences are determined by the balance between iodide and thiocyanate concentrations in the blood reaching the thyroid and in the thyroid itself (19).

Severe PEM affects thyroid function and the metabolism of thyroid hormones. Iodine malabsorption may be associated with PEM and thus contribute to endemic goiter, particularly where iodine intake is limited (20-22).

Selenium has been shown to be an essential component of iodothyronine 5'-deiodinase type I, II and III (23,24). Thyroxine (T_4), the major hormone product of the thyroid gland, is converted to the more biologically active hormone 3,5,3'-triiodothyronine by type I and type II iodothyronine 5'-deiodinase (25). The type III iodothyronine deiodinase converts T_4 and T_3 into inactive reverse-T_3 and diiodothyronine respectively, by catalyzing the inner ring deiodination (26,27). Therefore, selenium-deficient subjects have low tissue deiodinase activities and abnormal thyroid hormone metabolism (23,28).

The role of vitamin A in IDD was studied by Horvart and Maver (29) on the

island of Krk, Yugoslavia. The prevalence of goiter in a group of school children was decreased by 45% in those who received 3,000 IU/d vitamin A supplementation while it remained the same in a control group which was not supplemented. A study by Ingenbleek and de Visscher (30) has also shown that vitamin A affects iodine metabolism. They found that the concentration of transthyretin, retinol-binding protein and retinol levels decreased progressively with increase in goiter size while serum albumin levels and urinary iodine concentration were low in the goitrous subjects in Senegal. Wolde-Gebriel et al. (31) showed that Ethiopian children with goiter grade IB and II had lower serum retinol and retinol-binding protein levels compared with those with no goiter or grade IA goiter.

IODINE METABOLISM

Most of the iodine in the human body enters the circulation as iodide, where it becomes part of the iodine pool (32). The healthy adult human body contains 15-20 mg of iodine of which about 70-80% is in the thyroid gland which weighs only 15-25 g. Thus, the pool of iodine is concentrated mainly in the thyroid. The remainder is in tissues or in the circulation either as free iodine or protein-bound iodine.

The normal intake and requirement for children and adults are 100-150 μg per day. Excess iodide is readily excreted by the kidney. The level of excretion correlates well with the level of intake so that it can be used to assess the level of iodine intake (33). The thyroid has to trap about 60 μg of iodine per day to maintain an adequate supply of T_4. This is possible because of the very active iodide trapping mechanism which enables the thyroid to maintain concentration gradients for iodide (thyroid/plasma concentration ratios) of about 100 (34). In iodine deficiency, this gradient may exceed 400 in order to maintain the output of T_4. The amount of iodine in the gland is closely related to iodine intake and the content may drop to 1 mg or less in the iodine deficient thyroid gland (35).

About half of the iodine in the diet, absorbed from the intestine as inorganic iodide, is normally taken up by the thyroid gland (the rest is excreted in urine) and there incorporated into protein (thyroglobulin, Tg) to form mono- and di-iodothyrosine (MIT and DIT), precursors of tetraiodothyronine (T_4) and triiodothyronine (T_3). These hormones are then released into the blood, often over quite long periods, in response to various stimuli controlled by thyroid stimulating hormone (TSH). TSH which is secreted by the anterior pituitary, is the principal active regulator and

accelerates iodoprotein synthesis. The release of TSH is stimulated by thyrotropin releasing hormone (TRH), which is produced by the hypothalamus. Both TRH and TSH secretion are triggered by a decline in blood thyroid hormone levels, so the system maintains these blood concentrations at functional levels over a wide range of iodine status (34).

Iodine exists in the blood as T_4, T_3 and as inorganic iodine. The level of inorganic iodine falls in iodine deficiency and rises with increased intake. T_4 is the major form of thyroid hormone secreted by the thyroid: it is converted to either T_3 or reverse T_3 (rT_3). The T_4 and T_3 are mainly (>99%) bound to three plasma proteins i.e.: thyroxine binding globulin, thyroxine binding prealbumin and albumin, and only about 0.5 percent is free in human serum. In the bound state, T_4 and T_3 are not biologically active. It is the concentration of unbound hormone which determines the level to which the target cells are exposed (34). Thus the level of free T_4 is an important determinant of tissue levels of thyroid hormone and is necessary for the brain. Determination of the level of free T_4 in serum is the optimum method for assessment of thyroid status and for the diagnosis of hypothyroidism and hyperthyroidism (36). A study in iodine deficient rats showed that low fetal brain T_3 increased the activity of 5' deiodinase II activity (37), this means that the developing fetal brain is highly dependent on a supply of T_4 because it is converted to T_3 by intracellular deiodination (38).

The synthesis and availability of the thyroid hormone is reduced in iodine deficiency. Hence blood levels of T_4 and FT_4 as well as of TSH and Tg, can be used for assessing thyroid status. Although much of the basic physiology of thyroid hormones and effects of deficiency of thyroid hormones are reasonably understood and well-described, the mechanism of action of the hormones, and hence the pathological effects of deficiency, remain to be fully worked out (36).

INDICATORS FOR ASSESSING THE EXTENT OF IDD IN POPULATIONS

Indicators are essential for measuring the extent of iodine deficiency, whether and which intervention is necessary and for evaluating program implementation and impact. Indicators can be classified as: outcome indicators which provide a measure of iodine status, and process indicators which measure progress in implementing an IDD control program. The outcome indicators can be further classified according to whether the assessment is clinical or biochemical. WHO/UNICEF/ICCIDD (39)

generally recommends that at least two indicators should be used. No single parameter reflects the entire IDD picture and resulting changes in the thyroid. In cases of severe deficiency, initial emphasis may be on lowering rates of goiter and cretinism. Even though several indicators to evaluate the extent of iodine deficiency are established, further study on specificity and sensitivity of outcome indicators among iodine deficient population are still needed. Therefore in this thesis outcome indicators for determining iodine status are examined.

Outcome indicators: clinical.

Thyroid Size. The size of the thyroid gland changes inversely in response to alterations in iodine intake. Thyroid size can be determined by palpation and ultrasonography. The preferred target group is children aged 8-10 years but can be extended to children aged 6-12 years old. There is a practical reason for not measuring very young age groups: the smaller the child, the smaller the thyroid and the more difficult it is to perform palpation, and the consideration for not measuring the older group is the puberty period. The classification of goiter currently used is as follows (39):

Grade 0 : No palpable or visible goiter.

Grade 1 : A mass in the neck that is consistent with an enlarged thyroid that is *palpable but not visible* when the neck is in the normal position. It moves upward in the neck as the subject swallows. Nodular alteration(s) can occur even when the thyroid is not visibly enlarged. Previously grade 1 goiter was divided into IA (palpable) and IB (visible with neck extended).

Grade 2 : A swelling in the neck that is visible *when the neck is in the normal position* and is consistent with an enlarged thyroid when the neck is palpated. Previously grade 2 goiter was divided into II (visible at close range with head in normal position) and III (visible at distance with head in normal position).

Palpation is quantitative only in the crude sense. Total goiter rate describes the proportion of total goiter grade 1 and 2 in the population. Specificity and sensitivity of palpation are low in grades 0 and 1 due to a high inter-observer variation, misclassification can be as high as 40%, especially but not exclusively in the assessment of smaller enlargements of the thyroid. Low goiter rates, especially when found following a sustained intervention, should be confirmed by ultrasound,

which provides a more objective measure of thyroid size (39-43). However, there are several advantages of palpation as a method of measurement. It is a technique that requires no instrumentation, can reach large numbers in a short period of time, is not invasive and makes relatively limited demands on the skills of the observer. Nevertheless, the ease with which accurate palpation can be conducted has been seriously overestimated in some instances as inadequately trained observers have been used (44).

Ultrasonography is a means of obtaining an image of the thyroid and can provide a more accurate assessment of thyroid size. This assessment also requires a trained operator, expensive equipment, and is not often practical for routine use in surveys. Ultrasonography provides a more precise measurement of thyroid volume than palpation and this becomes especially significant when the prevalence of visible goiter is small, and in monitoring iodine control programs where thyroid volumes are expected to decrease over time (43). The thyroid volume is calculated based on the length, width, and thickness of both lobes using an ellipsoid model (45). The calculated volume should be compared to the normative standard of a population with sufficient iodine intake (46). In iodine replete populations, the expected prevalence of thyroid volumes greater than the 97th centile would be 3%, and this figure can be compared with the observed prevalence. In addition, the median (50th centile) thyroid volume may be useful.

Cretinism. Endemic cretinism, which is the most dramatic consequence of iodine deficiency, is caused by thyroid hormone deficiency during development of the central nervous system during the prenatal period. The manifestation of endemic cretinism include mental retardation, severe growth retardation, squinting of eyes and deafness.

Outcome indicators: biochemical

Serum thyroid hormones. Measurement of thyroid hormones in blood might provide the ultimate tools for measuring IDD. Laboratory methods, usually radioimmunoassay techniques, exist for measuring blood levels of the major thyroid hormones, T_4, FT_4, T_3, Tg and TSH. While providing some important information, they have the disadvantages of being expensive, being generally unavailable in many developing countries, and requiring the collection of blood samples.

Urinary iodine concentration. Almost all iodine in the body is eventually excreted in the urine. Thus measurement of iodine in the urine provides a good

index of the iodine ingested. However, since an individual's level of urinary iodine varies daily and even during a given day, data can be used only for making a population-based estimate. The iodine concentration in early morning urine specimens (child or adult) provides an adequate assessment of a population's iodine status; 24-hour samples are not necessary. Urinary iodine concentration is preferably expressed per liter of urine (100 μg/L is equivalent to 0.79 μmol/L) rather than per gram of creatinine (47). Furnée et al. (47) found that the iodine-creatinine ratio in casual urine samples is an unsuitable indicator for evaluating iodine status in areas where large inter and intra individual variations in urinary creatinine concentration exist. A model for describing urinary iodine after oral dosing of iodized oil was developed by Furnée et al. (48), which reflects the mutual effects of the physiological mechanism involved in the retention and elimination of iodine.

Epidemiological criteria for assessing the severity of IDD

A summary of cut-off points and prevalence that are considered indicative of a significant public health problem for IDD is presented in Table 2.

Table 2. Summary of IDD prevalence indicators (outcome indicators) and criteria for a significant public health problem [a]

Indicator	Target population	Severity of public health problem		
		Mild	Moderate	Severe
Total goiter (by palpation, %) or thyroid volume > 97th centile by ultrasound[a] (%)	School age children, 6-12 y	5.0-19.9	20.0-29.9	≥ 30.0
Median urinary iodine level (μg/L) [b]	School age children, 6-12 y	50-99	20-49	< 20
TSH > 5 mU/L whole blood (%)	Neonates, 4-30 days	3.0-19.9	20.0-39.9	≥ 40.0
Median Tg (μg/mL serum)[c]	Children and adults, >1y	10.0-19.9	20.0-39.9	≥ 40.0

[a] Based on WHO/UNICEF/ICCIDD (39) modified by WHO/ICCIDD (46).

[b] Conversion factor: 100 μg/L = 0.79 μmol/L

[c] No international standards are yet available for this assay so criteria need to be established in each laboratory (49).

With the epidemiological criteria for establishing IDD severity, it should be understood that "mild" is a relative term; it does not imply that this category of IDD is of little consequence. With respect to goiter, a total goiter rate (goiter grades 1 and 2) of 5% or more in primary school children (age range approximately 6 to 12 years) signals the presence of a public health problem. This is based on the observation that in a normal iodine-replete population, the prevalence of goiter should be quite low. The cut-off of 5% allows some margin of inaccuracy of goiter assessment and for goiter that may occur in iodine-replete population due to other causes such as goitrogens and autoimmune thyroid diseases. The previously recommended 10% cut-off level has been revised downwards since it has been shown that goiter prevalence rates between 5% and 10% may be associated with a range of abnormalities, including inadequate urinary iodine concentration and/or abnormal levels of TSH among adults, children and neonates (39).

With respect to urinary iodine concentration, frequency distribution curves are necessary for full interpretation, since values from populations are usually not normally distributed, and therefore the median value is used rather than the mean. Iodine deficiency is indicated when the median value for iodine concentration in urine is less than 0.79 μmol/L, i.e. when 50% of the samples have values less than 0.79 μmol/L.

The specificity of TSH for IDD screening has not been clearly quantified. Individuals with mild elevations of TSH can now be detected by using the newer sensitive whole-blood TSH assay. IDD screening programs are not designed to follow up individuals but to direct population-based interventions. Reference data for TSH are available among neonates because they are routinely collected as part of neonate congenital hypothyroid screening programs. TSH values are currently in whole blood units or serum units. A TSH cut-off point of 20-25 mU/L whole blood (approximately 40-50 mU/L serum) is commonly used to screen for congenital hypothyroidism. IDD may present with TSH levels which are only mildly elevated. While further study of iodine-replete populations is needed, a cut-off of 5 mU/L in whole blood is regarded as appropriate for epidemiological studies of IDD in neonates.

Individuals (children and adults) with sufficient iodine intake show a median Tg serum level of 10 ng/ml and a normal upper limit, for individuals, of 20 ng/ml in most assay techniques. The results obtained from a survey should be expressed as a median and as the percentage of Tg levels above 20 ng/ml (39). However it should

be noted that no international standards are yet available for this assay so criteria need to be established in each laboratory (49).

Process indicators of IDD control programs

As programs are implemented for the control of IDD in a country, it is important to establish mechanisms for monitoring and evaluating these activities. Included in such monitoring protocols will be both indicators associated with the process of the programs, as well as indicators of the impact realized through the implementation of the control activities. Depending upon the specific characteristics of the IDD control programs, distinct indicators will need to be considered and different techniques employed in their monitoring. Although most countries will have iodized salt as the primary control activity, other programs, where implemented, will need to be monitored, even if they are used as short-term measures while salt iodization is being established.

Salt iodization programs. All countries with a significant public health IDD problem should undertake a situation analysis of salt available for human and animal consumption, from points of production (or importation) through distribution channels to the consumption level. Such salt is referred to as *food grade salt*, which includes crude salt for direct edible use by people, and for livestock; and refined salt for edible use and for use in most processed foods (50).

The iodization of salt involves the addition of a small quantity of iodine (30 to 100 mg of iodine per kg salt, or parts per million - ppm), usually in the form of potassium iodide or potassium iodate. The joint FAO/WHO Expert Committee on Food Additives noted in 1991 that "potassium iodate has been shown to be a more suitable substance for fortifying salt than potassium iodide, because of its greater stability, particularly in warm, damp or tropical climates" (51).

Iodized oil programs. The program evaluation should permit a monitoring of periodic recording of distribution of the oral iodized oil capsules and assess an output e.g. number of people at risk of iodine deficiency receiving the capsules.

INDONESIAN IDD CONTROL PROGRAMS

The Government of Indonesia has endorsed the goals of the 1990 World Summit for Children and the recommendations of the 1991 World Health Assembly for the elimination of IDD by the year 2000. To attain the goal that by the year 2000

no cretinious baby will be born, the IDD National Program in Indonesia has established the following strategies (52).

Iodized salt for human consumption. To strengthen the iodized salt program, the government issued a joint decree of four Ministries (Industry, Health, Trade and Home Affairs), that all salt for human consumption in Indonesia should be iodized to 40-50 ppm with potassium iodate (KIO_3). Indonesia has had a law mandating the fortification of salt with iodate since 1994; the lower limit has been set at 30 ppm I. Results of the national survey in 1996 (14) found that half of the salt consumed in 200,000 households was adequately iodized.

Iodized injectable and orally administered oil in severely endemic areas. The iodized oil supplementation program has been operating since 1974. So far 11 million people have received iodized oil injections. Starting from 1993, injected oil supplementation has been replaced by iodized oil through oral administration (12,53).

The program of iodized oil has shown good results in many endemic areas and the approach of salt iodization, has shown progress in Indonesia. Administration of iodized oil by oral may become a more widely used method in the future. The major advantages of iodized oil administration are that it can be implemented immediately, and does not involve the complexities of altering salt production and trade. Thus, the usual places for iodized oil are for the areas of significant iodine deficiency where iodized salt is unlikely to be successfully implemented soon and correction is needed promptly. In many such areas, the iodized oil program will be necessary for at least several years, and for some remote areas it may be semi-permanent (54).

USE OF ORAL IODIZED OIL FOR CONTROLLING IODINE DEFICIENCY

There is evidence from several studies in Algeria (55), Bolivia (56), Malawi (47) and Zaire (57), that oral administration of a single dose of iodized oil is effective for several years in protecting against iodine deficiency. Experience with oral iodized oil is more limited than that with the injected material, and precise guidelines for its optimal dose and duration of effectiveness are not available.

At present it is suggested that a single oral dose of 1 mL (480 mg iodine) will provide adequate iodine for one to two years after administration. A previous study in Zaire suggests that smaller doses may be equally effective, at least for a year (57). A study by Furnée et al. (47) showed that a single dose of an iodized oil in which the iodized fatty acids from poppyseed oil are present as triacylglycerol esters (675 mg iodine) maintained urinary iodine concentration above 0.40 μmol/L for approximately one year whereas the duration of effectiveness of iodized oil (490 mg iodine) which consist of a mixture of ethyl esters of iodized fatty acids, lasted only 3-4 months. While effectiveness is shorter than that of injection, oral administration avoids the need for syringes, needles, and sterile techniques, and can be administered by responsible persons without medical training. Capsules of iodized oil containing approximately 200 mg iodine are available and can be administered directly (58).

Iodized oil is based on either triacylglycerol esters or ethyl esters of unsaturated fatty acids (59). When the unsaturated fatty acids react with potassium iodide, saturation of the double bound takes place with the addition of iodine to one of the carbon atoms involved (35). Up until now, the most widely available preparations have been based on poppyseed oil and have been manufactured by Guerbert Laboratories, France. Preparations containing triacylglycerol ester were marketed under the brand name of Oriodol® while those containing ethyl ester are marketed under the name of Lipiodol® UF. The fatty acid composition of poppyseed oil on a weight basis is: linolenic acid (C18:2, n-6), 73%; oleic acid (C18:1, n-9), 14%; stearic acid (C18:0), 3%; and palmitic acid (C16:0), 9% (60).

A Study by Van der Heide et al. (61) in both man and rats, showed that iodine was retained longer from a preparation prepared from ethyl oleate compared with a preparation prepared from ethyl linoleate or from ethyl esters derived from poppyseed oil. While the work described in this thesis was under way, Ingenbleek et al. (62) reported on the effectiveness of iodized rapeseed oil compared to iodized poppyseed oil. These authors found that iodized rapeseed supplying 752 mg I gave longer protection in moderate iodine deficient adults (30 wk) compared to iodized poppyseed supplying 729 mg (17 wk) when an iodine concentration in urine of 0.79 μmol/L was taken as the cut-off point. Most of iodine in the rapeseed oil preparation was bound to oleic acid and in poppyseed oil preparation to linoleic acid (62).

Use of oral iodized oil in Indonesia

The iodized oil capsule supplementation program started in Indonesia in 1992/1993. The iodized oil supplement is distributed in moderate and severely endemic areas which were indicated by prevalence of total goiter rate 20-29% and 30% and above respectively. The target group of this program is all males aged 0-20 years and females aged 0-35 years, including pregnant and lactating women in moderate and severe endemic areas (63). In general, iodized oil should be avoided over the age of 45 years because of the possibility of precipitating hyperthyroidism (63). Pregnancy is not regarded as a contra-indication. It is desirable for the male population to be included in an iodized oil program even though the other groups already mentioned are more at risk. The experiences of males of the benefits will include greater productivity and quality of life which are important to community acceptance (63).

An Indonesian pharmaceutical firm has introduced Yodiol® into the market. Yodiol® is prepared by iodization of peanut oil which has about three times more oleic acid and half the amount of linoleic acid compared with the established orally administered iodized oil which is prepared from poppyseed oil. Therefore, we decided to compare the efficacy of a preparation of iodized peanut oil with that of the iodized poppyseed oil preparation.

OBJECTIVES AND HYPOTHESES OF THE STUDY

The objectives and hypotheses (written in *italics*) of this study are as follows:

Main objectives and hypotheses

(1). To investigate and compare the efficacy of orally administered iodized peanut oil containing a high proportion of monounsaturated fatty acids and iodized poppyseed oil containing a high proportion of polyunsaturated fatty acids among Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

The efficacy of iodized peanut oil is higher than that of iodized poppyseed oil among Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

(2). To evaluate different outcome indicators of IDD status: casual urinary iodine concentration, goiter size (measured by palpation and by ultrasound) and blood levels of FT_4 and TSH at baseline and after oral iodized peanut oil supplementation in Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

Urinary iodine concentration, goiter size (measured by palpation and by ultrasound) and blood levels of FT_4 and TSH at baseline and after oral iodized oil supplementation, indicated the same level of severity of iodine deficiency in Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

Secondary objectives and hypotheses

(3). To investigate the effect of iodine supplementation on cognitive performance of Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

Iodine supplementation improves the cognitive performance of Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

(4). To investigate the relationship between nutritional status and cognitive performance of Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

School children living in an endemic iodine deficient area with adequate nutritional status, have better cognitive performance than malnourished school children.

Tertiary objective and hypothesis

(5). To investigate the relationship between iodized salt consumption and the iodine status of Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

Lower iodine intake from iodized salt is associated with lower status of iodine in Indonesian school children aged 8-10 years living in an endemic iodine deficient area.

OUTLINE OF THE THESIS

The research described in this thesis was conducted between October 1996 and December 1997 in an endemic iodine deficient area in Cilacap district, Central Java, Indonesia.

Chapter 2 describes the efficacy of different oral preparations of iodized oil among school children living in an endemic iodine deficient area (Objective 1).

Chapter 3 describes the comparison of indicators for measuring iodine status in population and the impact of iodized oil supplementation in school children living in an endemic iodine deficient area (Objective 2).

Chapter 4 describes the effects of oral iodized oil and nutritional status on cognitive performance in school children living in an endemic iodine deficient area (Objectives 3, 4).

Chapter 5 describes the impact of compulsory salt iodization on the iodine status of Indonesian school children living in an endemic iodine deficient area, as indicated by urinary iodine concentration, thyroid palpation and thyroid volume measured by ultrasound, and blood levels of FT_4 and TSH (Objective 5).

Chapter 6 discusses the most important findings of the research described in this thesis.

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Chapter 2

Efficacy of oral iodized peanut oil is greater than that of iodized poppyseed oil among Indonesian school children

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ABSTRACT

Oral iodized poppyseed oil is the major alternative to iodized salt for correcting iodine deficiency. There is a need for a more effective and cheaper iodized oil preparation. The aim of this study was to compare the efficacy of iodized peanut oil with that of iodized poppyseed oil. Randomly selected school children aged 8-10 y (n=251) in an endemic iodine deficient area in Indonesia were allocated to five groups and supplemented with a single oral dose of iodized peanut oil (200, 400 or 800 mg I); iodized poppyseed oil (400 mg I); or peanut oil (placebo). Urinary iodine concentration was measured at 0, 4, 12, 25 and 50 wk. Except at baseline, urinary iodine concentration of all treatment groups was higher than in the placebo group. Urinary iodine concentration of the group supplemented with iodized peanut oil supplying 200 mg I was similar to the concentration of the group supplemented with iodized poppyseed oil. Comparing preparations supplying 400 mg I using a mathematical model, iodine retention from the peanut oil preparation was three times higher and the protection period twice as long as that of the poppyseed oil preparation. Reduction of thyroid volume in the iodized oil groups was greater than in the placebo group. There were no significant differences in serum thyroid stimulating hormone and serum free thyroxine among groups before or after treatment. Iodized peanut oil is more efficacious than iodized poppyseed oil containing the same amount of iodine in controlling iodine deficiency.

INTRODUCTION

Effective control of iodine deficiency is still a challenge in developing countries (1). Despite the success of universal salt iodization (2,3), provision of iodized salt is sometimes ineffective because of economic conditions, a shortage of iodized salt in local markets, inadequately iodized salt, loss of iodine from salt because of excessive exposure to moisture, light and heat, and the use of non-iodized local salt (4-6). Single intramuscular injections of iodized oil provide adequate iodine for two to three years (7) but injections have serious disadvantages, including the potential to serve as a vector for communicable diseases and the expense involved (8). Oral administration of iodized oil has been advocated as an alternative, but experience with this method is limited (9) and the optimal dose and the frequency of dosing remain uncertain (10).

Until recently, the main raw material for iodized oil has been poppyseed oil. A study by Van der Heide et al. (11) indicated that iodine from iodized oil prepared from ethyl oleate was retained longer in both man and rats than that prepared from ethyl linoleate or ethyl esters of poppyseed oil fatty acids. Oils, such as peanut oil, which are rich in oleic acid, also have the advantage that they are cheaper as raw material than poppyseed oil. Therefore, we decided to compare the efficacy of a preparation of iodized peanut oil introduced onto the Indonesian market with that of the established iodized poppyseed oil preparation. While this work was under way, Ingenbleek et al. (12) reported on the efficacy of iodized rapeseed oil, the composition of which is not unlike that of iodized peanut oil. Preliminary results from the study presented in this paper have been published previously (13).

SUBJECTS AND METHODS

Subjects

All school children (n=355) aged 8-10 y attending four primary schools in Cilacap district, Central Java Province, Indonesia, where goiter is highly prevalent (>30%) (14), were examined by a medical assistant from the Sub-district Health Center. Only apparently healthy subjects were considered for entry into the study.

Study design

This study was designed as a community based, double-blind, placebo-controlled supplementation trial. A sample size of 50 per group was calculated with a

power index of 2.80, α=0.05 and β=0.20 to obtain a significant difference of 10% in urinary iodine concentration between groups with an expected drop out rate of 20%. From the eligible children (n=347), children were randomly selected and randomly allocated to one of 5 groups (50 per group), to receive one of the following preparations: 1 mL of peanut oil as placebo; 0.5 mL, 1.0 mL and 2.0 mL of iodized peanut oil (Yodiol®, 400 mg I/mL, PT Kimia Farma, Indonesia), providing 200 mg, 400 mg and 800 mg I respectively; or 1 mL of ethyl esters of iodized poppyseed oil (Lipiodol® UF, 400 mg I/mL, Guerbet Laboratory, France) providing 400 mg I. The placebo group was used to control whether the subjects were exposed to extraneous iodine during the study. The fatty acids composition of peanut oil compared with that of poppyseed oil is shown in **Table 1**.

Table 1. Fatty-acid profiles of poppyseed and peanut oils.

	Proportion of fatty acids, g/100g	
	Poppyseed oil[1]	Peanut oil[2]
Saturated		
Palmitic acid (C16:0)	9.0	14.6
Stearic acid (C18:0)	3.0	0.2
Unsaturated		
Oleic acid (C18:1, n-9)	14.0	41.1
Linoleic acid (C18:2, n-6)	73.0	38.9
α-Linolenic acid (C18:3, n-3)	0.0	1.5
Long chain fatty acids (C≥20)	0.0	1.8
Other	1.0	1.9

[1] Reference (15).
[2] PT Kimia Farma, Indonesia.

In a previous study by Furnée et al. (16), the retention of iodine from orally administered iodized oil was found to be reduced significantly by intestinal parasitic infestation. Therefore, one week prior to iodized oil administration, all subjects were dosed with the broad spectrum anti-helminth albendazole (400 mg per dose, SmithKline Beecham, Indonesia) to control *Ascaris lumbricoides* as it is known that these are endemic (17).

The iodine status of the children was assessed by 4 different indicators, i.e.: thyroid volume, urinary iodine concentration, serum TSH and serum FT_4 at baseline and 25 and 50 wk after supplementation. Additional measurements on urinary iodine concentration were done at 4 and 12 wk.

Methods

Measurement of thyroid volume. Measurement of the thyroid volume using ultrasound was carried out by the main researcher (JU) who had been trained in the technique. The ultrasonography was performed on each subject in the sitting position using equipment with a transducer of 7.5 MHz (Phillips SDR 1480, Eindhoven, the Netherlands). The transducer was first kept horizontal at an upright angle to the neck to observe the cross section of the thyroid, measuring maximal width (w) and maximal depth (d). Next, the length (l) of each lobe was determined by longitudinal application of the transducer to the subject's neck. A co-worker recorded the observations of the ultrasonography and provided a continuous flow of persons to be examined. The volume was calculated using the following formula: $V=0.479 \times d \times w \times l$ (cm^3) (18). The thyroid volume was the sum of the volumes of each lobe. Results of ultrasonography from the study population were compared to normative data from populations with sufficient iodine intake (19).

Serum concentrations of thyroid stimulating hormone (TSH) and serum free thyroxine (FT_4). Venous blood samples (3 mL) were drawn from an antecubical vein from non-fasting subjects between 08.30 and 12.00 using EDTA as anti coagulant. Immediately after collection, the blood was placed on ice, protected from light, and within 2-3 h, centrifuged at the laboratory of the district health center to obtain serum. Serum was frozen in a series of containers at -70 °C before being transferred, packed in dry ice, to the laboratory of Endocrinology, Academic Medical Center (Amsterdam, the Netherlands) for analysis.

Serum concentration of TSH was measured by immunoluminometric assay using a commercial kit (Brahms Diagnostica Gmbh, Berlin, Germany) and FT_4 was measured by time-resolved fluoro immunoassay after immuno-extraction using a commercial kit (Delfia™, Wallac Oy, Turku, Finland). The coefficient of variation of intra-assay and inter-assay for TSH were 2.4% and 4.5% respectively, and for FT_4 were 3.6% and 6.4% respectively. Values for both TSH and FT_4 obtained were within 10% of the target value of normal and elevated samples provided every two months by the Dutch national external quality control scheme for hormones in serum (LWBA). Reference range of iodine replete subjects for serum TSH is 0.4-4.0 mU/L and for FT_4 is 9-24 pmol/L (20).

Urinary iodine concentration. A casual urine sample (5 mL) was collected between 08.30 and 12.00 on 2 consecutive days at baseline and 4, 12, 25 and 50 wk after treatment. The urine samples, preserved with approximately 1 g thymol,

were sent to the iodine laboratory of the Nutritional Research and Development Center in Bogor (Indonesia). Iodine concentration in urine was analyzed in duplicate after alkaline digestion using the Sandell-Kolthoff reaction (21), average values were calculated for each child.

The model for describing urinary iodine concentration after oral dosing of iodized oil developed by Furnée et al. (10) was used. The model reflects the effects of iodine retention and elimination on urinary iodine concentration.

Thus, $I_T=(\alpha_0+\alpha_1)T^{-(\beta_0+\beta_1)}$ (*equation 1*), where:

I_T = Urinary iodine concentration at time T (μmol/L)

α_0 = Iodine retention for placebo subjects (μmol/L)

α_1 = Iodine retention for supplemented subjects (μmol/L)

T = Time after dosing with iodized oil (wk)

β_0 = Rate of iodine elimination for placebo subjects (μmol/L/wk)

β_1 = Rate of iodine elimination for supplemented subjects (μmol/L/wk)

Statistical methods

The Kolmogorov-Smirnov test was used to check the normality of data. Data are reported as mean and SD or SEM for normally distributed parameters and as median and 25^{th} - 75^{th} percentile for non-normally distributed parameters. Differences among groups were examined by analysis of variance (ANOVA) for normally distributed parameters and by the Kruskal-Wallis test for non-normally distributed parameters. If significant differences were indicated, comparisons among groups were made with the least significant difference test for normally distributed data and the Bonferroni's multiple comparison test at a significant level of $P<0.01$ for non-normally distributed data.

The mathematical functions, transformed into log-linear equivalents, were fitted to the four values of urinary iodine concentrations in the four treatment groups. The parameters α, β and T were estimated using the maximum likelihood estimation technique (22) based on the average urinary iodine concentration measured in individuals on consecutive days.

The SPSS software package (Windows version 7.5.3, SPSS Inc., Chicago, IL) was used for all statistical analyses and a P value<0.05 was considered significant.

Ethical Considerations

The ethical guidelines of the Council for International Organizations of Medical Sciences (23) were followed. The Ethical Committee for Studies on Human Subjects, Faculty of Medicine, University of Indonesia approved the study. Informed consent was obtained from parents of each subject before the start of the study. Iodized oil was given at the end of the study to those children who were still considered iodine deficient.

RESULTS

Subject characterization

There were no significant differences in age, thyroid volume, urinary iodine concentration, serum TSH and serum FT_4 among the groups at baseline (**Table 2**). The children were, on average aged 9.45±0.76 y and moderately iodine deficient, with a median urinary iodine of 0.36 μmol/L (25^{th}, 75^{th} percentile; 0.27, 0.63 μmol/L). The prevalence of goiter was 24% (based on thyroid volume) and the median of thyroid volume of all children was 4.51 mL (25^{th}, 75^{th} percentile; 3.96, 5.33 mL). There were no statistical significant differences in thyroid volume, urinary iodine concentration, serum TSH and serum FT_4 between boys and girls.

Urinary iodine concentration

Patterns of urinary iodine concentration after oral iodized oil supplementation in the different groups are shown in **Figure 1**. All treated groups had significantly higher urinary iodine concentration ($P<0.001$) at all periods of follow-up compared to the placebo group which received peanut oil. The higher the dosage of iodine in iodized peanut oil, the higher the urinary iodine concentration ($P<0.001$). Urinary iodine concentration of the group supplemented with iodized poppyseed oil supplying 400 mg I was similar of that of the group supplemented with iodized peanut oil supplying 200 mg I and significantly lower than that of other supplemented groups at all periods of follow up ($P<0.001$).

Table 2. Baseline demographic and iodine status of the group studied

Characteristics	Iodized poppyseed oil, 400 mg I (n=49)	Iodized peanut oil			Peanut oil (n=51)
		200 mg I (n=50)	400 mg I (n=51)	800 mg I (n=50)	
Boys/Girls	19/30	26/24	23/28	29/21	20/31
Age (y)[1]	9.54±0.77	9.36±0.79	9.53±0.78	9.39±0.71	9.41±0.75
Thyroid volume (mL)[2]	4.45 (3.72-4.92)	4.51 (4.00-5.27)	4.68 (3.81-5.35)	4.92 (4.23-5.69)	4.33 (3.65-5.47)
Urinary iodine concentration (μmol/L)[2]	0.35 (0.28-0.71)	0.37 (0.29-0.60)	0.34 (0.30-0.64)	0.37 (0.23-0.62)	0.38 (0.24-0.64)
Serum thyroid stimulating hormone concentration (mU/L)[2]	1.60 (1.10-2.38)	1.50 (0.96-2.20)	1.90 (1.10-2.60)	1.80 (1.58-2.50)	1.70 (1.20-2.30)
Serum free thyroxine concentration (pmol/L)[1]	16.86±2.53	16.78±1.96	16.81±2.07	16.98±2.78	16.74±2.66

[1] Mean ± SD
[2] Median (25^{th} -75^{th} percentile)

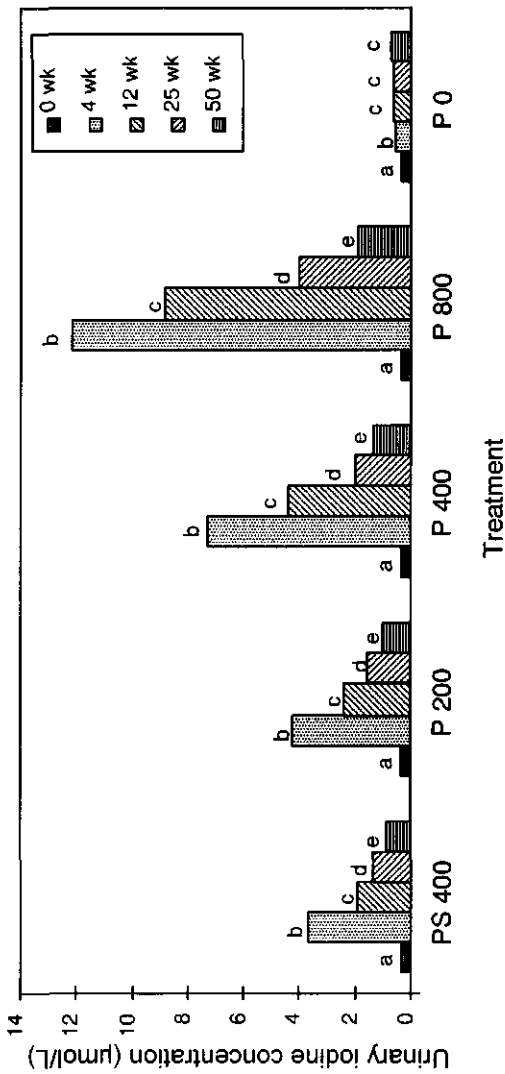

Figure 1. Median urinary iodine concentration before and after five treatments of supplementation (PS 400= Poppyseed oil, 400 mg I; P200= Peanut oil, 200 mg I; P400=Peanut oil, 400 mg I; P800=Peanut oil, 800 mg I and P0=Peanut oil; values with different letters are significantly different from one another within group (Mann Whitney test)).

The regression model of urinary iodine concentration

The efficacy coefficients of iodine retention, iodine elimination rate, and the protection period for different groups of treatment are shown in **Table 3**. The increases in iodine retention, elimination rate and protection period of the treatments were significantly different among the four groups ($P<0.001$) except the protection period for the iodized poppyseed oil supplying 400 mg I and iodized peanut oil supplying 200 mg I. Urinary iodine concentrations, as predicted by the regression model, after oral iodized oil supplementation for different groups of treatment are given in **Figure 2**. From week 4, iodine excretion declined exponentially. If an urinary iodine concentration of 0.79 μmol/L is taken as the cut-off point, below which the recommended dietary allowance is not being met, then the protection period of iodized poppyseed oil supplying 400 mg I was about 42 wk, iodized peanut oil supplying 200 mg I, 400 mg I and 800 mg I were 49 wk, 77 wk and 124 wk respectively (Table 3).

Table 3. Iodine retention, elimination and the model-based of protection period after oral administration of different iodized oil treatments for school children[1]

Treatment	Iodized poppyseed oil, 400 mg I	Iodized peanut oil		
		200 mg I	400 mg I	800 mg I
Iodine retention, α_1 (μmol/L)	5.88 (1.16)[a]	8.59 (1.15)[b]	17.55 (1.15)[c]	40.41(1.14)[d]
Iodine elimination rate, β_1 (μmol/L/wk)	0.45 (0.05)[a]	0.53 (0.05)[b]	0.64 (0.05)[c]	0.75 (0.05)[d]
Protection period, T(wk)[2]	42.3 (33.8, 60.0)[a]	49.2 (40.0, 69.2)[a]	76.9 (62.1, 112.7)[b]	123.6 (96.0, 171.7)[c]

[1] See Equation 1 for method of calculation, values in parentheses are SE.

[2] Time after dosing when the urinary iodine concentration remained above 0.79 μmol/L (100 μg/L) after correcting for changes in the urinary iodine concentration in the peanut oil (placebo) group, values in parentheses are 95% CI. Values within a row with different superscript letters are significantly different from one another using Bonferroni's multiple comparisons test.

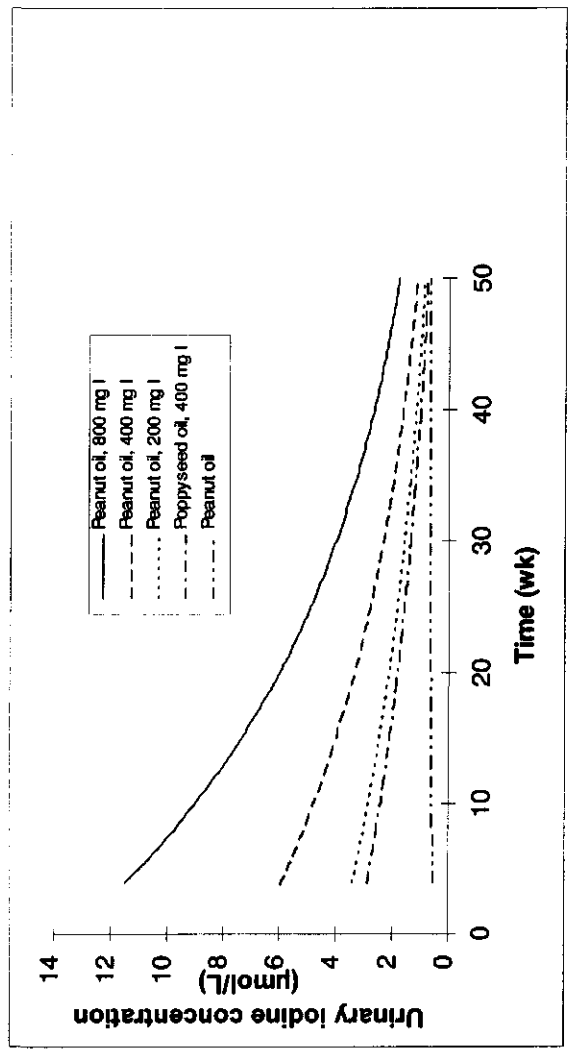

Figure 2. Urinary iodine concentration by five treatments of supplementation as described by the regression equation, $IT=\alpha T^{-\beta}$

Goiter volume

The goiter volumes measured by ultrasound for different groups of treatment are presented in **Table 4.** There were no significant differences in thyroid volumes among groups at baseline (P=0.085), but after supplementation there were significant differences in goiter volumes for all treated groups compared to the placebo group which received peanut oil. After a year of supplementation, reduction in goiter volumes were significantly higher in the supplemented groups compared to the placebo group at all period of follow up (P<0.001). There was no difference in the reduction of goiter volume among subjects supplemented with iodized peanut oil supplying 200 mg I or 400 mg I and those supplemented with iodized poppyseed oil supplying 400 mg I.

Serum concentrations of TSH and FT_4

Initial median values of TSH were not different among the five groups and were within the normal range, but 2.8% of individuals had values above 5 mU/L. At 50 wk after treatment, values of TSH remained within the normal range (median (25^{th} - 75^{th} percentiles); placebo, 1.60 (1.18-2.30) mU/L; iodized oil groups, 1.80 (1.30-2.70) mU/L) and none had levels above 5 mU/L. Mean serum FT_4 concentrations at baseline were in the normal range and were not different among the five groups. There was a small non-significant increase of serum FT_4 concentrations at 25 wk among all groups including the placebo (mean ± SD; placebo, 17.32 ± 3.08 pmol/L; iodized oil groups, 17.98 ± 3.13 pmol/L), and values returned to baseline at 50 wk (mean ± SD; placebo, 16.74 ± 3.05 pmol/L; iodized oil groups, 16.97 ± 2.51 pmol/L).

DISCUSSION

This study shows that oral iodized oil is an effective alternative to salt iodization for the control of iodine deficiency. This study also found that the fatty acids composition of the iodized oil determines the efficacy of the treatment. Four outcome indicators were used to assess the efficacy of different oral iodized oil supplementation: urinary iodine concentration, thyroid volume, serum TSH and serum FT_4 concentrations.

Urinary iodine concentrations showed large variability and were very high in some subjects. Urinary iodine concentration was increased significantly among all

Table 4. Goiter volume at baseline and after supplementation[1]

Period	Iodized poppyseed oil	Iodized peanut oil			Peanut oil
	400 mg I (n=49)	200 mg I (n=50)	400 mg I (n=51)	800 mg I (n=50)	(n=51)
Baseline	4.24 (3.72-4.92)	4.51(4.00-5.27)	4.68 (3.81-5.35)	4.92 (4.23-5.69)	4.33 (3.65-5.47)
25-wk	3.22 (2.96-3.68) [a]	3.64 (3.05-4.29) [b]	3.53 (2.99-4.26) [b]	3.88 (3.21-4.61) [b]	4.08 (3.44-5.26) [c]
50-wk	3.11 (2.73-3.31) [a]	3.31 (2.91-3.68) [b]	3.25 (2.81-3.63) [b]	3.21 (2.86-3.48) [b]	4.10 (3.70-5.35) [c]
Reduction[2], %	28.6±11.9 [d]	23.1±15.7 [d]	26.6±17.8 [d]	33.5±14.3 [e]	3.0±3.5 [f]

[1] Values in mL are expressed as median (25^{th}-75^{th} percentile) or mean ± S.D.
[2] Reduction in thyroid volume at 50 wk compared to baseline, %.
Values within a row with different superscript letters are significantly different from one another, using Bonferroni's multiple comparisons test with $P<0.01$ (a-c) or using least significant difference test with $P<0.05$ (d-f).

groups of treatments and placebo between 0 and 4 wk. The slight differences in urinary iodine concentration of the placebo group ($P<0.05$), could indicate that some children might have been exposed to an extraneous source of iodine, possible iodized salt (2,24). The urinary iodine concentration after supplementation of all groups of treatments at different periods of follow up (4, 12, 25 and 50 wk) were significantly higher than those of the placebo group.

The efficacy of the iodized poppyseed oil preparation supplying 400 mg I as indicated by urinary iodine concentration, was similar to iodized peanut oil supplying 200 mg I and significantly lower than iodized peanut oil supplying 400 or 800 mg I at all periods of follow up. Based on a mathematical model (10), comparing the iodized oil preparations supplying 400 mg I after adjustment for the increase of urinary iodine concentration in the placebo group, three times more iodine was retained from the iodized peanut oil preparation than from the iodized poppyseed oil preparation. In addition, iodized peanut oil gave a period of protection against iodine deficiency twice as long as that provided by iodized poppyseed oil (77 wk vs. 42 wk respectively). These findings confirmed the results from previous studies in rats and man (11), in which it was shown that iodine was retained longer from a preparation prepared from ethyl oleate compared with a preparation prepared from ethyl linoleate or from ethyl esters derived from poppyseed oil.

A study by Ingenbleek et al. (12) on the effectiveness of iodized rapeseed oil appeared while this study was being carried out. These authors found that iodized rapeseed supplying 752 mg I gave a longer period of protection in moderate iodine deficient adults (30 wk) compared to iodized poppyseed supplying 729 mg (17 wk) when an iodine concentration in urine of 0.79 μmol/L was taken as the cut-off point. Most iodine in the rapeseed oil preparation was bound to oleic acid (52.5%) and in poppyseed oil preparation to linoleic acid (72.7%). Comparing iodized peanut oil with iodized poppyseed oil, the proportion of iodine derived from iodized oleic acid is higher (41 vs. 14%) and from linoleic acid is lower (39 vs. 73%) respectively. Our data show that iodized peanut oil supplying 400 mg I is estimated to have a protection period of about 77 wk, and iodized peanut oil supplying 800 mg I gives a protection period of 124 wk in moderate iodine deficient school children. Apart from the type of oil used and the location, our study differed in a sense that the subjects from Chad (12) were older (18-40 y) and were more iodine deficient than the children from our study.

Compared to the previous studies in school children (**Table 5**), our results showed that the same preparation of oral iodized poppyseed oil supplying 400 mg I, could protect school children from iodine deficiency for 42 wk, which was about twice as long as that of Benmiloud et al. (20) and three times longer than that was found by Furnée et al. (10) who used a cut-off point for urinary iodine concentration of 0.40 μmol/L. Differences in results among these studies might be due to the severity of iodine deficiency. The median urinary iodine concentration at baseline was 0.21 μmol/L and 0.16 μmol/L in the study of Benmiloud et al. (20) and Furnée et al (10) respectively. Other possible factors are exposure to goitrogenic substances, nutritional status, the indicators employed and cut-off points used.

We have also evidence that a high dose of 800 mg I is able to correct iodine deficiency, without any side-effects as found in the study by Elnagar et al. (25) in Sudan. They found that doses of 400 mg I and 800 mg I were slightly less effective than the 200 mg I and induced some adverse reactions, such as iodine induced inhibition of hormone synthesis (Wolff-Chaikoff effect).

Thyroid volumes of the iodized oil supplemented groups were significantly lower than in the placebo group. Median thyroid volume decreased significantly in all groups, and the reduction of thyroid volume in all treatment groups was significantly higher than that in the placebo group. The reduction of thyroid volume in the placebo group might be due to introduction of iodized salt in the area during the study (24). The reduction of thyroid volume was positively correlated with the change of urinary iodine concentration among all groups (r=0.22). The thyroid volumes of previously iodine deficient children decreased to normal values in groups receiving either iodized poppyseed oil or iodized peanut oil, which suggest that the treatment of iodine deficient subjects using oral iodized oil effectively reduced goiter size.

The efficacy of treatment indicated by the normalization of urinary iodine concentrations and thyroid volumes was not supported by changes in serum concentrations of TSH and FT_4. Our results contrast with those reported by Eltom et al. (9), Elnagar et al. (25) and Tonglet et al. (26). They found that the efficacy of oral iodized oil supplementation could be demonstrated by normalization of serum T_4 and TSH concentrations, reduction of goiter size measured by palpation or by an increase in urinary iodine concentration. Our data showed that median TSH concentrations were in the normal range before iodine treatment and only 2.8%

Table 5. Comparison on the protection periods of different oral iodized preparations from different studies

Study	Vehicle	Dose (mg I)	Target group	Cut-off point (μmol/L)	Protection period (wk)
Furnée et al. (10)	Poppyseed oil[1]	490	School children	0.40	14
	Poppyseed oil[2]	675	8-10 y	0.40	55
Benmiloud et al. (20)	Poppyseed oil[1]	120	School children	0.79	4
		240	6-11 y		26
		480			26
		960			52
Ingenbleek et al. (12)	Rapeseed oil	752	Adults	0.79	30
	Poppyseed oil[1]	729		0.79	17
Our study	Peanut oil	200	School children	0.79	49
		400	8-10 y		77
		800			124
	Poppyseed oil[1]	400			42

[1] Ethyl esters of fatty acids
[2] Triacylglycerol esters of fatty acids

were higher than the upper normal limit. The responses of serum TSH were not correlated to the dose or type of iodized oil. The mean level of serum FT_4 before iodine treatment was in the normal range, and slightly increased after iodine treatments, it did not differ significantly among the placebo and treatment groups. Our results concur with those of Gutekunst et al. (27) and Delange et al. (28) who observed no relationship between serum TSH and thyroid volume. Bourdoux (29) reported that the circulating levels of thyroid hormones and TSH in mild iodine deficient population, are not different from those observed in iodine-replete population. While in moderate iodine deficient population, with the prevalence of goiter ranging from 20 to 50%, it was observed that the levels of circulating T_3 and T_4 were still in the normal range (29). The finding that urinary iodine concentration and thyroid volume of iodine deficient children became normal after supplementation, although serum TSH and serum FT_4 concentrations did not show the same response to treatment, suggests that serum TSH and FT_4 might be less reliable indicators for assessing and monitoring treatment of moderate iodine deficiency in school children than urinary iodine concentration or thyroid volume (30).

We conclude that a single oral dose of iodized peanut oil compared to a single oral dose of iodized poppyseed oil results in three times higher iodine retention leading to a period of protection twice as long in iodine deficient school children. Thus iodized oil prepared from oleic acid rich oils, such as peanut oil and rapeseed oil should be given preference above preparation based on poppyseed oil in programs to control iodine deficiency.

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Chapter 3

Comparison of indicators to assess iodine status and its improvement through supplementation with iodized oil

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ABSTRACT

Sensitivity and specificity of indicators for assessing iodine status in populations and measuring the impact of programs aimed to reduce iodine deficiency are critical factors for selecting such indicators. The present study examined the relationship among primary indicators for assessing iodine deficiency and monitoring effectiveness of oral administration of iodized oil. Goiter prevalence by palpation, thyroid volume by ultrasound, urinary iodine concentration, serum concentrations of thyroid stimulating hormone (TSH) and free thyroxine (FT_4) were measured in 186 school children in an endemic iodine deficient area in Indonesia, at baseline, 25 and 50 wk after oral administration of iodized oil. Serum thyroglobulin (Tg) concentration was assessed in a subsample of 40 school children at baseline. Goiter prevalence at baseline was 22% and 23% by palpation and ultrasound respectively, and the median urinary iodine concentration was 0.36 μmol/L, suggesting that the area was moderately iodine deficient. However, the median of serum TSH and Tg concentrations and mean serum FT_4 concentration at baseline were in the normal range. Thyroid volume was positively related to goiter assessed by palpation, however there was about 40% misclassification. After one year of treatment, thyroid volume and goiter prevalence were significantly reduced and urinary iodine concentration increased. Serum FT_4 concentration increased within the normal range, but serum TSH concentration remained the same. Reduction of thyroid volume was associated with goiter grade at baseline and change in urinary iodine concentration. Urinary iodine concentration and thyroid volume are useful but serum concentrations of TSH and FT_4 are not useful as indicators for assessing iodine status and measuring the impact of oral iodized oil supplementation among moderately iodine deficient school children.

INTRODUCTION

In 1990 it was estimated that worldwide about 1600 million people were at risk of developing iodine deficiency disorders (IDD) (1). The prevalence and severity of iodine deficiency within a population, and the progress towards its elimination after intervention, can be assessed through various outcome indicators. The selection of an indicator is dependent on the acceptance of the indicator by the target population and field staff performing the assessment, on the ease of use in field conditions, and on the available resources in terms of money, laboratory equipment and staff (2). Another consideration for indicator selection is the performance in terms of sensitivity and specificity (3-6). A commonly used indicator is the prevalence of goiter as assessed through palpation. However, grading of goiter size by palpation has large intra and inter-observer variability. Therefore, in addition, other indicators of iodine or thyroid status are often used (7).

WHO/UNICEF/ICCIDD (2) recommend the measurement of thyroid size using palpation and ultrasonography, the measurement of iodine concentration in urine and thyroid hormone concentrations (8). The use of single indicators, or combinations for studies or surveys, are not fully standardized but depend on study specific circumstances. So far the number of studies comparing the relative sensitivity and specificity between indicators in assessing iodine status of a population is limited and have given conflicting results (3-5,8). A similar lack of information exists for the assessment of the degree of change in iodine status after intervention such as salt iodization. For example, the prevalence of goiter in a population may remain unchanged after successful salt iodization whereas iodine concentration in the urine has increased (9).

The aim of the present study was to compare iodine concentration in casual urine sample, goiter prevalence by palpation, thyroid size by ultrasound, and serum concentrations of free thyroxine (FT_4), thyroid stimulating hormone (TSH) and thyroglobulin (Tg) for the assessment of iodine status in a population of school children. Furthermore, changes in these indicators were compared after oral supplementation with iodized oil.

SUBJECTS AND METHODS

Subjects

Subjects were randomly selected from school children aged 8-10 years (n=186) attending four primary schools in Cilacap district, Central Java Province, Indonesia. This study was designed as a part of a community based, oral iodized oil supplementation trial. A sample size of 186 was calculated with a power of 0.8 for a significance level at 0.05 to obtain a significant difference of 11% between indicators. The study area was classified as a high-risk area for iodine deficiency, with an estimated total goiter rate of more than 30% (10). All subjects were examined by a medical assistant from the Sub-district Health Center, and only apparently healthy subjects were considered suitable for entry into the study.

Study design

At baseline the iodine status of subjects was assessed using five indicators: goiter grade measured by palpation, thyroid volume measured by ultrasonography, urinary iodine concentration, and serum concentrations of TSH and FT_4 . After the baseline assessment all subjects were supplemented with an oral dose of iodized oil, which was large enough to cover iodine requirements for at least 49 wk. Details about the dose and type of iodized oil are presented elsewhere (11). Iodine status by all five indicators was again assessed at 25 wk and 50 wk after treatment with iodized oil. Additionally, measurement of urinary iodine concentration was done at 4 and 12 wk. The concentration of serum Tg was measured in a subsample of 40 children at baseline.

Methods

Measurement of thyroid size. Thyroid size was assessed using palpation and ultrasound techniques. Palpation of the thyroid was carried out by a district health worker who was experienced in the assessment according to WHO/UNICEF/ ICCIDD criteria (2).

Measurement of the thyroid volume using ultrasound was carried out by the main researcher (JU) who had been trained in the technique. Ultrasonography was performed on each subject in the sitting position using equipment with a transducer of 7.5 MHz (Phillips SDR 1480, Eindhoven, the Netherlands). The transducer was first kept horizontal at an upright angle to the neck to observe the cross section of the thyroid, measuring maximal width (w) and maximal depth (d). Next, the length (l)

of each lobe was determined by longitudinal application of the transducer to the subject's neck. A co-worker recorded the observations of the ultrasonography and provided a continuous flow of persons to be examined. The volume was calculated using the following formula: V (cm^3) =0.479 x d x w x l (6). The thyroid volume was the sum of the volumes of both lobes. Results of ultrasonography from the study population were compared to normative data from populations with sufficient iodine intake (12).

Serum concentrations of thyroid stimulating hormone (TSH), free thyroxine (FT_4) and thyroglobulin (Tg). Venous blood samples (3 mL) were drawn from an antecubical vein from non-fasting subjects between 08.30 and 12.00 using EDTA as anticoagulant. Immediately after collection, the blood was placed on ice, protected from light, and within 2-3 h, centrifuged at the laboratory of the district health center to obtain serum. Serum was frozen in a series of containers at -70 °C before being transferred, packed in dry ice, to the laboratory of Endocrinology, Academic Medical Center (Amsterdam, the Netherlands) for analysis.

Serum concentration of TSH was measured by immuno luminometric assay using a commercial kit (ILMA; Brahms Diagnostica Gmbh, Berlin, Germany) and FT_4 by time-resolved fluoro immunoassay after immuno-extraction using a commercial kit (Delfia™, Wallac Oy, Turku, Finland). The coefficient of variation of intra-assay and inter-assay for TSH were 2.4% and 4.5% respectively, and for FT_4 were 3.6% and 6.4% respectively. Values for both TSH and FT_4 obtained, were within 10% of the target value of normal and elevated samples provided every two months by the Dutch national external quality control scheme for hormones in serum (LWBA). Reference range of iodine replete subjects for serum TSH is 0.4-4.0 mU/L and for FT_4 is 9-24 pmol/L (13).

The serum concentration of Tg was measured by ILMA using a commercial kit (Brahms Diagnostica Gmbh, Berlin, Germany). The method was standardized in house using serum differing four-fold in target concentrations. Intra-assay and inter-assay coefficient of variation were 7-10% and 6-7% respectively depending on concentration. From a sample of 250 persons stratified by sex into five age groups from 20 to 70 y, the concentration of Tg varied from 1 to 45 pmol/L and values were not related to age and sex. Up until the present time, external quality control materials are still under development (14).

Urinary iodine concentration. A casual urine sample (5 mL) was collected between 08.00 h and 12.00 h on 2 consecutive days at baseline and 4, 12, 25 and

50 wk after treatment. The urine samples, preserved with approximately 1 g thymol, were sent to the iodine laboratory of the Nutritional Research and Development Center in Bogor (Indonesia). Iodine concentration in urine was analyzed based on alkaline digestion using the Sandell-Kolthoff reaction (15). Urinary iodine level was measured in duplicate and the average calculated for each child.

Statistical methods

The Kolmogorov-Smirnov test was used to check whether the distribution of the variables was normal. Data are reported as mean and SD for normally distributed parameters and as median and 25^{th} - 75^{th} percentile for non-normally distributed parameters. Correlation between normally distributed parameters was measured by Pearson test and for non-normally distributed parameters by Spearman rank test. Differences between groups were examined by analysis of variance (ANOVA) for normally distributed parameters and by the Mann Whitney and Kruskal-Wallis test for non-normally distributed parameters.

The software package of SPSS (windows version 7.5.2, SPSS Inc., Chicago, IL) was used for all statistical analyses and a P value<0.05 was considered significant.

Ethical Considerations

The guidelines of the Council for International Organizations of Medical Sciences (16) were followed. The ethical committee for studies on human subjects, Faculty of Medicine, University of Indonesia approved the study. Informed consent was obtained from parents of each subject before the start of the study. Iodized oil was given at the end of the study to those children who were still considered iodine deficient.

RESULTS

The average age of the subjects was 9.4 ± 0.8 y, and the sample included 84 boys and 102 girls. The average body weight and height were 22.5 ± 3.2 kg and 121.1 ± 5.9 cm respectively. At baseline the prevalence of goiter as assessed by palpation was 21.5% whereas it was 22.6% as assessed by ultrasound. The median urinary iodine concentration of the population was 0.36 μmol/L, suggesting that the

subjects were moderately iodine deficient. However, the median serum concentration of TSH and mean serum concentration of FT_4 at baseline were in normal ranges (**Table 1**). The median serum level of Tg in a subsample of 40 children was 10.5 (6.0-17.5) pmol/L. All but one value were in the normal range (1-45 pmol/L).

Table 1. Iodine status of the school children expressed by different indicators at different time periods during the study (n=186).

Period	Thyroid volume[1] (mL)	Goiter by palpation (%)	Urinary iodine concentration[1] (μmol/L)	Serum thyroid stimulating hormone[1] (mU/L)	Serum free thyroxine[2] (pmol/L)
Baseline	4.54 (3.99-5.30)	22	0.36 (0.29-0.65)	1.8 (1.2-2.5)	16.9 ± 2.4
25 wk	3.57 (2.99-4.25)	20	1.98 (1.20-3.51)	1.7 (1.1-2.2)	17.9 ± 3.1
50 wk	3.20 (2.86-3.48)	9	1.12 (0.84-1.90)	1.8 (1.3-2.7)	17.0 ± 2.5
P	<0.001[3]	<0.01[4]	<0.001[3]	NS	<0.01[5]

[1] Median (25^{th} - 75^{th} percentile)
[2] Mean ± SD
[3] Kruskal-Wallis test
[4] Spearman test
[5] ANOVA

The sensitivity and specificity of goiter measured by palpation against ultrasound were 57% and 89% at baseline, and 60% and 81% at 25 wk, while at 50 wk of follow up, none of the school children had goiter as measured by ultrasound. There was a significant agreement ($P<0.001$) between goiter grades by palpation and thyroid volume measured by ultrasound at baseline and 25 wk (**Table 2**). The thyroid volume was significantly greater in subjects with goiter than in normal subjects, and it was also greater in subjects with grade 2 than with grade 1 goiter. There was no significant agreement between thyroid grades measured by palpation and thyroid volumes at 50 wk of follow-up (P =0.45).

There was a significant reduction in thyroid volumes and in the prevalence of goiter measured by palpation at 50 wk after supplementation with oral iodized oil. The reduction in the goiter grade measured by palpation was significantly associated

Table 2. Relationship between goiter grade (palpation) and other outcome indicators of iodine status among Indonesian school children at different time periods during the study (n=186)

Period	Palpation	N	Thyroid volume[2] (mL)	Goiter by ultrasound[3]	Urinary iodine concentration[2] (µmol/L)	Serum thyroid stimulating hormone[2] (mU/L)	Serum free thyroxine [4] (pmol/L)
Baseline	Normal	146	4.46 (3.75-4.93)	18 (12%)	0.37 (0.29-0.64)	1.70 (1.10-2.40)	16.74±2.24
	Goiter	40[6] [1]	5.56 (4.37-6.79)	24 (60%)	0.36 (0.31-0.66)	2.10 (1.30-2.70)	17.45±2.77
P			<0.001[5]	<0.001[6]	NS[5]	NS[5]	NS[7]
25 wk	Normal	149	3.44 (2.95-3.95)	2 (1%)	2.09 (1.19-3.63)	1.70 (1.10-2.20)	17.55±2.81
	Goiter	37[3] [1]	4.68 (3.59-5.26)	3 (8%)	1.78 (1.26-2.82)	1.90 (0.94-2.53)	19.27±3.86
P			<0.001[5]	<0.05[6]	NS[5]	NS[5]	NS[7]
50 wk	Normal	169	3.20 (2.85-3.47)	0	1.11 (0.84-1.92)	1.80 (1.30-2.70)	17.00±2.54
	Goiter	17[2] [1]	3.23 (2.89-3.76)	0	1.46 (0.92-1.66)	1.30 (0.99-2.88)	16.95±2.53
P			NS[5]	NS[6]	NS[5]	NS[5]	NS[7]

[1] Figures in square parentheses are goiter grade 2
[2] Median (25^{th} - 75^{th} percentile)
[3] Mean ± SD
[4] Enlargement of thyroid corresponding to goiter was assessed by ultrasound
[5] Mann Whitney test
[6] Spearman test
[7] ANOVA

with the reduction in thyroid volume, and the changes in thyroid volume were significantly greater for subjects who initially had goiter (P <0.001) (Table 2). Median urinary iodine concentration was significantly increased at 25 wk compared to baseline and reduced between 25 and 50 wk after supplementation. However all children maintained urinary iodine concentrations above 0.4 μmol/L (Table 2). A weak, but statistically significant, inverse correlation was found between the logarithm of urinary iodine concentration and thyroid volume at baseline (r=-0.15; P<0.05, **Figure 1**). Urinary iodine concentration was not related to any other indicators at baseline or any indicators at any periods of measurements (**Table 3**).

There were no significant associations between goiter grades (palpation) and urinary iodine concentration, serum concentrations of TSH and FT_4 at baseline and at all periods of follow up (Table 2). Goiter grade (palpation) at baseline was also not related to serum Tg concentrations in a subsample of 40 children at baseline (data not shown). Subjects with a palpable goiter did not have lower urinary iodine, higher serum TSH, or lower serum FT_4 concentrations than subjects without goiter at any time of measurement.

Serum TSH and serum FT_4 did not respond significantly to treatment with iodized oil. The mean of serum FT_4 slightly increased at 25 wk in both goiter and normal groups, and went down to initial levels after 50 wk of treatment. The changes of FT_4 were not significant and there was no difference between the normal and goiter groups (Table 2). A significant inverse correlation was found between the serum concentrations of TSH and of FT_4 (r=-0.18; P<0.05, **Figure 2**) and a significant correlation was also found between the serum concentrations of TSH and of Tg in a subsample of the population (r=0.52; P <0.01).

There were significant differences in the mean change of urinary iodine concentration between goitrous and normal subjects. Children who had goiter at baseline had greater iodine retention in their bodies at 4, 12 and 25 wk after treatment, compared to the non-goitrous children. At the 50th wk after intervention, both groups had a median urinary iodine within normal range and none of the children had goiter as measured by ultrasound (**Table 4**).

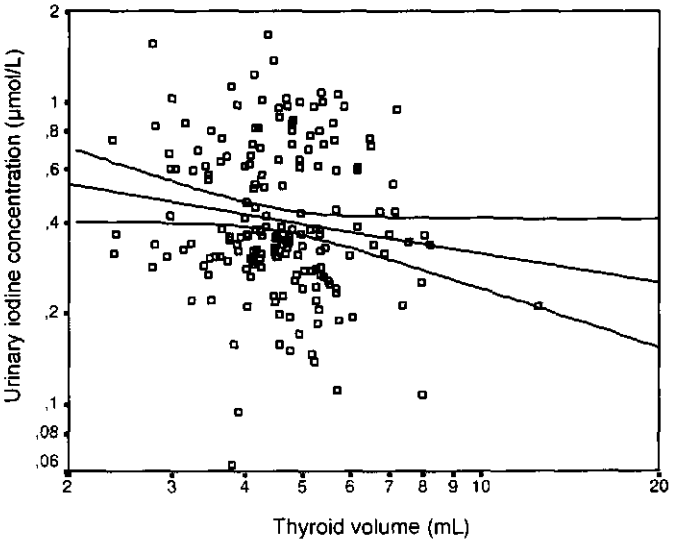

Figure 1. Linear logarithm relationship between thyroid volume and urinary iodine concentration (n=186; r=-0.15, $P<0.05$). The curved lines indicate the 95% CI.

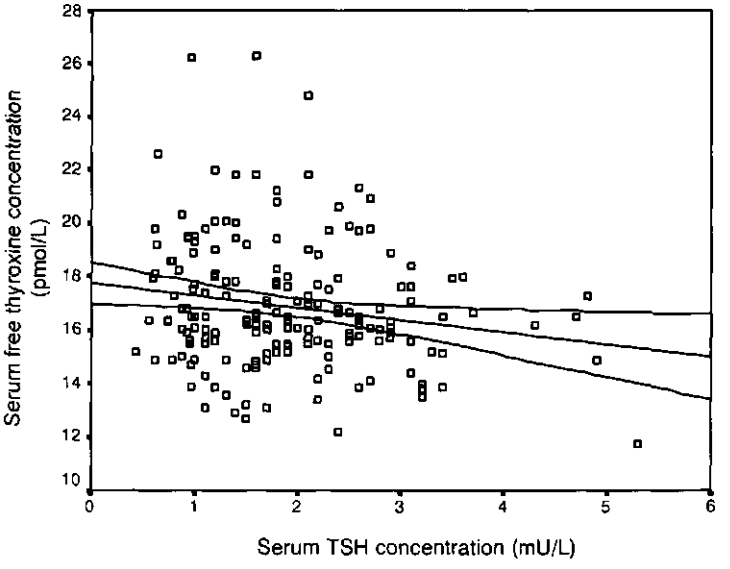

Figure 2. Relationship between thyroid stimulating hormone (TSH) and serum free thyroxine (n=186; r=-0.18, $P<0.05$). The curved lines indicate the 95% CI.

Table 3. Relationship between urinary iodine concentration and other outcome indicators of iodine among Indonesian school children living in an endemic iodine deficient area at different time periods during the study (n=186).

Period	Urinary iodine concentration (μmol/L)	N	Thyroid volume[1] (mL)	Goiter by ultrasound[3]	Serum thyroid stimulating hormone[1] (mU/L)	Serum free thyroxine[2] (pmol/L)
Baseline	< 0.16	9	5.16 (3.89-5.73)	1 (11%)	1.80 (1.15-2.65)	17.97±2.53
	0.16-0.39	101	4.55 (4.03-5.31)	22 (22%)	1.80 (1.20-2.60)	16.82±2.21
	0.40-0.78	46	4.24 (3.64-5.30)	10 (22%)	1.90 (1.50-2.30)	16.57±2.47
	≥0.79	29	4.57 (4.07-5.23)	9 (31%)	1.70 (0.93-2.13)	17.27±2.69
P			NS[4]	NS[5]	NS[4]	NS[6]
25 wk	< 0.16	0	-	0	-	-
	0.16-0.39	0	-	0	-	-
	0.40-0.78	11	3.03 (2.73-3.36)	0	1.50 (1.18-2.45)	16.75±2.42
	≥0.79	173	3.61 (3.00-4.32)	5 (3%)	1.90 (1.30-2.70)	17.04±2.55
P			NS[4]	NS[5]	NS[4]	NS[6]
50 wk	< 0.16	0	-	0	-	-
	0.16-0.39	0	-	0	-	-
	0.40-0.78	27	3.15 (2.75-3.39)	0	1.50 (1.18-2.45)	16.75±2.42
	≥0.79	159	3.22 (2.86-3.55)	0	1.90 (1.30-2.70)	17.04±2.55
P			NS[4]	NS[5]	NS[4]	NS[6]

[1] Median (25^{th} - 75^{th} percentile)
[2] Mean ± SD
[3] Enlargement of thyroid corresponding to goiter was assessed by ultrasound
[4] Kruskal Wallis test
[5] Spearman test
[6] ANOVA

Table 4. Relationship between changes of urinary iodine concentration at different time periods and goiter measured by ultrasound before and after intervention

Goiter (ultrasound)		N	Changes of urinary iodine concentration[1]			
Before	End		4 wk	12 wk	25 wk	50 wk
Normal	Normal	144	4.98	3.01	1.37	0.83
			(2.40-9.61)	(1.55-6.27)	(0.73-2.60)	(0.39-1.33)
Goiter	Normal	42	8.48	5.11	2.01	0.78
			(3.53-13.94)	(1.95-8.86)	(0.79-3.69)	(0.47-1.46)
P [2]			<0.05	<0.01	<0.05	NS

[1] Median (25^{th}-75^{th} percentile), urinary iodine concentration after treatment at baseline, μmol/L.
[2] Mann Whitney test

DISCUSSION

The results of this study illustrate some difficulties and inadequacies usually encountered in assessing iodine status of a population and monitoring the changes in status after intervention. The school children in this study had been judged as moderately iodine deficient at baseline. This judgment was based on the prevalence of goiter measured by palpation and ultrasound, at 21.5% and 22.6% respectively, and on a median urinary iodine concentration of 0.36 μmol/L (2). However, the serum TSH, serum FT_4 and serum Tg concentrations were in the normal range, suggesting that the population had adequately compensated for a low iodine intake.

Measurement of thyroid size

Surveys for currently assessing the prevalence of goiter mostly rely on thyroid palpation (7,17), and the presence of goiter is usually expressed according to the WHO classification (2). In populations suffering from moderate or severe iodine deficiency, especially among adults, thyroid palpation provides a reliable method for goiter assessment. However, the assessment becomes more problematic in areas with mild iodine deficiency especially when children are surveyed, because most iodine deficient subjects would, even in extreme cases, only have small goiters (4,18).

Gutekunst and Martin-Teichert (19) showed that palpation often wrongly classifies thyroid size, when compared with ultrasound measurements. A study

among school children in northern and central Italy, found a discrepancy of more than 20% between thyroid palpation and ultrasound (4). The present study shows that about 43% of the children judged to have palpable goiter did not have goiter according to ultrasound measurements, and may therefore be wrongly classified. Gutekunst et al. (5,18) reported that among cases with palpable grade 1 goiter, an error rate as high as 30% might occur. Our study found that sensitivity and specificity of palpation against goiter measured by ultrasonography were 57% and 89% respectively at baseline, and the positive and negative predictive value was 60% and 88% respectively. These data show that palpation cannot provide an accurate assessment of the extent of iodine deficiency among children with mild to moderate iodine deficiency, since the sensitivity relative to ultrasonography is not very high. Thus, assessment of thyroid volume by ultrasound is preferable to thyroid palpation especially for monitoring the effectiveness of iodine deficiency control program (4,18,20,21). However, palpation still has a useful role in identifying those areas and populations with iodine deficiency (2).

Urinary iodine concentration

Urinary iodine concentration is widely recognized as a valid means for determining iodine intake in a population (3,17). Several approaches to classify the severity of iodine deficiency in a population have been proposed (2,22), the criteria used by WHO/ICCIDD/UNICEF (2), which are based on median urinary iodine concentration in casual samples, being used most commonly . The present study found that the urinary iodine concentration was not significantly associated with thyroid palpation grading. This might be due to the fact that all the school children had a deficient or marginally deficient status at baseline. Furthermore, iodine excretion is a marker for dietary iodine intake and reflects current iodine status (2), while goiter represents the integration of events extending over time, it is a historical relic that does not necessary indicate the present state of iodine nutrition (23). Therefore, individuals with goiter might have adequate urinary iodine status.

Although there was no association between urinary iodine and goiter assessed by thyroid palpation, a significant inverse correlation was found between the logarithm of the urinary iodine concentration and thyroid volume, indicating that with higher urinary iodine concentrations, thyroid volumes were smaller.

Thyroid hormones

Generally there was no relationship between serum TSH and FT_4 and the other iodine status indicators. This finding corresponds with those reported by Delange et al. (24), Gutekunst et al. (5) and Pardede et al. (3) who also failed to observe a correlation between serum TSH and thyroid volume in children and adults. A rise in serum TSH is observed when iodine deficiency leads to chronic inadequate production of T_4 and T_3 in severe endemic areas (25). Studies have shown that the thyroids of iodine depleted rats are much more sensitive to TSH than those with normal urinary iodine concentrations (26). Gutekunst et al. (5) suggested that the reduced TSH level is a physiological response to protect the thyroid from additional growth and it is still discussed whether TSH is indeed a growth factor for the thyroid cell. In addition, the thyroid has an enormous capacity to store iodine and can buffer the hormone secretion rate. Thus serum TSH may not reflect recent dietary iodine as indicated by urinary iodine concentration. Indeed, in most endemic iodine deficient areas, measurement of serum TSH concentrations of subjects with goiter, have been well within normal limits (23).

Our data show that serum concentrations of TSH, FT_4 and Tg were in the normal range, although the prevalence of goiter was more than 20% and the median urinary iodine concentration less than 0.40 μmol/L. A similar observation of normal levels of circulating T_3, T_4 and TSH was made in countries where the prevalence of goiter was 20 to 50%, and the urinary iodine concentration indicated mild iodine deficiency (22).

Even though serum concentrations of TSH, FT_4 and Tg were in the normal range, there was a significant inverse correlation between serum concentrations of FT_4 and of TSH at baseline ($r=-0.18$) and between serum concentration of TSH and of Tg in a subsample ($r=0.52$). This observation is probably related to the reported high turnover of the small iodine pool in the thyroid, which supposedly occurs in non-adult subjects (22).

Monitoring impact of interventions

At 25 wk of follow up, the prevalence of goiter measured by ultrasound was reduced from 23% to 3%, while urinary iodine concentration increased from 0.36 μmol/L to 1.98 μmol/L in which about 6% of the population had urinary iodine concentration less than 0.79 μmol/L. However, the prevalence of goiter measured by palpation only slightly reduced, from 22% to 20% at 25 wk of follow up, and the

serum TSH and FT_4 concentrations both remained in the normal range. These data showed that both urinary iodine concentration and goiter measured by ultrasound indicated the same level of improvement on iodine status, but goiter measured by palpation, serum TSH and serum FT_4 concentration indicated different levels of iodine status.

After 50 wk of treatment with oral iodized oil, there was a significant reduction in thyroid volumes, prevalence of goiter and an increase in the median urinary iodine concentration. A significant increase in serum FT_4 was also observed, even though both the initial and final level were within normal range. However, there was no significant change on the serum TSH concentration. This results suggest that in the population investigated, thyroid volume measured by ultrasound, thyroid palpation and urinary iodine concentration all gave a similar indication of the impact after 50 wk of iodine supplementation, which was not so with serum TSH and FT_4. This finding confirms the results of a previous study among iodine deficient school children in Algeria (13).

The reduction of thyroid volumes at the 50 wk were significantly greater for children with higher grade of goiter at baseline and iodine was retained longer in the body until 25 wk for goitrous children compared to their non-goitrous counterpart. These results suggested that the efficacy of oral iodized oil supplementation was higher in subjects with more severe iodine deficiency, and there was agreement between the changes as indicated by the different indicators.

We conclude that urinary iodine concentration and thyroid volume measured by ultrasound are the most useful epidemiological indicators for assessing iodine status and measuring the impact of iodized oil supplementation among moderately iodine deficient school children. These parameters found the same degree of iodine deficiency at baseline and after supplementation. The other indicators did not show concordant levels of iodine deficiency either at baseline or after treatment, suggesting that palpation, serum TSH, serum Tg and serum FT_4 concentrations might be less reliable indicators for assessing and monitoring treatment in moderately iodine deficient school children than urinary iodine concentration or thyroid volume. Although these data highlight the limitations of thyroid palpation, this technique still has a useful place in assessing iodine status because no sophisticated equipment is required. However it is necessary for observers to be trained in the technique.

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Chapter 4

Effect of stunting, iodine deficiency and oral iodized oil supplementation on cognitive performance in school children from an endemic iodine deficient area of Indonesia

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ABSTRACT

Previous studies have shown that nutritional supplementation of undernourished children has a beneficial effect on their intellectual capacity. The aim of this study was to examine which factors were related to cognitive performance in children living in an iodine deficient area in Central Java, Indonesia. In addition, the effect of oral dosing with iodized oil was examined in a randomized placebo-controlled trial in which cognitive performance was measured at baseline and 50 wk after treatment using Cattell's culturally fair intelligence test. Height, weight, thyroid volume, urinary iodine concentration, serum thyroid stimulating hormone and serum thyroxine were also measured at baseline and 50 wk after dosing. This work was part of a larger study examining the efficacy of iodized oil preparations in school children aged 8-10 years. Thus the placebo group (n=43) was compared with 121 children receiving 200 mg, 400 mg or 800 mg of iodine from iodized peanut oil.

The median cognitive performance at baseline was low (82; 25^{th}-75^{th} percentiles, 77-95) compared with the norm of 100, 32% of the children were underweight, 58% were stunted, 3% were wasted, and 40% were anemic. Multiple regression analysis showed that father's education and hemoglobin concentration were the main determinants of cognitive performance at baseline, and urinary iodine concentration and height for age Z-score were the most important determinants for improvement in cognitive performance after supplementation with iodized oil. Compared with the placebo group, there was a significant increase in urinary iodine concentration and reduction in thyroid volume but no change in the other parameters measured.

We can conclude that cognitive performance after iodized oil supplementation did improve in those children who had at baseline low urinary iodine concentration or who were stunted. We also can conclude that anemia at baseline and father's education do play a role in cognitive performance.

INTRODUCTION

There is a considerable body of evidence suggesting that iodine deficiency limiting mental development. Such evidence comes from ecological studies comparing children in iodine adequate and iodine deficient areas (1-4), case-control studies (5), studies in which mothers were treated with iodized oil (6) and comparisons of iodized oil dosed children with undosed children in another area (7,8). However, from such studies, it is not possible to determine whether iodine supplementation of iodine deficient children can stimulate their mental performance. When Bautista et al. (9) examined the effect of iodine supplementation on mental performance in a double-blind, placebo-controlled study, they found no difference between treated and untreated children based on the Stanford-Binet and Bender-Gestalt tests. In a subsequent double-blind, placebo-controlled study group using a series of tests covering the full range of seven factors identified as primary mental abilities by Thurstone, Shresta et al. (10) showed that iodine supplementation increased IQ by about 10 points compared with the control group.

Early studies suggested that the administration of oral iodized oil resulted in a significant reduction in the prevalence and size of goiter in the population (11-13). A controlled trial study with oral iodized oil in a small highland village in Bolivia, showed in the iodine supplementation study of Bautista et al. (9) mentioned above, that the decrease in goiter size was significantly associated with improvement in IQ score particularly in girls, even though correction of iodine deficiency did not increase mental performance. More data are required to show whether there would be a possible effect of oral iodized oil administration on the development of cognitive performance in iodine deficient school children.

Underweight, stunting and iron deficiency are other risk factors for impaired cognitive performance (14-18). Populations at risk for iodine deficiency disorders (IDD) are also likely to have concurrent deficiencies of these risk factors. Physical growth retardation in infancy and early childhood are associated with poorer performance on cognitive tests (15,16,19,20). In addition, previous studies have shown that correcting nutritional anemia improves cognitive performance (21-23). The effect of supplementation with iodine and iron have been shown to be additive (10).

This study aimed to investigate the association between stunting, anemia, iodine deficiency and cognitive performance among iodine deficient school children, and to measure the impact of iodine supplementation on cognitive performance.

SUBJECTS AND METHODS

Subjects

Subjects were randomly selected from school children aged 8-10 years (n=164) attending four primary schools in Cilacap district, Central Java Province, Indonesia, where goiter is highly prevalent (total goiter rate >30%) (24). All selected subjects were examined by a medical assistant from the sub-district health center, and only apparently healthy subjects were considered for entry into the study.

Study design

This study was in two phases: first, a cross-sectional phase and then a double-masked, placebo-controlled intervention phase. In the second phase, one group of children was given a single oral liquid dose of iodized peanut oil and a control group was given an oral dose of pure peanut oil in order to check whether the subjects were exposed to extraneous iodine during the study. A sample size of at least 36 subjects per group was calculated with a power index of 2.8, α=0.05 and β=0.20 which was regarded as sufficient to obtain a significant difference of 10% in cognitive performance between groups. This study was part of a larger study examining the efficacy of iodized oil preparations in school children aged 8-10 years. Thus the placebo group (n=43) was compared with 121 children receiving 200 mg (n=41), 400 mg (n=40) or 800 mg (n=40) of iodine from iodized peanut oil. The urinary iodine concentration and thyroid volume of all treatment groups were significantly improved after the supplementation, but there were no differences among the supplemented groups in cognitive performance. Therefore we combined the three iodized oil supplemented groups into one group.

A previous study in Malawi showed that the duration of effectiveness of orally administered iodized oil was significantly reduced by intestinal parasitic infestation (25). Therefore, one week prior to administration of iodized oil, all subjects in this study, were dosed with the broad spectrum anti-helminth albendazole (400 mg per dose, SmithKline Beecham, Indonesia) to control *Ascaris lumbricoides* as it was known that these parasites are endemic in the study area (26).

Methods

Measurement of thyroid size. Thyroid size was measured at baseline and 50 wk after treatment using ultrasound by the main researcher (JU) who had been trained in the technique. Ultrasonography was performed on each subject in the

sitting position. First, the transducer was kept horizontal at an upright angle to the neck to observe the cross section of the thyroid, measuring maximal width (w) and maximal thickness (d). Next, the length (l) of each lobe was determined by longitudinal application of the transducer to the subject's neck. A co-worker recorded the observations of the ultrasonography and provided a continuous flow of persons to be examined. The volume (V) was calculated using the following formula: V (cm^3) =0.479 x d x w x l (27). The thyroid volume was the sum of the volumes of both lobes. Result of ultrasonography from the study population was compared to normative data from populations with sufficient iodine intake (28).

Biochemical measurements. Venous blood samples (3 mL) were drawn from an antecubical vein from non-fasting subjects between 08.30 and 12.00 using EDTA as anticoagulant. Immediately after collection, the blood was placed on ice, protected from light and within 2-3 h centrifuged at the laboratory of the district health center to obtain serum. A sample of blood was taken for determination of the concentration of hemoglobin (only at baseline) using a HemoCue portable hemoglobinometer (29). Serum was frozen in a series of containers at -70 °C before being transferred, packed in dry ice, to the laboratory of Endocrinology, Academic Medical Center (Amsterdam, the Netherlands) for analysis. Serum levels of thyroid stimulating hormone (TSH) were measured by immunoluminometric assay techniques using a commercial kit (Brahms Diagnostica Gmbh, Berlin, Germany) and serum free thyroxine (FT_4) was measured by time-resolved fluoro immunoassay after immuno-extraction using a commercial kit (Delfia™, Wallac Oy, Turku, Finland). The coefficient of variation of intra-assay and inter-assay for TSH were 2.4% and 4.5% respectively, and for FT_4 were 3.6% and 6.4% respectively. Values obtained for both TSH and FT_4, were within 10% of the target value of normal and elevated samples provided every two months by the Dutch national external quality control scheme for hormones in serum (LWBA). The reference range of iodine replete subjects for serum TSH is 0.4-4.0 mU/L and for FT_4, 9-24 pmol/L (13).

A urine sample was collected between 08.00 h and 12.00 h on two consecutive days at baseline and at 50 wk after treatment. The samples, preserved with approximately 1 g thymol, were sent to the iodine laboratory of the Nutritional Research and Development Center in Bogor (Indonesia) for analysis. Iodine concentration in urine was analyzed based on alkaline digestion using the Sandell-Kolthoff reaction (30) and was measured in duplicate and the average calculated for each child.

Assessment of cognitive performance. This was determined using Cattell's "Culture-Fair Intelligence Test" (CFIT) consisting of four subtests: series, classifications, matrices and conditions (topology) (31) at baseline and 50 wk after treatment by a team of district psychologists. This test is available in three levels: scale 1, for ages 4 to 8 y and mentally retarded adults; scale 2, for ages 8 to 13 and average adults; and scale 3, for grades 10 to 16 and superior adults. The CFIT scale 2, which has been adapted to the Indonesian language, was used in this study. The average of cognitive scores considering as normal is 100 (range, 90-109) (31,32).

Anthropometric measurements. The measurements were made in duplicate (33) by a trained assistant before and 50 wk after intervention. Height was measured to the nearest mm using a microtoise, weight to nearest 0.1 kg using an electronic scale, and mid-upper arm circumference (MUAC) to the nearest mm using a measuring tape. Results are expressed as the mean and, if two measurements differed by 2 mm for height , 0.1 kg for weight and by 1 mm for MUAC, they were repeated. Anthropometric indices were calculated using Epi Info ver. 6.0 software and the data were presented as Z-scores of weight-for-age (WAZ), height-for-age (HAZ), and weight-for-height (WHZ). These indices were compared to reference data of the National Center of Health Statistics (33) to judge whether the subjects were underweight, stunted or wasted respectively using a cut-off point of -2 SD.

Statistical methods

The Kolmogorov-Smirnov test was used to check the normality of data. Data are reported as mean and SD or SEM for normally distributed parameters and as median and 25^{th} - 75^{th} percentiles for non-normally distributed parameters. Differences between two groups were examined by student's t-test for normally distributed parameters or by the Mann Whitney test for non-normally distributed parameters. When more than two groups were compared, analysis of variance (ANOVA) for normally distributed data or the Kruskal-Wallis test for non-normally distributed data, were used to test whether there were significant differences. If significant differences were indicated, comparisons among groups were made with the least significant difference test for normally distributed data and the Bonferroni's multiple comparison test at a significant level of $P<0.01$ for non-normally distributed data. Correlation between continuous variables was determined by multiple regression analysis or Pearson test. The software package of Epi Info version 6

(CDC, Atlanta, GA) and SPSS Windows version 7.5.2 (SPSS Inc., Chicago, IL) was used for all statistical analyses, and a P value<0.05 was considered significant.

Ethical Consideration

The guidelines of the Council for International Organizations of Medical Sciences (34) were followed for ethical considerations. The ethical committee for studies on human subjects, Faculty of Medicine, University of Indonesia approved the study. Informed consent was obtained from parents of each subject before the start of the study. At the end of the study, iodized oil was given to those children who were still iodine deficient, and iron capsules were distributed to children who were anemic.

RESULTS

Subjects characteristics

The mean height, weight and mid-upper arm circumference (MUAC) of the school children who participated in this study were 121.1 cm, 22.3 kg and 17.3 cm respectively. Overall 32% of the children were underweight, 58% stunted and 3% wasted. As the median urinary iodine concentration of the children was 0.36 μmol/L the population was moderately iodine deficient, however the prevalence of goiter measured by ultrasonography was 35%, suggesting that the population was severely iodine deficient (35). Based on hemoglobin <110 g/L, 40% of the children were anemic. There were no significant differences in age, anthropometric status, hemoglobin concentration (**Table 1**) and iodine status (**Table 2**) at baseline between placebo and supplemented groups.

Iodine status, anthropometric status and cognitive performance

The median value of cognitive performance scores of the population studied was 84 (25^{th}-75^{th} percentiles; 77-95) and there was no difference between the placebo and supplemented group at baseline. After 50 wk supplementation with oral iodized peanut oil, there were significant increases in urinary iodine concentration and reduction in thyroid volume in the supplemented group compared to the control group. However, the serum TSH and serum FT_4 concentrations did not respond to the treatment and remained in the normal range. Cognitive performance tended to increase but there was no significant difference between the increase in the

supplemented group and the placebo group (Table 2). There was a significant positive correlation between thyroid volume and stunting at all different periods of measurement: baseline (r=0.29, P<0.01); 25 wk (r=0.30, P<0.01) and 50 wk (r=0.30, P<0.01).

Table 1. Baseline characteristics of the school children[1]

	Peanut oil (Placebo) (n=43)	Iodized peanut oil (n=121)
Age (y)	9.29±0.70	9.27±0.70
Males/females	15/28	61/60
Hemoglobin concentration (g/L)	113.0±18.1	114.4±17.2
Anemia (Hb <110 g/L; %)	36.4	48.4
Height (cm)	120.4±5.5	120.6±5.9
Weight (kg)	22.4±3.3	22.3±3.1
Mid-upper arm circumference (cm)	17.2±1.5	17.5±1.4
Stunting, HAZ<-2 (%)	62.8	55.4
Underweight, WAZ<-2 (%)	30.2	29.8
Wasting, WHZ<-2 (%)	0.0	3.4

[1] Mean ± SD

Factors related to cognitive performance

Urinary iodine concentration (P<0.05), hemoglobin status (P<0.05), father's education (P<0.01) and school performance (P<0.05) were associated with cognitive performance scores of the school children at baseline (**Table 3**). There was no significant difference in cognitive performance between boys and girls. However, multiple regression analysis between log transformed cognitive performance score at baseline and parameters which were related to cognitive performance in a univariate analysis showed that only hemoglobin concentration and father's education remained significant (P<0.05) (**Table 4**).

Analysis of variance showed that changes in cognitive performance after 50 wk of supplementation were significantly associated with urinary iodine concentration (P<0.01), HAZ (P<0.01) and school performance (P<0.05) at baseline, and the changes in cognitive performance were significantly different between the supplemented group and placebo group (Table 3). The same independent variables, examined using a multiple regression analysis with changes in cognitive performance over 50 wk as dependent variable, showed that urinary iodine concentration and HAZ at baseline were the only significant determinants (P<0.05).

Table 2. Iodine status, anthropometric status and cognitive performance at baseline and 50 wk after supplementation among Indonesian school children aged 8-10 y[1]

	Period	Peanut oil (Placebo) (n=43)	Iodized peanut oil (n=121)
Urinary iodine concentration (μmol/L)	Baseline	0.38 (0.26-0.63)	0.36 (0.28-0.61)
	50 wk	0.70 (0.61-0.83)	1.46 (0.95-1.94)†
	Difference	0.30 (0.10-0.45)	0.96 (0.50-1.50)†
Thyroid volume (mL)	Baseline	4.89±1.50	5.14±1.32
	50 wk	4.73±1.43	3.58±0.57 *
	Difference	-0.17± 0.18	-1.57±1.20 *
Serum thyroid stimulating hormone concentration (mU/L)	Baseline	1.80 (1.27-2.50)	1.70 (1.10-2.40)
	50 wk	1.70 (1.38-2.58)	1.80 (1.30-2.70)
	Difference	0.00 ((-0.50)-0.50)	0.10 ((-0.34)-0.80)
Serum free thyroxine concentration (pmol/L)	Baseline	16.8±2.7	16.9±2.1
	50 wk	16.8±3.3	17.2±2.4
	Difference	0.0±3.1	0.4±2.4
Weight for age Z-score	Baseline	-1.62±0.60	-1.60±0.72
	50 wk	-1.50±0.65	-1.52±0.71
	Difference	0.02±0.22	0.00±0.23
Height for age Z-score	Baseline	-2.14±0.73	-2.12±0.88
	50 wk	-1.87±0.76	-1.88±0.84
	Difference	0.16±(-0.03)	0.14±(-0.03)
Cognitive performance scores	Baseline	82 (74-98)	84 (80-93)
	50 wk	88 (81-103)	89 (81-95)
	Difference	4 ((-13)-6)	2 ((-11)-8)

[1] Values are expressed as mean ± SD or median (25^{th}, 75^{th} percentiles).
Differences between groups of normally distributed data using student t-test: *, $P<0.01$; differences between groups of non-normally distributed data using Mann-Whitney test: †, $P<0.01$

Table 3. Factors related to cognitive performance of Indonesian school children living in an iodine deficient area[1]

Parameters at baseline	n	Cognitive performance at baseline	Changes in cognitive performance			
			n	Peanut oil (Placebo)	n	Iodized peanut oil
Father's education (y)						
3-6	151	83 (77-91)	36	5.03 ± 1.46	108	2.31±0.90
7-12	13	98 (86-105) **	4	9.50 ± 5.56	9	3.67±3.70
Mother's education (y)						
3-6	158	84 (77-93)	39	5.64±1.44	112	2.09±0.89
7-12	6	91 (83-104)	1	-1.00	5	9.80±4.04
School performance (ranking)						
1-5	47	89 (81-102) [a]	13	6.00±2.87	34	5.68±1.90 [c]
6-10	44	82 (77-89) [b]	11	8.64±2.97	32	-0.31±1.22 [d]
>10	70	84 (77-90) [b]	16	2.88±1.42	51	1.96±1.30 [d]
Urinary iodine concentration (μmol/L)						
< 0.158	10	80 (77-84) [a]	3	4.00±3.00	5	8.60±7.22 [e]
0.158-0.395	92	82 (77-91) [a]	21	7.48±2.42	68	4.35±1.04 [f]
0.395-0.79	45	87 (81-97) [b]	14	3.43±1.55	29	-2.31±1.53 [g]
>0.79	17	87 (81-97) [b]	2	1.00±0.00	15	0.73±2.66 [g]
Thyroid volume						
Normal	106	83 (77-95)	29	5.41±1.88	74	2.96±1.14
Goiter	58	84 (77-90)	11	5.64±1.53	43	1.49±1.37
Blood hemoglobin concentration (g/L)						
<110	47	81 (77-87) *	14	3.93±2.32	31	2.39±1.56
≥ 110	72	84 (77-97)	14	5.21±2.26	55	3.00±1.35

Table 3. Continued

Parameters at baseline	n	Cognitive performance at baseline	Changes in cognitive performance			
			n	Peanut oil (Placebo)	n	Iodized peanut oil
Height for age Z-score						
Non stunted, ≥-2	70	84 (80-95)	14	8.86±2.46	53	4.92±1.46[e]
Stunted, <-2	94	84 (77-95)	26	3.65±1.66	64	0.34±0.99[f]
Weight for age Z-score						
Non underweight, ≥-2	115	84 (78-95)	27	5.15±1.68	81	2.84±1.15
Underweight, <-2	49	84 (77-94)	13	6.15±2.72	36	1.47±1.22

[1] Values are expressed as median (25^{th} - 75^{th} percentiles) or mean ± SE.
Differences between two groups were examined using student's t-test when normally distributed or Mann-Whitney test when not normally distributed (*, $P<0.05$; **, $P<0.01$).
Differences among >2 groups were examined using Kruskal-Wallis test when not normally distributed and if significant ($P<0.05$) were tested using Bonferroni's post-hoc multiple comparisons test: values of each parameter with different superscripts letters (a, b) are significantly different from one another ($P<0.01$).
Differences among >2 groups were examined using ANOVA test when normally distributed and if significant, were tested using least significant differences multiple comparisons test: values of each parameter with different superscripts letters (c, d when $P<0.05$ and e, f, g when $P<0.01$) are significantly different from one another.

Table 4. Multiple regression analysis relating cognitive performance at baseline and the change over 50 wk with parameters which were related to cognitive performance in a univariate analysis.

Dependent variables	Cognitive performance (log) at baseline		Change in cognitive performance			
			Peanut oil (Placebo)		Iodized peanut oil	
	β	*P*	β	*P*	β	*P*
Independent variables at baseline						
Urinary iodine concentration (μmol/L)	-	NS	-	NS	-10.36	<0.05
Hemoglobin concentration (g/L)	0.002	<0.05	-	NS	-	NS
Height for age Z-score	-	NS	-	NS	2.19	<0.05
Father's education (y)	0.11	<0.05	-	NS	-	NS
Constant	4.06				0.70	
R square	0.12				0.10	

NS =Not significant

DISCUSSION

The results indicate that iodine status and stunting are linked to changes in child cognitive performance after the children were supplemented with iodized oil. Iodized oil supplementation did not increase cognitive performance in the supplemented group as a whole. However subjects supplemented with iodized oil, who were iodine deficient at baseline, increased their cognitive performance more than those who were more iodine replete. A previous study in Indonesia showed that thyroid volume and urinary iodine concentration of iodine deficient school children were significantly related to cognitive performance (36). In a placebo-controlled study in Bolivia, Bautista et al. (9), showed that decrease in goiter size was significantly associated with improvement in IQ scores particularly in girls, but there was no difference in mental performance between supplemented and placebo groups. A study in Malawi showed that iodine supplementation increased IQ by about 10 points compared with the control group (10).

The measurement of cognitive performance using Cattell's CFIT adapted to the Indonesian language, was used in this group of iodine deficient school children. The population studied had low scores of cognitive performance and suffered from a number of nutritional problems, including iodine deficiency, anemia and stunting. We found that cognitive performance was positively correlated with baseline values of urinary iodine concentration, hemoglobin concentration and father's education. However, multiple regression analysis indicated that hemoglobin concentration and father's education, both at baseline, were the most important determinants of cognitive performance. We did not find a positive correlation between the education of mothers and cognitive performance of school children, probably as the majority of the mothers (96%) had 6 years of education or less. The higher the education of father, the higher the cognitive scores and the higher the educational achievement of the school children as indicated by school grades. Intelligence is a complex variable and depends on many factors (37) including stimulation from the environment, such as education level of parents.

There is much evidence that iron deficiency anemia impairs cognitive development (23,38-40). We found that 40% of the school children were anemic and the cognitive scores of the anemic children (Hb<110 g/L) were 3 points lower than their non-anemic counterparts. We suggest that anemia adversely affected the cognitive performance of these school children. Our findings are in line with the results of previous study in Malawi that showed iron supplementation resulted in

improvement of IQ by 3.7 points (10).

Oral iodized oil supplementation resulted in an improvement of iodine status as indicated by an increase in urinary iodine concentration and decrease in thyroid volume. However, the iodine supplementation did not result in a larger improvement in cognitive performance scores compared to the placebo group, as the average cognitive performance score did not improve one year after treatment with oral iodized oil. Such a finding was also reported from a previous study in Spain (8) where supplementation with oral iodized oil did not improve mental and psychomotor performance of children from an iodine deficient area.

Although there was no difference between the changes in cognitive scores of the iodine supplemented and placebo groups 50 wk after dosing, this is not necessarily inconsistent with previously reported effects of supplementation with iodized oil on cognitive performance. Firstly, since there was an inverse correlation between urinary iodine concentration at baseline and increase in cognitive score, this would suggest that iodine deficient children did benefit from iodine supplementation. In the study of Shresta et al. (10), the median urinary iodine concentration was 0.15 μmol/L compared with 0.36 μmol/L in our study population. Children with a baseline urinary iodine concentration <0.40 μmol/L in the iodized oil supplemented group had greater changes in cognitive performance than their more iodine replete counterparts. Secondly, the strength of the relationship observed with baseline iodine status as measured by urinary iodine concentration is attenuated. Although urinary iodine concentration is a good indicator of iodine status at the group level, it is a poor indicator at the individual level because of the large intra-individual variation in urinary iodine concentration (41,42). Thirdly, the effect observed had been attenuated by exposure of the population, both the iodized oil supplemented group and the placebo group, to iodine derived from iodized salt which has become increasingly available in the area during the study period (43).

The significant reduction in thyroid volume in the supplemented group, was associated with a trend towards increased cognitive performance scores, but this did not reach statistical significance (P=0.42), possibly because of the reasons mentioned above in relation to urinary iodine concentration. Changes in serum concentrations of TSH and FT_4 were not correlated with changes in cognitive performance. However, this would be expected as there was no change in the serum concentration of these hormones with iodine supplementation as discussed earlier (42). Pardede et al. (36) also found no relationship between cognitive

performance and serum TSH concentration in a cross-sectional study of school children in East Java.

Stunting was also found to be related to increased cognitive performance in this study. There has been much debate about whether stunting is a harmless adaptation to poor dietary intakes or has a functional consequence (44). A study in Jamaica found that the deficit in mental development of stunted children was attributable to under-nutrition (15,45) and a previous study in Indonesia also showed a positive correlation between cognitive performance and HAZ among iodine deficient school children (36). In a study of children with endemic goiter in Northeastern Sicily, Vermiglio et al. (46) showed that children with cognitive deficiency had stunted growth and delayed skeletal maturity. Stunting may not directly cause poor intellectual development in children, but the same underlying factors that cause stunting such as socio-economic status of the family, may also impair children's intellectual growth (47). Most of the children in this study were from poor families, and their dietary intakes were below the recommended dietary intakes.

In addition, normal linear growth is determined by variable contributions from genetic, nutritional and endocrine factors and continues until bone maturation in early adulthood. One of the major hormones that influence growth during childhood is triiodothyronine (48): before puberty, it may be the major determinant for normal maturation of bone (49). Untreated hypothyroidism in children results in profound growth retardation and delayed skeletal maturation. Linear growth is almost completely halted, but can be resumed quickly by replacement of thyroid hormones to produce a rapid catch-up period of growth (50). In this study we found a positive correlation between thyroid volume and stunting at all periods of measurement.

We can conclude that cognitive performance after iodized oil supplementation did improve in those children who had at baseline low urinary iodine concentration or who were stunted. We also can conclude that anemia at baseline and father's education do play a role in cognitive performance. This illustrates the role of nutrition and social factors in cognitive development and performance in children.

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Chapter 5

Impact of salt iodization on iodine status of Indonesian school children living in a moderately iodine deficient area

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ABSTRACT

Objective: To evaluate the impact of the Indonesian salt iodization program on iodine status of school children living in an endemic iodine deficient area, as indicated by urinary iodine concentration, goiter size measured by palpation and ultrasound, serum thyroid stimulating hormone (TSH) concentration and serum free thyroxine (FT_4) concentration.

Design: A longitudinal prospective cohort study among Indonesian school children.

Setting: Subjects living in an endemic iodine deficient area were enrolled voluntarily.

Subjects: Fifty one apparently healthy school children aged 8-10 y in an iodine deficient area in Central Java, Indonesia, were recruited.

Methods: Thyroid size measured by palpation and ultrasonography, urinary iodine concentration, serum TSH and serum FT_4 concentrations were measured on three occasions at 0, 25 and 50 wk. At the same time periods, subjects were requested to bring salt samples that were used at their homes.

Results: After one year of introduction on salt iodization, the proportion of household used adequately iodized salt increased significantly, from 2% to 54%, but there was inconsistency in using iodized salt within households during the study period. Median urinary iodine concentration of population studied improved from 0.38 μmol/L to 0.70 μmol/L, but this level is still below 0.79 μmol/L which is regarded as adequate iodine status. Iodine status as indicated by urinary iodine concentration and thyroid volume, of children who consumed iodized salt was significantly higher than those consumed non-iodized salt. However, the prevalence of goiter, concentrations of serum FT_4 and serum TSH of children consuming iodized salt were not significantly different than those who consumed non-iodized salt.

Conclusions: The impact of legislation requiring iodized salt for the Indonesian population is not successful although significant progress has been made in recent years. Consequently, iodine deficiency is still a serious public health problem in Indonesia and increased effort is needed to eradicate iodine deficiency.

INTRODUCTION

The cause of iodine deficiency is mainly geological rather than social and economic. Iodine deficiency cannot be eliminated by changing dietary habits nor by eating specific kinds of foods grown in the same area. Therefore, correction of the deficiency has to be achieved by supplying iodine from an external source. This can be done in a number of ways including periodic supplementation of deficient populations with iodized oil capsules or other preparations, or by fortifying foods with iodine. The food most commonly chosen is salt. The iodization of salt is the approach most commonly proposed in order to provide a long term and sustainable solution as it is expected that this will enable iodine to reach the entire population (1-3). A major international effort to implement the process has begun. Fortification of salt has been successful in eliminating iodine deficiencies in many countries (4). It was estimated that nearly 60 per cent of edible salt in the world is now iodized, and among those countries in the world with a recognized iodine deficiency problem, the majority has passed appropriate legislation to ensure universal salt iodization (4). However, data on the effectiveness of iodized salt for controlling iodine deficient population is still scanty.

Indonesia has had a law mandating the fortification of salt with iodate (KIO_3) since 1994: the minimum level of fortification has been set at 30 mg I/kg. A recent study showed that about one half of the salt in the market in Indonesia was adequately iodized (5). Salt is iodized in more than 300 processing plants distributed over 24 provinces in the country, many of these are small and do not operate continuously (6), which might endanger a sustainable program of salt iodization.

Considering a wide variation in salt iodine content at the national level, this study examines the impact of the introduction of salt iodization program on the iodine status of school children living in an iodine deficient area, as indicated by urinary iodine concentration, thyroid size measured by palpation and ultrasound, serum thyroid stimulating hormone (TSH) and serum free thyroxine (FT_4) concentrations.

SUBJECTS AND METHODS

Subjects

Subjects (n=51) were randomly selected from school children aged 8-10 years attending four primary schools in Cilacap district, Central Java Province,

Indonesia, where goiter is highly prevalent (total goiter rate >30%) (7). All selected subjects were examined by a medical assistant from the Sub-district Health Center, and only apparently healthy subjects were considered for entry into the study.

Study design

This study was designed as a longitudinal study as part of a larger study on the efficacy of iodized oil (8). A sample size of at least 49, was calculated based on the possibility to estimate the prevalence of adequately iodized salt with a confidence level of 90% and a CI width of 10% using a design effect of 2 and an assumption that the prevalence would be about 10%. A total of 51 school children participated voluntarily in this study. Each of them was asked to submit samples of salt that were used in their home at three occasions, i.e.: 0, 25 and 50 wk. Urinary iodine concentration, thyroid size measured by palpation and ultrasound, serum TSH and FT_4 concentrations were determined at the same period of salt samples collection. Anthropometric parameters were measured as described previously (9).

Methods

Measurement of thyroid size. Thyroid size was measured by palpation and ultrasound (10). Palpation of the thyroid was performed by one trained experienced medical officer at the Sub-district Health Center at 0, 25 and 50 wk. Measurement of thyroid volume using ultrasound was carried out at the same time as palpation by the main researcher (JU) who had been trained in the technique. Ultrasonography was performed on each subject in the sitting position. First, the transducer was kept horizontal at an upright angle to the neck to observe the cross section of the thyroid, measuring maximal width (w) and maximal depth (d). Next, the length (l) of each lobe was determined by longitudinal application of the transducer to the subject's neck. A co-worker recorded the observations of the ultrasonography and provided a continuous flow of persons to be examined. The volume was calculated using the following formula: V (cm^3) =0.479 x d x w x l (11). The thyroid volume was the sum of the volumes of both lobes. Result of ultrasonography from the study population were compared to normative data from populations with sufficient iodine intake (12).

Serum concentrations of TSH and FT_4. Venous blood samples (3 mL) were drawn from an antecubical vein from non-fasting subjects between 08.30 and 12.00 using EDTA as anticoagulant. The blood was placed on ice, protected from light, and within 2-3 h centrifuged at the laboratory of the district health center to obtain

serum. Serum was frozen in a series of containers at -70 °C before being transferred, packed in dry ice, to the laboratory of Endocrinology, Academic Medical Center (Amsterdam, the Netherlands) for analysis.

The method used for measuring blood levels of the TSH was immunoluminometric assay techniques using a commercial kit (Brahms Diagnostica Gmbh, Berlin, Germany) and FT_4 was measured by time-resolved fluoro immunoassay after immuno-extraction using a commercial kit (Delfia™, Wallac Oy, Turku, Finland). The coefficient of variation of intra-assay and inter-assay for TSH were 2.4% and 4.5% respectively, and for FT_4 were 3.6% and 6.4% respectively. Values for both TSH and FT_4 obtained, were within 10% of the target value of normal and elevated samples provided every two months by the Dutch national external quality control scheme for hormones in serum (LWBA). Reference range of iodine replete subjects for serum TSH is 0.4-4.0 mU/L and for FT_4 is 9-24 pmol/L (13).

Urinary iodine concentration. A casual urine sample (5 mL) was collected between 08.00 h and 12.00 h on 2 consecutive days at 0, 25 and 50 wk of study. The urine samples, preserved with approximately 1 g thymol, were sent to the iodine laboratory of the Nutritional Research and Development Center in Bogor (Indonesia). Iodine concentration in urine was analyzed, based on alkaline digestion using the Sandell-Kolthoff reaction (14), for duplicate and the average calculated from each child.

Semi-quantitative salt iodine spot test. Children were requested to bring to school samples of salt used at their homes at 0, 25 and 50 wk. To limit any possible exchange of samples, each child was given a sealed plastic container with his name on it. A commercial spot test kit (Biofarma, Indonesia) was used for detecting the levels of potassium iodate (KIO_3) in salt samples. The test gave approximate concentration of the iodine content in salt. Using a color chart, the iodine levels in a salt sample were estimated (3).

Statistical methods

The normality of data was tested by the Kolmogorov-Smirnov test. Data are reported as mean and SD for normally distributed parameters and as median and 25^{th} - 75^{th} percentile for non-normally distributed parameters. Differences among groups were examined by analysis of variance (ANOVA) for normally distributed parameters or by the Kruskal-Wallis for non-normally distributed parameters. If significant differences were indicated, comparisons among groups were made with

the least significant difference test for normally distributed data and the Bonferroni's multiple comparison test at a significant level of $P<0.01$ for non-normally distributed data. Correlation between continuous normally distributed variables was analyzed using Pearson test and for non-normally distributed variables by Spearman rank test. The software package of SPSS (Windows version 7.5.2, SPSS Inc., Chicago, IL) was used for all statistical analyses and a P value<0.05 was considered significant.

Ethical Considerations

The guidelines of the Council for International Organizations of Medical Sciences (15) were followed for ethical considerations. The Ethical Committee for Studies on Human Subjects, Faculty of Medicine, University of Indonesia approved the study. Informed consent was obtained from parents of each subject before the start of the study.

RESULTS

Subjects characteristics

The subjects of this study were 20 boys and 31 girls with an average age of 9.4±0.7 y, and the mean weight and height were 22.5±3.3 kg and 120.8±5.8 cm respectively. Overall 31.4% of the children were underweight (weight for age Z-score<-2 SD), 58.8% stunted (height for age Z-score<-2 SD) and none was wasted (weight for height Z-score<-2 SD).

Iodized salt in the households

The proportion of adequately iodized salt increased significantly during one year of study ($P<0.001$). At the beginning of the study, about two years after salt legislation was promulgated, 2% of the samples were adequately iodized at more than 30 mg I/kg and 34% were not iodized at all. One year after the start of the study, 54% of the collected salt samples were adequately iodized and 11% of the samples were not iodized (**Table 1**). However, inconsistency in using iodized salt was found within the households (**Table 2**). None of the subjects submitted adequately iodized salt at all three sampling periods during the study; only 14% twice submitted adequately iodized salt; and 35% of subjects never submitted adequately iodized salt.

Table 1. Number of household salt samples at 0, 25 and 50 wk containing different levels of iodine brought to school by 51 children in Cilacap, Central Java, Indonesia[1]

	Time of salt collection (wk)		
	0	25	50
Salt not iodized (0 mg I/kg)	18 (35%)	9 (18 %)	5 (10%)
Salt not adequately iodized (<30 mg I/kg)	32 (63%)	23 (46%)	18 (36%)
Salt not iodized (≥30 mg I/kg)	1 (2%)	18 (36%)	27 (54%)
Total	51	50	50

[1] Spearman rank test, $P<0.001$,

Iodine indicators and type of salt used in the households

The prevalence of goiter measured by palpation remained at 17% at 50 wk. However, the prevalence of goiter measured by ultrasound was significantly reduced to 14% at 25 wk and 50 wk. Urinary iodine concentration of children studied was significantly increased at 25 wk, but serum TSH and serum FT_4 concentrations remained in the normal range (**Table 3**).

Children who brought salt which was adequately iodized, had a better iodine status than children who brought inadequately iodized salt ($P<0.001$). The higher the concentration of iodine in the salt the higher the urinary iodine concentration (**Table 4**). Analysis of variance showed that children who consumed adequately iodized salt had smaller thyroid volumes ($P<0.05$) than those who consumed non-iodized salt. However, serum FT_4 and TSH concentrations of school children consuming iodized salt were not significantly different to those who consumed non-iodized salt (Table 3).

Table 2. Distribution number of salt samples with variation iodine content collected from the same subject at different times.

0 wk	25 wk	50 wk			Total
		Not iodized	Not adequately iodized	Adequately iodized	
Salt not iodized (0 mg I/kg)	Not iodized	1	4	-	5
	Not adequately iodized	2	2	1	5
	Adequately iodized	-	2	5	7
Salt not adequately iodized (<30 mg I/kg)	Not iodized	-	1	2	3
	Not adequately iodized	1	6	11	18
	Adequately iodized	1	2	7	10
Salt adequately iodized (≥30 mg I/kg)	Not iodized	-	-	1	1
	Not adequately iodized	-	-	-	-
	Adequately iodized	-	-	-	-
Total		5	17	27	49

Table 3. Parameters of iodine status at 0, 25 and 50 wk in school children in Cilacap, Central Java, Indonesia[1].

	Time of salt collection (wk)		
	0 (n=51)	25 (n=50)	50 (n=50)
Thyroid volume (mL)	4.68±1.51	4.48± 1.43	4.54±1.45
Prevalence of goiter (%)			
Palpation	17.7	16.7	16.7
Ultrasound	26.0 [a]	14.3 [b]	14.3 [b]
Urinary iodine concentration (μmol/L)	0.38 (0.24-0.64) [c]	0.67 (0.50-1.02) [d]	0.70 (0.61-0.83) [d]
Serum thyroid stimulating hormone concentration (mU/L)	1.70 (1.20-2.30)	1.60 (0.96-2.20)	1.60 (1.18-2.30)
Serum free thyroxine concentration (pmol/L)	16.74±2.66	17.32±3.08	16.74±3.05

[1] Values are presented as mean ± SD or median (25^{th} - 75^{th} percentile).
Correlation between non normally distributed variables were examined using Spearman rank test: values with different superscripts letters (a, b) are significantly different from one another ($P<0.05$). Differences among >2 groups were examined using Kruskal-Wallis test when not normally distributed and if significant ($P<0.05$) were tested using Bonferroni's post-hoc multiple comparisons test: values of each parameter with different superscripts letters (c, d) are significantly different from one another ($P<0.01$).

DISCUSSION

This study indicates that salt iodization was significantly associated with improvement of urinary iodine status in Indonesian school children living in an endemic iodine deficient area. In rural areas of many developing countries, where iodine deficiency is most severe, populations are largely dependent on subsistence foods. Their diet is typically based on one or two cereals, tubers or pulses. If households have livestock, some dairy products are also consumed. Therefore, the only way for such people to obtain iodine is from outside sources such as iodized salt or iodized oil supplements.

Table 4. Relationships between parameters of iodine status in school children in Cilacap, Central Java, Indonesia and iodine content of salt samples which were pooled from three periods of collection (0, 25, 50 wk)[1].

	Iodine content in salt (mg/kg)		
	0 (n=32)	<30 (n=73)	≥30 (n=46)
Thyroid volume (mL)	4.89±1.32 [a]	4.65±1.55 [a]	4.21±1.35 [b]
Urinary iodine concentration (μmol/L)	0.40 (0.27-0.69)	0.60 (0.37-0.77) [c]	0.71 (0.60-0.85) [d]
Serum thyroid stimulating hormone concentration (mU/L)	1.70 (1.30-2.30)	1.60 (1.00-2.00)	1.70 (1.10-2.50)
Serum free thyroxine concentration (pmol/L)	17.84±6.07	17.08±2.96	16.97±2.76

[1] Values are presented as mean± SD or median (25^{th} - 75^{th} percentile).
Differences among >2 groups were examined using ANOVA test when normally distributed and if significant, were tested using least significant differences multiple comparisons test: values of each parameter with different superscripts letters (a, b) are significantly different from one another ($P<0.05$). Differences among >2 groups were examined using Kruskal-Wallis test when not normally distributed and if significant were tested using Bonferroni's post-hoc multiple comparisons test: values of each parameter with different superscripts letters (c, d) are significantly different from one another ($P<0.01$).

The first national IDD program in Indonesia, which began in 1974, provided iodized oil injections to people in endemic areas and began to iodize salt. UNICEF selected universal salt iodization as the means of reaching the goal of eliminating IDD. Progress towards this goal is determined by estimating the proportion of households with adequately iodized salt in countries affected by IDD (2). By the early 1990s, about half of Indonesia's salt was iodized. Indonesia introduced a law in 1994, mandating the fortification of salt with iodate to the minimum level of fortification of 30 mg I/kg. The national program involves teachers and school children who learn about IDD and the use of iodized salt to avoid the problem (4). In 1995, a national survey of iodized salt consumption in 220,000 households showed that half of them were using adequately iodized salt (≥30 mg I/kg), 28% inadequately iodized salt (<30 mg I/kg) and the rest non-iodized salt (5), which is in line with our results. Over a period of one year, the proportion of adequately iodized

salt (≥30 mg I/kg) in the area studied was significantly increased from 2% to 54%, the inadequately iodized salt (<30 mg I/kg) was proportionally reduced from 63% to 36% and non-iodized salt was reduced from 35% to 10%.

Our data suggests that there was progress in increasing the proportion of iodized salt used in the area studied, although about 45% salt used in the households was not adequately iodized or not iodized at all. However, households were not consistent in their use of iodized salt during the one year study period. In addition, none of subjects studied used adequately iodized salt at all time periods and 35% of the subjects never brought adequately iodized salt from their homes. Our findings indicate that there was still a low awareness of the population at risk of the need to use adequately iodized salt. Cheaper non-iodized salt was found to be available in the market in the area studied and this subverted the effectiveness of the iodized salt program. This study underlines the importance of monitoring the salt iodization program as well as of educating the population on the importance of iodized salt.

In the Tiberina valley, in Italy, Aghini et al. (16) found that iodized salt prophylaxis was able to prevent the development of goiter in children born after the implementation of iodized salt consumption, and to control thyroid enlargement in older children. However, it was less effective in reducing the size of goiter in children exposed to iodine deficiency in the first years of life and later given access to iodized salt. In our study, one year after the introduction of salt iodization, urinary iodine concentration had increased from a median level at 0 wk of 0.38 μmol/L to 0.70 μmol /L, and prevalence of goiter measured by ultrasound decreased from 26% to 14%. Prevalence of goiter measured by palpation remained at 17%, but this could be attributed to misclassification in goiter measured by palpation compared to when measured by ultrasound (17). In addition palpation might not be sufficiently sensitive to detect small reduction in thyroid volume.

We found that children who consumed iodized salt had higher concentrations of urinary iodine and smaller thyroid volumes than those who did not. However, we did not find significant differences in serum FT_4 and serum TSH among children consuming salt that was iodized at different levels. These results are in line with those reported earlier with iodized oil (8,17). We have also shown that serum concentrations of FT_4 and TSH in children do not respond to dosing with iodized oil (17). It is also unlikely that the concentrations of other hormones in serum would be useful for monitoring changes in iodine status brought about either by the use of oral

iodized oil or iodized salt. For example, thyroglobulin concentration did not correlate in this population with urinary iodine concentration (17) and in addition, there are no international standard for its measurement (18). Serum FT_4 and TSH levels were initially and remained in the normal range after supplementation with iodized oil although urinary iodine concentration and thyroid volume did respond to dosing (17).

Our finding indicated that salt iodization is not simply a matter of passing legislation. Provision of iodized salt is sometimes ineffective because of economic conditions, a shortage of iodized salt in local markets, inadequately iodized salt, loss of iodine from salt because of excessive exposure to moisture, light and heat, and the use of non-iodized local salt (19-21). In addition, cooking practices of the population might influence the availability of iodine supplied by iodized salt. A study on the effect of Indonesian cooking practices on stability of iodized salt showed that some spices such as chili and acids might cause losses of iodine (22).

The hot Indonesian climate increases salt requirements and rice-eating populations also consume more salt than others because rice itself contain very little in salt (23). Legislation in Indonesia, requires salt to contain at least 30 mg I/kg. To counteract this iodine deficiency, a salt intake of 4-5 g per person per day is necessary to provide the iodine requirement of 120 μg for children aged 8-10 y. However little information is available on the intake of salt in Indonesia. It is assumed that per caput consumption is about 10 g/d of which 50% is discretionary. A study of salt intake using a lithium-labeled salt, showed that the average daily salt consumption in rural Guatemalan boys was 1.8± 0.6 g and Beninese boys 5.7 ± 2.8 g, of which 72 ± 12% and 50 ± 13% respectively came from discretionary sources (24). More information is required on average salt consumption in Indonesia.

It is concluded from the present study that the impact of legislation requiring iodized salt for the Indonesian population has not been successful although significant progress has been made in recent years. Consequently, iodine deficiency is still a serious public health problem in Indonesia and increased effort is needed to eradicate iodine deficiency.

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Chapter 6

General discussion

CONTROLLING IODINE DEFICIENCY

Iodized salt or iodized oil?

Universal salt iodization and iodized oil supplementation can both be used to control iodine deficiency. Universal salt iodization is the main strategy adopted worldwide for elimination of iodine deficiency disorders (IDD) (1). Although iodization of salt has been successful in many countries in reducing the prevalence of IDD, additional strategies are required to eradicate IDD for the coming decades because not all communities at-risk of IDD consume iodized salt yet.

Supplementation with oral iodized oil has shown good results in many endemic areas and may become a more widely used method. The major advantages of iodized oil administration are that it can be implemented quickly, has immediate impact, and does not involve the complexities of altering salt production and trade. Iodized oil has a role in areas of significant iodine deficiency where salt iodization is unlikely to be successfully implemented soon and correction is needed promptly. In many such areas, an iodized oil program will be necessary for at least several years, and for some remote areas it may be semi-permanent (2). At present, most countries depend on an oral iodized poppyseed oil preparation, which is made from a raw material derived from the opium poppy (*Papaver somniferum*). Since cultivation of this plant is tightly regulated, iodized oil has become relatively expensive (3). There is an urgent need to increase the production of iodized oil and to make available an alternative product which is cheaper and effective (4).

Which iodized oil?

Studies in rats and man by Van der Heide et al. (5) indicated that iodine from a preparation based on ethyl oleate was retained longer in the body than a preparation based on ethyl linoleate or from ethyl esters derived from poppyseed oil. A report of a study by Ingenbleek et al. (3) on the effectiveness of iodized rapeseed oil appeared while this study was being carried out. These authors reported that iodized rapeseed oil supplying 752 mg I gave a longer period of protection in moderate iodine deficient adults (30 wk) compared to iodized poppyseed oil supplying 729 mg I (17 wk) when an iodine concentration in urine of 0.79 μmol/L was taken as the cut-off point. Most of iodine in the rapeseed oil preparation was bound to oleic acid whereas in the poppyseed oil preparation the iodine is bound to linoleic acid.

In our study (*Chapter 2*) we compared iodized peanut oil with iodized poppyseed oil. Peanut oil contains three times more oleic acid and one half of the amount of linoleic acid than poppyseed oil. The duration of effectiveness of a single oral dose of iodized peanut oil was about twice that of the iodized poppyseed oil (77 wk vs 42 wk; both preparations contained 400 mg I) in moderate iodine deficient school children. Thus we have been able to confirm the results obtained by Ingenbleek et al. (3), with another iodized oil also based on an oleic acid rich oil and in another population and setting. Therefore, iodized oils prepared from peanut oil and rapeseed oil should be preferred above those from poppyseed oil in programs to control iodine deficiency.

Efficacy of oral iodized peanut oil

Although experience in using oral iodized oil is limited, previous studies in Algeria (6), Bolivia (7), Malawi (8,9) and Zaire (10) have demonstrated that a single oral dose of iodized oil can meet iodine requirements for one or two years. The study in Algeria by Benmiloud et al. (6) showed that a single oral dose of iodized poppyseed oil providing 240 mg I effectively protected iodine deficiency in children aged 6-11 y for 6 months and a dose of 480 mg I for 12 months. Furnée et al. (9) found that 1 mL of oral iodized poppyseed (490 mg I, ethyl esters of iodized fatty acids) effectively protected school children from moderately iodine deficiency (cut-off point 0.4 μmol/L) for 13.7 wk. Our results showed that the same preparation of oral iodized poppyseed oil supplying 400 mg I, could provide school children with enough iodine for 42 wk, which was about twice as long as that reported by Benmiloud et al. (6) and much longer than that found by Furnée et al. (9) who used a cut-off points of urinary iodine concentration half that used by Benmiloud et al (6) and by us. Our results are different from those reported previously probably because of the severity of iodine deficiency. Other factors include, external iodine intake, possible exposure to goitrogenic substances, nutritional status with respect to other nutrients, and the indicators and cut-off points used. Our data indicate that iodized peanut oil is efficacious for controlling iodine deficiency: a single dose 200 mg I effectively protected iodine deficient school children who have limited access to iodized salt for one year (*Chapter 2*).

ASSESSMENT OF IODINE DEFICIENCY AND MEASURING ITS IMPROVEMENT

The status of iodine deficiency in a population, and the progress towards its elimination after intervention, can be assessed through various outcome indicators. The choice of a single indicator, or a combination of indicators for studies or surveys, is not fully standardized but rather depends on the specific circumstances of the study. So far, the number of studies comparing the relative sensitivity and specificity between indicators in assessing iodine status of a population is limited and have given conflicting results (11-18).

The school children in the present study were judged to be moderately iodine deficient at baseline as indicated by a prevalence of goiter measured by palpation and ultrasound, at 22% and 23% respectively, and a median urinary iodine concentration of 0.36 μmol/L (19). However, serum TSH and serum FT_4 concentrations were in the normal range, suggesting that the population had an adequate iodine status. One year after treatment with oral iodized peanut oil, there were significant reductions in thyroid volume and prevalence of goiter and an increase in the median urinary iodine concentration of the population. A significant increase of serum FT_4 concentration was also observed half a year after supplementation, but both the initial and final levels were within the normal range. There was no significant change in the serum TSH concentration. The results suggest that thyroid volume measured by ultrasound and by palpation and urinary iodine concentration gave similar information on the severity of iodine deficiency and all indicated an improvement in iodine status after treatment with oral iodized oil. Serum TSH and FT_4 concentrations did not give any indications of iodine deficiency.

Although the prevalence indicated agreement, the sensitivity and specificity of palpation evaluated against goiter measured by ultrasonography were 55% and 90% respectively at baseline. The positive and negative predictive values were 60% and 88% respectively. These data show that palpation is of limited value for use in surveys of school children to identify communities suffering from iodine deficiency and to identify changes in iodine status. Such a conclusion has been drawn by others previously (13,16,20,21). Although these data highlight the limitation of thyroid palpation, this method still has a useful place in assessing whether or not a problem of iodine deficiency exist because no sophisticated equipment is required. However it is necessary for observers to be trained adequately in the technique.

Based on our studies, urinary iodine concentration and thyroid volume are the best indicators for assessing iodine status and measuring the impact of iodized oil supplementation among iodine deficient school children (*Chapter 3*).

EFFECT OF STUNTING, IODINE DEFICIENCY AND ORAL IODIZED OIL ON COGNITIVE PERFORMANCE

We found that the population studied had a low score for cognitive performance and suffered from multiple nutritional deficiencies: iodine deficiency, iron deficiency anemia and stunting. Earlier studies have shown that some improvement in cognitive performance can be achieved by appropriate supplementation (22-27). Our results showed that both nutritional and non nutritional factors played a role in cognitive performance of the school children. Father's education and hemoglobin concentration were the main determinants of cognitive performance at baseline, and urinary iodine concentration and stunting were the most important determinants for improvement in cognitive performance after supplementation with iodized oil. We did not find a positive correlation between the education of mothers and cognitive performance of school children, probably as the majority of the mothers (96%) had 6 years of education or less. The higher the education of father, the higher the cognitive scores and the higher the educational achievement of the school children as indicated by school grades.

There has been much debate about whether stunting is a harmless adaptation to poor dietary intakes or has a functional consequence (28). This study confirmed results of previous studies (11,24,29,30) that stunting has a role in cognitive development. Stunting may not directly cause poor intellectual development in children, but the same underlying factors that cause stunting such as socio-economic status of the family, may also impair children's intellectual growth (1). Most of the children in this study were from poor families, and their diets were below the recommended dietary intakes. In addition, we found a positive correlation between thyroid volume and stunting at all periods of measurement. Normal linear growth is determined by variable contributions from genetic, nutritional and endocrine factors and continues until bone maturation in early adulthood. One of the major hormones that influence growth during childhood is triiodothyronine (31): before puberty, it may be the major determinant for normal maturation of bone (32). Untreated hypothyroidism in children results in profound growth retardation and

delayed skeletal maturation. Linear growth is almost completely halted, but can be resumed quickly by replacement of thyroid hormones to produce a rapid catch-up period of growth (33).

We found that 40% of the school children were anemic and the cognitive scores of the anemic children (hemoglobin <110 g/L) were 3 points lower than their non-anemic counterparts. Our findings are in line with those earlier studies that showed iron deficiency anemia impairs cognitive development (22,23).

Previous studies in iodine deficient school children have shown impairment of school performance and IQ when compared to similar groups from iodine-replete areas (7). Iodine deficiency results in a shift of the distribution of cognitive skills of the entire population to a lower level. In iodine deficient populations, mild mental impairment has been shown to occur five times more frequently than in populations with normal iodine status (34) and that the IQ curve of the population can be shifted 10 points to the left (35). Although a single oral dose of iodized oil improved iodine status of our population, it did not result in improvement of cognitive performance compared to the placebo group. However, the changes in cognitive score were inversely correlated to the urinary iodine concentration which indicates that iodine deficient children did benefit more in cognitive performance from iodine supplementation than their more replete counterparts. This supports earlier findings that iodine supplementation can increase cognitive performance of school children (22).

This study suggest that iodine status as measured by urinary iodine concentration at baseline and stunting are related to the improvement of cognitive performance when children are dosed with iodized oil. In addition anemia and father's education play a role in cognition. This illustrates the role of nutrition and social factors in cognitive development and performance in children (*Chapter 4*).

IODIZED SALT FOR CONTROLLING IODINE DEFICIENCY

Universal salt iodization is the major public health nutrition measure for eliminating iodine deficiency on a long-term basis (36). Many countries have already made significant progress towards the elimination of IDD, largely as a result of salt iodization (37). In rural areas of many developing countries, where iodine deficiency is often most severe, populations are largely dependent on subsistence foods. Therefore, the main or only source of iodine in this kind of area is iodized salt or

supplementation with iodized oil. Although, it is well established that an adequate iodine intake prevents iodine deficiency disorders, data on the effectiveness of iodized salt for controlling iodine deficiency are still scanty.

During the one year of the study when there was increasing access to iodized salt, the proportion of adequately iodized salt used by households increased from 2% to 54%. However, households were nor consistent in their usage of iodized salt throughout the year, and the majority also used not-adequately iodized salt at least once. The median value of urinary iodine concentration of the school children improved from 0.38 μmol/L to 0.70 μmol/L and prevalence of goiter measured by ultrasound decreased from 26% to 14%. Prevalence of goiter measured by palpation remained at 17%, but this could be attributed to misclassification in goiter measured by palpation compared to when measured by ultrasound (*Chapter 3*), and palpation might not be sufficiently sensitive to detect small changes in thyroid volume. In addition, there were no significant differences in serum concentrations of TSH and FT_4 among children consuming salt that was iodized at different levels. These results confirm those described above on the use of thyroid palpation and serum concentrations of TSH and FT_4 for assessing the impact of iodine prophylaxis but with iodized oil (*Chapter 2; Chapter 3*).

Household use of iodized salt was related significantly to urinary iodine concentration and thyroid volume (*Chapter 5*). Although the use of iodized salt in households increased, about half of the salt available in the market was still not adequately iodized or iodized at all. The availability of cheaper non-iodized salt in the market, subverted the effectiveness of the iodized salt program. These findings indicate that iodine prophylaxis using iodized salt is not simply a matter of passing legislation, but should also include advocacy, education, marketing, an overall system of quality assurance and monitoring of the salt iodization program.

CONCLUSIONS

- A single oral dose of iodized peanut oil compared to a single oral dose of iodized poppyseed oil resulted in three times higher iodine retention leading to a period of protection twice as long in iodine deficient school children. Peanut oil is characterized by having a high proportion of oleic acid while poppyseed oil is rich in linoleic acid. Thus the iodized oil prepared from oils rich in oleic acid, such as

peanut oil, should be given in preference to preparations based on poppyseed oil in public health nutrition programs to control iodine deficiency.

- A single oral dose of iodized peanut oil supplying 200 mg I was effective in protecting school children living in endemic iodine deficient area for one year against iodine deficiency.
- Urinary iodine concentration and thyroid volume measured by ultrasound are the most useful indicators for assessing iodine status and measuring the impact of iodized oil supplementation in school children living in an endemic iodine deficient area. However palpation still has a useful place in assessing iodine status because no sophisticated equipment is required, but it is necessary for observers to be adequately trained in the technique.
- Iodine status as measured by urinary iodine concentration at baseline and stunting were related to the improvement of cognitive performance when children were dosed with iodized oil. In addition anemia and father's education played a role in cognition. This illustrates the role of nutrition and social factors in cognitive development and performance in children.
- The use of iodized salt was correlated with urinary iodine concentration and thyroid volume of the population studied. However, adequate iodine status was not achieved through the iodized salt program and more attention will be required to make it a success.

IMPLICATION FOR POLICIES TO CONTROL IODINE DEFICIENCY

Selection of strategies

Universal salt iodization is the main strategy for controlling iodine deficiency. Results showed that iodized salt has improved the iodine status of the population. However there is still a low awareness of the population at risk about using adequately iodized salt, especially when non-iodized cheaper salt is available in the market. More intensive social marketing strategies, improved education, better quality assurance and closer process monitoring of the salt iodization program are required.

Oral iodized oil is the best alternative and an additional strategy to iodized salt for controlling iodine deficiency, especially in areas of moderate to severe iodine deficiency where iodized salt is unlikely to be successfully implemented soon and correction is needed promptly. In many such areas, an iodized oil program will be

necessary for at least several years, and for some remote areas it may need to be semi-permanent. An oral iodized oil preparation based on an oleic acid rich oil such as peanut oil is more effective than a preparation based on poppyseed oil. A single dose of oral iodized peanut oil given to moderate or severe iodine deficient school children annually will control iodine deficiency adequately.

Measuring the extent of iodine deficiency and evaluating the effect of programs

A commonly used parameter to access the extent of IDD in a community is the prevalence of goiter as assessed through thyroid palpation. However, grading of goiter size by palpation has large intra and inter-observer variability. Even though thyroid palpation has its limitations, it still has a useful place in assessing iodine status because no sophisticated equipment is required. Therefore, it is necessary for observers to be trained adequately in the technique. In addition, other indicators of iodine or thyroid status should be used. This study suggested that urinary iodine concentration and thyroid volume measured by ultrasound are the most useful indicators for assessing iodine status and measuring the impact of treatment among populations of school children.

RECOMMENDATIONS FOR FUTURE RESEARCH

Research on the efficacy of different preparations of iodized oil should focus on:

- The metabolism of such preparations in the body to elucidate the relative rates of the various reactions and process involved.

Research on iodine indicators should focus on:

- Development of reliable and cost-effective indicators for measuring the iodine status of the population.

Research on cognitive performance should focus on:

- The relative importance of iodine supplementation in improving the cognitive performance of populations with multiple nutritional problems including iodine deficiency.

Research on efficacy of iodized salt should focus on:

- Measuring the average salt consumption in the population.
- The effect of food preparation including the method and duration of cooking and the spices used, on the stability of iodized salt.
- Determining optimal levels of fortification for controlling iodine deficiency in populations differing in the severity of iodine deficiency and other characteristics.

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Annex 1

Efficacy of different types of iodized oil

Lancet 1998;351:752-753 *(Letter)*

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Sir--Y Ingenbleek and colleagues(1) describe the preparation and use in severe endemic goitre of a new type of iodized oil based on rapeseed oil which is better than previously available preparations based on poppyseed oil. Iodized oil based on peanut oil was introduced in Indonesia in 1993. The composition of peanut oil (56% oleic acid and 26% linoleic acid) is similar to that of rapeseed oil (60% oleic acid and 20% linoleic acid), as reported by Ingenbleek. Apart from the scarcity of poppyseed oil, its high proportion of polyunsaturated fatty acids (73%) was another reason for seeking a new basis for iodized oil. Iodine from such oils is retained for a shorter time than iodine from oils with a high proportion of monounsaturated fatty acids (2).

We compared the efficacy of two iodized oils: oil A (ethyl esters of iodized fatty acids from poppyseed oil; Lipiodol®, Laboratoire Guerbet, Roissy, France) and oil B (iodized peanut oil; Yodiol®, PT Kimia Farma, Jakarta, Indonesia), under community conditions in a randomized, single-blind, placebo-controlled trial among 250, 8-10-year-old, Indonesian school children from Cilacap district, Central-Java, which is an area endemic for iodine deficiency disorders.

Children were de-wormed with 400 mg albendazole (SmithKline Beecham, Indonesia) 1 week before being supplemented. A urine sample was collected between 08.00 h and 12.00 h on 2 consecutive days at baseline and at 4 and 12 weeks' follow-up. Further samples will be taken at 25 and 50 weeks. Urinary iodine excretion was measured in duplicate and the average calculated for each child. The table shows details about treatment and preliminary results. Urinary iodine excretion at baseline was closely similar between groups. At 4 and 12 weeks urinary iodine excretion of all supplemented groups was significantly higher than in the placebo group (Mann-Whitney; $P<0.001$). Urinary iodine excretion of the group supplemented with oil A was similar to the urinary iodine excretion of the 200 mg oil B group, and significantly lower than urinary iodine excretion of the 400 mg oil B group ($P<0.001$) at both 4 and 12 weeks.

Table 1. Median urinary iodine excretion at the baseline and at 4 and 12 weeks after oral supplementation of school children with different types of iodized oil.

Treatment*	n	Median urinary iodine excretion [range], µg/L §		
		Baseline	4 week	12 week
Iodized oil A 400 mg	49	43.0 [8.0-195.5]	465.0 ‡¶ [51.5-1450.0]	239.0 ‡¶ [72.5-840.0]
Iodized oil B 200 mg	50	46.5 [20.0-157.0]	533.0 ‡¶ [124.5-3625.0]	347.5 ‡¶ [95.5-1797.0]
Iodized oil B 400 mg	51	43.5 [13.0-143.5]	925.0 ‡# [147.5-3700.0]	555.0 ‡# [115.0-1626.0]
Iodized oil B 800 mg	50	46.3 [12.0-212.5]	1517.5 ‡** [430.0-6450.0]	1119.0 ‡** [355.0-2590.0]
Placebo	51	47.5 [6.5-132.5]	67.0 §†† [15.5-385.0]	82.5 §†† [14.0-199.0]

* Iodized oil A, iodized fatty acid ethyl esters from poppy-seed oil; iodized oil B, iodized peanut oil; placebo, peanut oil.

† Based on the average urinary iodine excretion of two consecutive days for each person

Within-group changes compared to baseline: ‡, $P<0.001$; §, $P<0.05$ (Wilcoxon Matched-Pairs)

Different letters (¶, #, **, ††) indicate significant differences between groups of treatment ($P<0.0001$, Kruskal Wallis)

These results indicate higher iodine retention from iodized peanut oil than with ethyl esters of iodized fatty acids prepared from poppyseed oil. The short-term efficacy of iodized peanut oil, having a fairly high percentage of monosaturated fatty acid, is greater than that of the poppyseed oil preparation. This finding is in accord with that of Ingenbleek et al. (1). The continued follow-up will show whether iodized peanut oil will allow less frequent supplementation while maintaining a median urinary iodine excretion higher than 100 µg/L. Iodized oil capsules based on oils with a high percentage of monounsaturated fatty acids would allow eradication of iodine deficiency in areas in which immediate action is required.

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Summary

The research described in this thesis focused on the use of oral iodized oil to control iodine deficiency in school children living in an endemic iodine deficient area in Indonesia. Iodine deficiency is responsible for a series of disabilities which are collectively known as iodine deficiency disorders (IDD). Although goiter is the most manifest sign, iodine deficiency results in irreversible brain damage in the fetus and infant, retarded mental and psycho-motor development in the child, and also impaired reproductive function. The *World Summit for Children* in 1990 committed governments to eradicate iodine deficiency by the year 2000. Universal salt iodization has been set as the main strategy employed to eradicate iodine deficiency, and about 60% of all edible salt worldwide is iodized.

Various strategies have been used in Indonesia to combat iodine deficiency. The prevalence of goiter among school children decreased during the 1980s and adequately iodized salt used in households increased from one third in 1983-1984 to nearly one half in 1995. Legislation was promulgated in 1994 to bring about salt iodization with a minimum level of fortification set at 30 mg I/kg salt. Although the production and use of iodized salt to control iodine deficiency is now widespread, additional strategies are required where iodized salt cannot be made available in the short term or only with difficulty in the long term. The best alternative is probably oral iodized oil which is the subject of this thesis.

There is evidence from previous studies that a single oral dose of iodized oil is effective in controlling iodine deficiency for one to two years. The most widely available preparation is iodized poppyseed oil. Previous work has shown that iodine from iodized oil prepared from ethyl oleate was retained longer in both man and rats than that prepared from ethyl linoleate or ethyl esters of fatty acids from poppyseed oil which has a high proportion of linoleic acid and a low proportion of oleic acid. Oils rich in oleic acid, such as peanut oil, also have the advantage that they are cheaper than poppyseed oil.

Thus the efficacy of orally administered iodized peanut oil was compared with that of iodized poppyseed oil among school children aged 8-10 years living in an endemic iodine deficient area in Indonesia. In addition, the performance of different outcome indicators of iodine deficiency, the impact of nutritional status and iodine supplementation on cognitive performance, as well as the effectiveness of introduction of salt iodization in the population were investigated.

A single oral dose of iodized peanut oil compared to a single oral dose of iodized poppyseed oil resulted in three times higher iodine retention leading to a

period of protection twice as long. While this study was being carried out, similar results were obtained by others using iodized oil prepared from rapeseed oil which is also rich in oleic acid. Thus iodized oil prepared from oleic acid rich oils, such as peanut oil and rapeseed oil, should be given preference to poppyseed oil in programs to control iodine deficiency.

Iodine status and the effect of intervention in the population, can be measured using various outcome indicators. The selection of an indicator is dependent on the acceptance of the indicator by the target population and field staff performing the assessment, on the ease of use in field conditions, and on the available resources in terms of money, laboratory equipment and staff. Above all, the indicator must be valid. So far, the number of studies comparing the relative sensitivity and specificity of indicators for assessing iodine status of a population is limited and they have given conflicting results. We evaluated different outcome indicators for assessing iodine status and measuring the effect of oral iodized oil treatment. We found that urinary iodine concentration and thyroid volume measured by ultrasound are the most useful indicators for assessing iodine status and measuring the impact of iodized oil supplementation among iodine deficient school children. The other indicators, i.e.: palpation and serum concentrations of thyroid stimulating hormone (TSH) and free thyroxine (FT_4), did not show concordance for assessing iodine deficiency or the impact of treatment. Serum concentrations of thyroglobulin were also shown to be of limited value in assessing iodine status. Although these data highlight the limitations of thyroid palpation, this method still has a useful place in assessing iodine status because no sophisticated equipment is required. However it is necessary for observers to be trained in the technique.

Nutritional supplementation of undernourished children is known to have a beneficial effect on their intellectual capacity. The factors related to cognitive performance and the effect of oral dosing with iodized oil were examined using Cattell's culturally fair intelligence test. Median cognitive performance was low, 32% of the children were underweight, 58% were stunted, 3% were wasted, and 40% were anemic. Father's education and hemoglobin concentration were the main determinants of cognitive performance at baseline, and urinary iodine concentration and stunting were the most important determinants for improvement in cognitive performance after supplementation with iodized oil. These results illustrate the role of nutrition and social factors in cognitive development and performance in children.

Data on the effectiveness of iodized salt for controlling iodine deficiency is still

scanty. After one year of introduction of salt iodization, the proportion of households using adequately iodized salt increased significantly, from 2% to 54%, but there was inconsistency in its use within households during the study period. The use of iodized salt was related to urinary iodine concentration and thyroid volume. However the prevalence of goiter measured by palpation remained at 17% and serum concentrations of TSH and FT_4 did not respond to the salt iodization, indicating the poor performance of these indicators as mentioned above. These findings indicate that iodine prophylaxis using iodized salt is not only simply a matter of passing legislation, but should also include advocacy, education, marketing, an overall system of quality assurance and monitoring of the salt iodization program.

Samenvatting

Het onderzoek dat in dit proefschrift beschreven wordt, was gericht op het gebruik van gejodeerde olie om jodiumtekort te bestrijden bij schoolkinderen woonachtig in een endemisch jodium deficiënt gebied in Indonesië. Jodiumtekort is verantwoordelijk voor een aantal aandoeningen die bekend staan als het jodiumtekort syndroom (IDD). Hoewel struma het meest zichtbare symptoom is, geeft jodiumtekort ook onomkeerbare hersenschade in de foetus en zuigeling, vertraagde mentale en psycho-motorische ontwikkeling van het kind en ook een verminderde voortplantingsfunctie. Tijdens de *World Summit for Children* in 1990 verplichtten regeringen zich om jodium tekort voor het jaar 2000 uit te bannen. Het joderen van zout is de belangrijkste strategie om het jodiumtekort te bestrijden en wereldwijd is ongeveer 60% van het consumptiezout gejodeerd.

In Indonesië zijn diverse strategieën toegepast om jodiumtekort te bestrijden. De prevalentie van struma onder schoolkinderen is gedurende de jaren tachtig gedaald. Bovendien steeg het gebruik van zout dat voldoende gejodeerd is. In 1983-1984 gebruikte slechts een derde van de huishoudens dit zout terwijl dit in 1995 gestegen was tot bijna de helft van de huishoudens. In 1994 werd in de Indonesische wet vastgelegd dat al het zout ten minste 30mg jodium per kg moet bevatten. Hoewel de productie en het gebruik van gejodeerd zout ter bestrijding van jodiumtekort nu wijdverspreid is, zijn aanvullende strategieën nodig als gejodeerd zout niet snel beschikbaar is of alleen met moeite op lange termijn beschikbaar kan worden. Het beste alternatief is waarschijnlijk orale toediening van gejodeerde olie, het onderwerp van dit proefschrift.

Uit eerdere studies is gebleken dat een eenmalige dosis gejodeerde olie effectief is in het bestrijden van jodium tekorten voor een periode van 1 tot 2 jaar. Het meest beschikbare preparaat is gejodeerde papaverzaadolie. Eerder werk heeft laten zien dat jodium afkomstig van gejodeerde olie gemaakt van ethyl oleaat langer beschikbaar bleef in de mens en in ratten vergeleken met olie van ethyl linoleaat of ethyl esters van vetzuren van papaverzaadolie met een hoog gehalte aan linolzuur en een laag gehalte aan oliezuur. Oliën rijk aan oliezuur, zoals pindaolie, hebben ook als voordeel dat ze goedkoper zijn dan papaverzaadolie.

De doeltreffendheid van oraal toegediende gejodeerde pindaolie werd vergeleken met dat van gejodeerde papaverzaadolie in schoolkinderen van 8-10 jaar woonachtig in een endemisch jodium deficiënt gebied in Indonesië. Verder werden verschillende indicatoren van jodiumtekort, het effect van voedingsstatus en

jodiumsuppletie op de cognitieve verrichting als ook de effectiviteit van de introductie van het joderen van zout in de populatie, bestudeerd.

Een eenmalige orale dosis gejodeerde pindaolie resulteerde in een 3 maal zo hoge retentie van jodium met als gevolg een twee maal zo lange beschermende periode. Terwijl deze studie werd uitgevoerd, werden door anderen vergelijkbare resultaten met gejodeerde olie gemaakt van raapzaadolie, wat ook rijk is aan oliezuur. In programma's om jodiumtekort tegen te gaan, zou dus de voorkeur gegeven moeten worden aan gejodeerde olie bereid met oliezuurrijke oliën, zoals pindaolie en raapzaadolie, boven gejodeerde papaverzaadolie.

De jodiumstatus en het effect van interventies kan worden bepaald met verschillende indicatoren. De selectie van een indicator is afhankelijk van de acceptatie van de doelgroep en het personeel dat de meting moet uitvoeren, de bruikbaarheid van de indicator onder onderzoeksomstandigheden en de beschikbare bronnen in termen van geld, laboratoriumuitrusting en personeel. Bovenal moet de indicator valide zijn. Tot zover is het aantal studies beperkt welke de sensitiviteit en specificiteit van indicatoren voor de bepaling van de jodiumstatus van een populatie onderzoeken. Bovendien zijn de resultaten tegenstrijdig. We hebben verschillende indicatoren geëvalueerd voor de bepaling van de jodiumstatus en voor het meten van het effect van inname van gejodeerde olie. We vonden dat de jodiumconcentratie in de urine en de grootte van de schildklier gemeten door ultrasound de meest bruikbare indicatoren zijn voor het meten van de jodiumstatus en het meten van de uitwerking van suppletie met gejodeerde olie bij schoolkinderen met een jodiumtekort.

De andere indicatoren, zijnde: palpatie en serum concentraties van het schildklier stimulerend hormoon (TSH) en vrij thyroxine (FT_4) stemden niet overeen wat betreft het meten van jodiumtekort.of de uitwerking van de behandeling. Serumconcentraties van thyroglobuline bleken ook een beperkte waarde te hebben voor de bepaling van de jodiumstatus. Hoewel deze gegevens de beperkingen van schildklierpalpaties benadrukken, heeft deze methode nog steeds een bruikbare plaats in de bepaling van de jodiumstatus, omdat er geen geavanceerde apparatuur voor nodig is. Het is echter belangrijk dat de waarnemers de techniek goed onder de knie hebben.

Het is bekend dat de aanvulling van de voeding van ondervoede kinderen een gunstig effect heeft op hun intellectuele mogelijkheden. De aan de cognitieve verrichtingen gerelateerde factoren en het effect van orale dosering van gejodeerde

olie werden bestudeerd met behulp van de 'Cattell's culturally fair intelligency test'. Uit de test bleek dat de mediaan van de cognitieve verrichtingen laag was. Bovendien bleek 32% van de kinderen te licht te zijn voor hun leeftijd, 58% was te klein voor hun leeftijd, 3% had een te laag gewicht voor hun lengte en 40% had ijzergebreksanemie. De opleiding van de vader en de hemoglobineconcentratie van het kind waren de belangrijkste determinanten van de cognitieve verrichtingen aan het begin van de studie. De jodiumconcentratie in de urine en een te geringe lengte voor de leeftijd waren de belangrijkste determinanten voor verbetering in de cognitieve verrichting na suppletie met gejodeerde olie. Deze resultaten illustreren de rol van voeding en sociale factoren in de cognitieve ontwikkeling en verrichtingen van kinderen.

Gegevens over de effectiviteit van gejodeerd zout voor de bestrijding van jodiumtekort zijn schaars. Een jaar na de introductie van gejodeerd zout steeg het deel van de huishoudens dat zout gebruikte dat voldoende gejodeerd is significant van 2% naar 54%. Het werd echter niet consequent gebruikt binnen huishoudens gedurende de studieperiode.

De jodiumconcentratie in de urine en de grootte van de schildklier waren gerelateerd aan het gebruik van gejodeerd zout. Echter, de prevalentie van struma, zoals gemeten met palpatie bleef op 17%. De serumconcentraties van TSH en FT_4 reageerden niet op de jodering van het zout. Dit geeft aan dat, zoals reeds eerder vermeld, dit geen goede indicatoren zijn. Deze bevindingen duiden aan dat het gebruik van jodiumprofylaxe met behulp van gejodeerd zout niet slechts een aanpassing van de wetgeving vereist, maar daarnaast kan het zoutjoderingsprogramma ook niet zonder promotie, voorlichting, marketing en een allesomvattend systeem van kwaliteitscontrole.

Ringkasan

Penelitian ini berfokus pada penggunaan kapsul minyak beryodium untuk menanggulangi kekurangan yodium pada anak sekolah di daerah endemik kekurangan yodium di Indonesia. Kekurangan yodium berperanan dalam suatu seri bermacam gangguan yang secara keseluruhan disebut gangguan akibat kekurangan yodium (GAKI). Meskipun gondok adalah gangguan yang paling nyata, kekurangan yodium juga dapat menyebabkan gangguan perkembangan saraf pada fetus dan bayi, keterlambatan perkembangan mental dan psikomotor pada anak-anak dan gangguan sistem reproduksi. Konferensi *World Summit for Children* tahun 1990 mencetuskan komitment pemerintah untuk mengentaskan kekurangan yodium pada tahun 2000. Program iodisasi garam merupakan strategi utama dalam penanggulangan GAKI, dan sekitar 60% garam konsumsi yang tersedia di seluruh dunia, telah diiodisasi.

Berbagai strategi digunakan di Indonesia, untuk menanggulangi kekurangan yodium. Prevalensi gondok dari anak sekolah menunjukkan penurunan pada tahun 1980 an dan penggunaan garam beryodium di tingkat rumah tangga meningkat dari sepertiga di tahun 1983-1984 menjadi hampir setengah di tahun 1995. Kebijaksanaan pemerintah tentang penggunaan garam beryodium dituangkan dalam Keputusan Presiden pada tahun 1994, yang menetapkan iodisasi garam pada konsentrasi minimal 30 mg I/kg garam. Meskipun produksi dan penggunaan garam beryodium untuk menganggulangi GAKI telah meluas, strategi lain diperlukan untuk daerah-daerah dimana garam beryodium tidak dapat diterapkan dalam jangka waktu pendek atau hanya dapat diterapkan pada jangka waktu panjang dengan tingkat kesulitan yang cukup tinggi. Alternatif yang terbaik kemungkinan adalah kapsul minyak beryodium yang merupakan topik dari thesis ini.

Hasil penelitian-penelitian terdahulu menunjukkan bahwa pemberian dosis tunggal kapsul beryodium dapat secara efektif menanggulangi kekurangan yodium untuk jangka waktu satu sampai dua tahun. Produk minyak beryodium yang paling banyak tersedia saat ini adalah minyak beryodium dari *poppyseed*. Penelitian terdahulu menunjukkan bahwa yodium dari minyak beryodium dari preparasi ethyl oleat memiliki daya retensi dalam tubuh manusia maupun tikus, lebih lama dari preparasi ethyl oleate atau ethyl esters asam lemak dari minyak *poppyseed* yang memiliki proporsi kandungan asam linoleat yang tinggi dan proporsi asam oleat yang relatif rendah. Minyak yang kaya kandungan asam oleat, seperti minyak kacang, juga memiliki keunggulan bahwa harganya relatif lebih murah dari minyak *poppyseed*.

Oleh karena itu, penelitian ini bertujuan untuk membandingkan efikasi dari kapsul minyak kacang dengan kapsul minyak *poppyseed* pada anak sekolah usia 8-10 tahun. Selain itu, penggunaan berbagai indikator dari status yodium, dampak suplementasi yodium terhadap fungsi kognitif juga efektifitas dari iodisasi garam pada masyarakat diteliti lebih lanjut.

Dosis tunggal kapsul yodium minyak kacang menunjukkan retensi yodium tiga kali lebih tinggi dan menghasilkan masa proteksi dua kali lebih lama dibandingkan dengan dosis tunggal kapsul yodium minyak *poppyseed*. Pada saat studi ini dilakukan, hasil yang sama didapatkan pada preparasi yodium minyak *rapeseed*, yang juga kaya kandungan asam oleatnya. Oleh karena itu, kapsul minyak beryodium yang kaya kandungan asam oleat, seperti minyak kacang dan minyak *rapeseed*, adalah merupakan produk yang akan lebih disukai dibanding dengan preparasi minyak beryodium *poppyseed*, dalam menanggulangi GAKI.

Status yodium dan dampak dari intervensi pada masyarakat, dapat diukur dengan berbagai indikator. Pemilihan indikator adalah tergantung dari penerimaan indikator tersebut oleh populasi yang diukur dan petugas lapang yang melakukan pengukuran, kemudahan melakukan pengukuran tersebut di lapangan, dan ketersediaan sumber daya dalam pengertian dana, peralatan laboratorium dan staff. Selain itu, yang paling utama adalah indikator tersebut harus valid. Hingga saat ini, berbagai penelitian dengan membandingkan sensitifitas and spesifisitas dari bermacam indikator untuk mengukur status yodium pada masyarakat sangat terbatas dan hasilnya saling bertentangan. Penelitian ini mengevaluasi berbagai macam indikator untuk mengukur status yodium dan dampak dari perlakuan kapsul beryodium. Hasil penelitian ini menunjukkan bahwa konsentrasi yodium urin dan volume tiroid merupakan indikator-indikator yang terbaik untuk mengukur status yodium dan dampak dari perlakuan kapsul beryodium pada anak sekolah. Indikator-indikator yang lain, yaitu: palpasi tiroid, konsentrasi serum *thyroid stimulating hormone* (TSH) dan *thyroxine* bebas (FT_4), tidak menunjukkan hasil yang seiring dalam mengukur status kekurangan yodium dan dampak dari perlakuan. Konsentrasi serum *thyroglobulin* juga menunjukkan hasil yang kurang memuaskan dalam mengukur status yodium. Meskipun data menunjukkan bahwa palpasi tiroid memiliki kekurangan, namun palpasi tiroid tetap memiliki peranan dalam mengukur status yodium, karena tidak diperlukan peralatan yang canggih. Akan tetapi, dibutuhkan training yang cukup dalam teknik palpasi.

Suplementasi zat gizi tertentu pada anak-anak kekurangan zat gizi tersebut

menunjukkan hasil yang positif bagi perkembangan kapasitas intelektual mereka. Penelitian ini juga bertujuan untuk menginvestigasi faktor-faktor yang berkaitan dengan fungsi kognitif dan dampak dari penggunaan kapsul minyak beryodium terhadap perkembangan fungsi kognitif yang diukur dengan *Cattell's culturally fair intelligence test*. Nilai median dari fungsi kognitif anak-anak dalam penelitian ini adalah relatif rendah, selain itu 32% dari populasi memiliki berat badan kurang (berat badan menurut usia), 58% memiliki tinggi badan kurang (tinggi badan menurut usia), 3% menderita berat menurut tinggi badan kurang, dan 40% menderita anemia gizi. Penelitian ini menunjukkan bahwa pendidikan ayah dan status hemoglobin darah memiliki peranan dalam fungsi kognitif, sementara konsentrasi yodium urin dan tinggi badan menurut usia merupakan faktor yang paling menentukan perkembangan fungsi kognitif setelah suplementasi dengan kapsul minyak beryodium. Hasil penelitian ini mengilustrasikan peranan dari faktor gizi dan faktor sosial dalam perkembangan fungsi kognitif pada anak-anak.

Data tentang efektifitas garam beryodium dalam menanggulangi kekurangan yodium masih sangat terbatas. Setelah satu tahun penerapan iodisasi garam, proporsi rumah tangga yang menggunakan garam beryodium dengan konsentrasi yang memenuhi persyaratan, meningkat dari 2% ke 54%, namun ditemukan adanya ketidak konsistenan dalam penggunaan garam beryodium di rumah tangga. Penelitian ini menunjukkan bahwa penggunaan garam beryodium berkaitan dengan status yodium yang diindikasikan dengan konsentrasi yodium urin dan volume tiroid. Namun prevalensi gondok menurut palpasi tetap pada 17% dan konsentrasi serum TSH dan FT_4 tidak menunjukkan respon terhadap penggunaan garam beryodium, hal ini menunjukkan kelemahan performan dari indikator tersebut seperti yang telah dipaparkan terdahulu. Hasil penelitian ini mengindikasikan bahwa dalam penerapan penggunaan garam beryodium selain peraturan, dibutuhkan pula promosi, pendidikan, pemasaran, dan sistem yang menyeluruh dalam pengendalian mutu dan pemonitoran program iodisasi garam.

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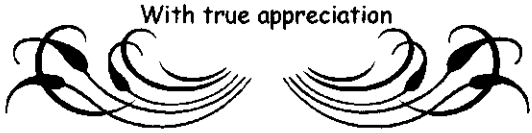

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Juliawati Untoro was born on 4 July 1967 in Magelang, Indonesia. She completed her secondary high school (SMA 1 – Teladan, Yogyakarta, Indonesia) in 1986 and graduated from Gadjah Mada University (UGM), Indonesia in 1991 with an Ingenieur (BSc) degree in Food Technology & Nutrition Science. From 1991 to 1992, she joined PT Astra International Inc, as a corporate research analyst in the Service Quality Management and Management Development Division. From 1992 to 1994, she studied for her MSc in Nutrition at the South East Asian Ministries of Education Organization - Tropical Medicine (SEAMEO Tropmed), Regional Center for Community Nutrition, at the University of Indonesia. On graduation, she joined the SEAMEO Tropmed Center as a member of the teaching staff with the role of coordinator of the regional post graduate training program in Community Nutrition and was also involved in several nutrition research projects. From 1996 to early 1999, she carried out the work described in this thesis, within the framework of collaboration between SEAMEO Tropmed, GTZ (German Technical Cooperation) and the Division of Human Nutrition and Epidemiology, Wageningen Agricultural University.

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