Comparative Studies on Iodine Levels in Gallstones and Bile of Japanese and Thais (Chiang Mai and Bangkok)

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Abstract

We measured the iodine content of gallstones and bile from patients in three areas (Kawasaki in Japan, and Chiang Mai and Bangkok in Thailand) by means of neutron activation analysis. The mean values for iodine content in three types of gallstones (cholesterol, pigment and rare stones) and bile from patients living in Chiang Mai were clearly smaller than those from patients living in Kawasaki and Bangkok. The low iodine intake by Chiang Mai patients continued from the start of gallstone formation until the time when the stones were excised, and the iodine intake was low when bile was collected. The PBI levels in the sera of Chiang Mai residents with low iodine intake over a long period were clearly lower than those of Bangkok patients with normal intake, and the levels in goiter patients were similar to those in healthy people and patients with gallstones among Chiang Mai residents.

Key word : Gall Stone, Bile, Iodine Level, Japanese, Thai

The pathogenesis and chemical composition of gallstones have been extensively studied(1). From the trace elements and substances in gallstones derived from the diet and environment, the correlation between disease and the intake of elements and substances has been analyzed(2,3). Iodine deficiency causes goiter and cretinism in young animals, particularly early retardation of development of the fetal brain,(4,5) and iodine deficiency may function as a strong tumor promoter in man(6). In view of these functions, the prevention of iodine deficiency disorder (IDD) is being attempted throughout the world(7). The authors, therefore, thought that quantitative analysis of iodine content

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in gallstones and bile might tell us of the subject's iodine environment and provide a history of iodine intake from the start of gallstone formation until the time when the stones were removed, and when the bile was collected.

In this study we measured the amount of iodine in the gallstones and bile of patients living in Japan and Thailand (Chiang Mai and Bangkok) by neutron activation analysis. The comparison of these three areas gives an idea of the amount of iodine intake from the diet of patients during the period of gallstone formation. We compared the amount of protein-bound iodine (PBI) in sera from people with a low iodine and a sufficient iodine environment for a long period. This comparison shows that PBI levels clearly decrease in the low iodine area.

MATERIAL AND METHOD

Subjects and classification of gallstones

The gallstones and bile were surgically obtained from patients suffering from cholelithiasis. In Japan, an iodine containing compound {iotroxic acid (3,3'-2,2'-oxydiethylene-dioxyacetamido bis-[2,4,6-triiodobenzoic acid]} (Biliscopin) was used as a contrast medium for the X-ray cholangiography at Second Hospital, Nippon Medical School. The contrast medium was used with the intravenous dose, and the shortest period between the injection and operation was 2 weeks at the Second Hospital. Contrast medium was not used at the Department of Surgery, Maharaj Nakorn Chiang Mai Hospital and Siriraj Hospital (Bangkok) in Thailand for patients with cholelithiasis. The gallstones were classified as cholesterol, pigment or rare stones by morphology and infrared spectra according to the criteria of the Japanese Society of Gastroenterology[8].

Gallstones, bile and serum

Japanese

The gallstones and bile used were obtained at the Department of Surgery, Second Hospital, Nippon Medical School, Kawasaki (the adjacent city to Tokyo), Japan, from 1984 to 1990. Serum samples were obtained from patients operated on for cholelithiasis at the same Department and healthy men and women on the occasion of medical examinations at Shin-Yokohama Hospital (near the Second Hospital).

Thai People

Chiang Mai Patients

The Chiang Mai gallstones and bile samples were obtained at the Department of Surgery, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Thailand. Chiang Mai serum samples were collected during medical examinations. The donors were classified as apparently healthy subjects, subjects with gallstones, and subjects with goiter who were determined by clinical symptoms, visual inspection and ultrasonography.

Bangkok Patients

The Bangkok gallstones and bile samples were obtained at the Department of Surgery, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Serum samples were obtained from patients operated on for cholelithiasis at the same Department.

Quantitative analysis of iodine

Measurement of iodine content in gallstones and bile by neutron activation analysis

Each gallstone was ground to powder, weighed, and packed in a polyethylene bag. Each bile sample was also weighed and packed in a bag. The filter paper containing 0.7486 μg of iodine and Orchard Leaves (National Institute of Science and Technology, Certificate of Analysis, Standard Reference Material 1571, Washington, D.C., U.S.A.) were used as a standard for iodine analysis. These standard samples were packed in a bag. All the sample bags were irradiated for 180 sec in F-position ($1X10^{12}$ n_{th} cm^{-2} s^{-1} at 100 kW) with a pneumatic tube in a TRIGA MARK II Reactor at the Institute for Atomic Energy, Rikkyo University, Yokosuka, Japan. After cooling for 300 sec, the activities of ^{128}I (half life: 24.99m) in the samples were measured for 300 sec with a conventional 4096 multi channel pulse height analyzer and 52.4 cm^3 or 80 cm^3 pure Ge Detector by using a characteristic gamma peak at 443 keV. The activities were corrected for decay to the end of the irradiation. To normalize the differences in thermal neutron fluxes between the irradiation sites, and the counting conditions, the activities of standard samples were used. We determined the iodine content of gallstones and bile by calculating the ratio of the activities of iodine in the gallstones and bile, and the standard samples. The detection limit under our measuring conditions was less than 4 ng.

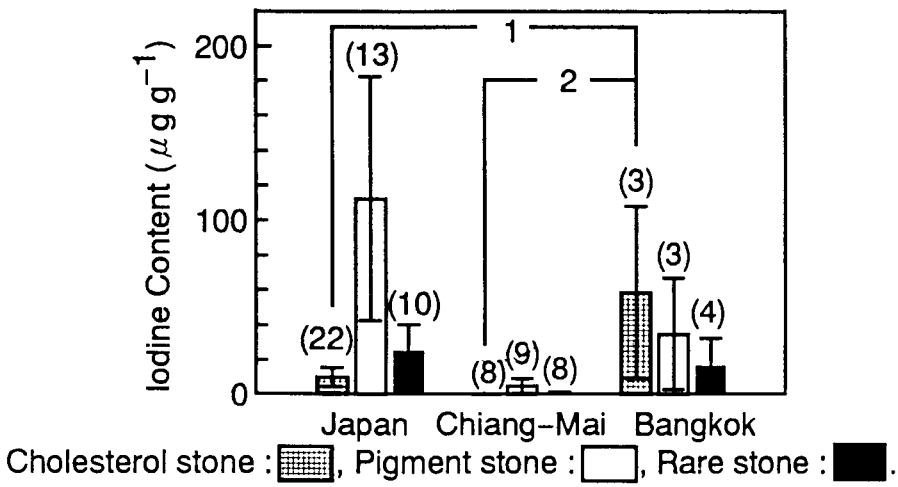

Fig. 1. Iodine in cholesterol, pigment, and rare stones from patients living in Japan and Thailand (Chiang Mai and Bangkok). The results are the mean ± SE. Values in parentheses are the numbers of gallstones analyzed. 1: P <0.011, 2: P <0.004.

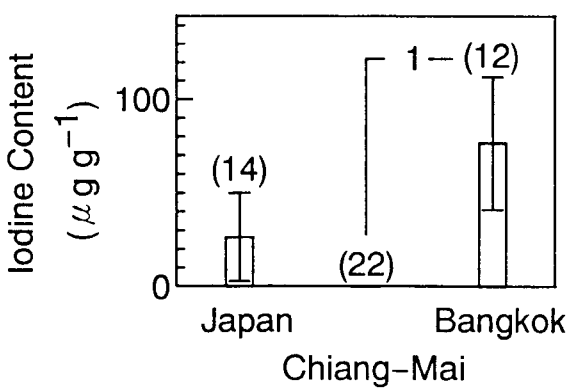

Fig. 2. Iodine in bile from patients living in Japan and Thailand (Chiang Mai and Bangkok) (μg g^{-1}). The results are the mean ± SE. Values in parentheses are the numbers of samples. 1: P <0.012.

Conditions for storage of serum

After a blood sample was taken, the serum was separated by centrifugation. The serum was stored in a freezer (-80°C). During transportation from Thailand to Japan by air, the frozen serum samples were stored in an ice box filled with dry ice.

Quantitative analysis of protein-bound iodine (PBI) in serum

The amount of PBI in the samples was determined with a Technicon AutoAnalyzer after pre-treatment with anion-exchange resin by Sumitomo Metal Bio-Science, Inc., Kanagawa[9].

Statistical analysis

Values were expressed as the mean ± SE. We performed the Duncan multiple range test (D test) for multiple comparisons of means of significant differences among Japanese and Thais (Chiang Mai and Bangkok). We used STATISTICA (StatSoft, Inc., Tulsa, Okla.) as statical analysis software. In two tests, we carried out the statistical analysis as ND (below the limit of detection) was zero.

RESULTS

Cholesterol, pigment and rare stones from patients living in Japan and Thailand (Chiang Mai and Bangkok)

The mean values for iodine content in the cholesterol, pigment and rare stones from the patients living in Chiang Mai were obviously smaller that those in patients living in Japan and Bangkok, as shown in Fig. 1. The significant differences between the values in cholesterol stones from Chiang Mai and Bangkok patients, and from Japanese and Bangkok patients were found, but the values in cholesterol, pigment and rare stones from the patients

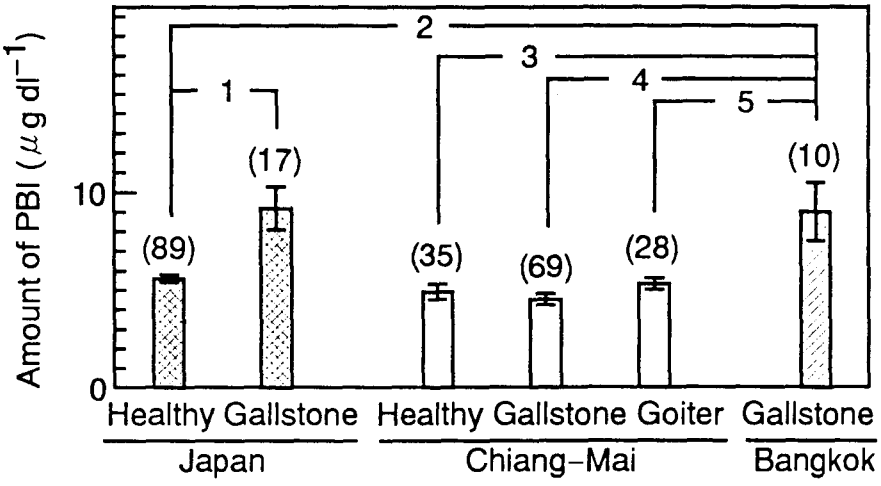

Fig. 3. Amount of protein-bound iodine in sera from people living in three areas (Japan, Chiang Mai and Bangkok). The results are the mean ± SE. Values in parentheses are the numbers of samples. 1: $P < 1.1 \times 10^{-4}$, 2: $P < 9 \times 10^{-6}$, 3: $P < 1.2 \times 10^{-5}$, 4: $P < 3 \times 10^{-6}$, 5: $P < 1.5 \times 10^{-5}$.

Table 1. The numbers of bile and gallstone analyzed from patients and people living in Japan, Chiang Mai, and Bangkok.

Areas	Bile	Gallstones		
		Cholesterol stones	Pigment stones	Rare stones
Japan	14*	22	13	10
Male	2	8	4	3
Female	12	14	9	7
Chiang Mai	22**	8	9	8
Male	3	1	1	1
Female	19	7	8	7
Bangkok	12***	3	3	4
Male	2	1	0	1
Female	10	2	3	3

* Only 14 bile samples were analyzed, because other bile samples were lost.
** Twenty-two analyzed samples of bile and gallstones were obtained from the same patients.
*** Ten analyzed samples of gallstones and bile were obtained from the same patients.

living in Japan and Bangkok had a large standard deviation.

Iodine in bile from patients living in Japan and in Thailand (Chiang Mai and Bangkok)

The mean value for iodine content in bile from Chiang Mai patients was evidently smaller than in Japanese and Bangkok patients, as shown in Fig. 2. A significant difference was found between the values in Chiang Mai and Bangkok patients, but the value in Japanese patients had a large standard deviation.

Amount of protein-bound iodine (PBI) in sera from people Living in Japan and Thailand (Chiang Mai and Bangkok)

Table 2. Iodine content of cholesterol, pigment, and rare stones from patients living in Japan and Thailand (Chiang Mai and Bangkok) (μg g^{-1}).

	Cholesterol stones	Pigment stones	Rare stones
Japan: Range of Iodine Content	0.05 - 120.64	0.61 - 711.15	0.63 - 153.97
Mean ± SE	9.83 ± 5.55 (22)	112.45 ± 69.75 (13)	25.16 ± 15.10 (10)
Chiang-Mai: Range of Iodine Content	0.03 - 0.14	0.03 - 39.00	ND* - 4.33
Mean ± SE	0.08 ± 0.01 (8)	4.79 ± 4.28 (9)	0.89 ± 0.54 (8)
Bangkok: Range of Iodine Content	0.72 - 157.37	1.50 - 99.69	0.50 - 63.90
Mean ± SE	58.62 ± 49.62 (3)	34.99 ± 32.36 (3)	16.77 ± 15.71 (4)

Values in Parentheses are the number of gallstones analyzed.
* below the limit of detection (<4 ng). 1: P <0.011, 2: P <0.0040.

Table 3. Iodine content of bile from patients living in Japan and Thailand (Chiang Mai and Bangkok) (μg g^{-1}).

	Japan	Chiang-Mai	Bangkok
The number of bile samples analyzed	14	22	12
Range of Iodine	ND* - 331.00	ND - 0.28	0.04 - 336.10
Contents Mean ± SE	26.41 ± 23.57	0.05 ± 0.01	76.64 ± 35.48

* below the limit of detection (< 4 ng). 1: P <0.012.

The mean PBI value for the amount of PBI in sera from Chiang Mai residents was clearly smaller than that in Bangkok patients, as shown in Fig. 3. The mean PBI value in serum from Bangkok patients was significantly greater than those from Chiang Mai residents with goiter, healthy Chiang Mai residents and Chiang Mai residents with gallstones, as shown in Fig. 3. The mean PBI value in serum from Bangkok patients was significantly greater than that in the Japanese.

The mean PBI value in Japanese patients was significantly greater than that of healthy people, as shown in Fig. 3. Because this suggested that the PBI value in Japanese patients was influenced by a contrast medium used for X-ray cholangiography before the operation, we did not perform the Duncan test for Japanese patients.

DISCUSSION

Iodine deficiency in food is a hazardous cause of cretinism which retards the growth and development of young animals. There are about 800 million people with iodine deficiency in the world[7]. As a part of the effort to control IDD, we thought studies of diet and living conditions in relation to iodine intake, and of residents suffering from iodine deficiency over a prolonged period for gallstone formation would be useful. In fact, so far, no such studies have been reported. We investigated the amounts of iodine in gallstones and bile that suggest iodine intake over a period of time until the present. We also investigated the relationship between the amount of iodine in gallstones and bile, and PBI levels.

Table 4. Amount of Protein-Bound Iodine (PBI) in sera from people living in Japan and Thailand (Chiang Mai and Bangkok) (μg dl^{-1}).

	Japan		Chiang Mai			Bangkok
	Healthy People	People with Gallstones	Healthy People	People with Gallstones	People with Goiter	People with Gallstones
Range of PBI						
	2.8-9.4	4.0-22.8	3.0-19.0	1.9-24.0	3.0-10.6	5.0-18.0
Mean ± SE						
	5.6 ± 0.2	9.2 ± 1.1	4.9 ± 0.4	4.5 ± 0.3	5.3 ± 0.3	9.0 ± 1.5
	(n = 89)	(n = 17)	(n = 35)	(n = 69)	(n = 28)	(n = 10)

Values in parentheses are the number of sera analyzed. 1: $P < 1.1 \times 10^{-4}$, 2: $P < 1.1 \times 10^{-5}$, 3: $P < 4 \times 10^{-6}$, 4: $P < 3 \times 10^{-6}$, 5: $P < 9 \times 10^{-6}$.

We studied the iodine content of the gallstones and bile of patients living in Japan (Kawasaki) and Thailand (Chiang Mai and Bangkok) in an attempt to determine the iodine intake from the start of gallstone formation till the present when the stones were removed, and when the bile was obtained. We studied the PBI value for people living in areas where low and normal iodine intake continues.

It is said that the iodine intake of the Japanese is sufficient[10]. It has been reported that Thai people with goiter caused by iodine deficiency in the Chiang Mai district of northern Thailand still outnumber those in Bangkok[11]. Furthermore, female goiter patients account for about 80 per cent of the total according to studies on iodine nutrition at Ban Sam Gong school in Chiang Rai province (northern Thailand)[11]. Analysis of the water and soil in the village of Wang Poong (about 150 km east of Chiang Mai) showed very low levels of iodine, with 1/4 to 1/7.5 of the values found in the Bangkok area. Furthermore, analysis of vegetables from Wang Poong village showed iodine levels of 1/6 to 1/16 of those found in the same types of vegetables obtained in Bangkok. These results indicate that the Wang Poong villagers reside in an environment with a chronic shortage of iodine in both the water and the diet[12]. We thought that Chiang Mai people would have a similar iodine intake to Wang Poong villagers. The presence of goitrogens was not found in a study of villagers from Wang Poong in Thailand[12]. Iodine deficiency is the most important etiological factor in goiter production in this area[11].

The roles of the gastrointestinal tract and liver in the metabolism of thyroid hormones have been discussed[13]. From experiments on oral ingestion of ^{131}I in humans, 3.9 per cent of the administered ^{131}I existed in the liver[14]. This percentage was the largest for any tissues except the thyroid gland, and urine[14]. The ^{131}I labeled thyroxine was transferred from the liver to the gastrointestinal tract mainly by way of the bile, and subsequent gastrointestinal re-absorption could occur[15]. A large proportion of the substances in bile was glucuronide conjugate with a smaller proportion of tetraiodothyropyruvic acid[15]. It is known that gallstones are formed as a consequence of the coagulation of substances contained in bile. Therefore, we thought that the iodine content in gallstones could reflect the iodine intake level over a long period from the start of gallstone formation until the time when stones were excised.

We investigated whether the amount of iodine in gallstones from patients living in Japan, Chiang Mai and Bangkok reflected a difference in the iodine intake among the three areas. The mean values for iodine content in the three types of gallstones (cholesterol, pigment and rare stones) from patients living in Chiang Mai were clearly smaller than in the gallstones of patients living in Japan and Bangkok. We, therefore, conclude that the amounts of iodine in gallstones reflect iodine intake. Moreover, it is clear that the low level of iodine intake of the residents of the Chiang Mai district has continued for a long period until gallstones were removed.

We then investigated whether the amount of iodine in bile from patients living in the three areas reflected a difference in the iodine intake at the time when bile was collected. The mean value for iodine content in bile from Chiang Mai patients was smaller than those in Bangkok and in Japanese patients. This agreed with our finding on iodine in gallstones. Gallstones are formed as a consequence of the coagulation of substances contained in bile. The noncholesterol sterols in gallstones are derived from the sterols in the diet, and their amounts can be altered by variations in dietary content[3]. Our results on iodine levels in gallstones and bile agreed with those reports.

Excretion of (Pheniodol) {sodium ß-(4-hydroxy-3, 5-diiodo-phenyl)-α-phenylpropionate} used as the X-ray contrast medium after intravenous administration was reported[16]. This medium was not present in feces after 8 days, but this medium was still present in urine after 10 days[16]. The mean values for the contrast media (Iohexol, Iopamidol, Iopromide, and Iosimide) eliminated in 24-hour urine were between 85 and 95 per cent of the intravenous dose[17]. The shortest period between the injection of the contrast medium Biliscopin and operation at the Second Hospital, Nippon Medical School, was 2 weeks. Consequently, we thought that the medium we used did not affect the iodine content in gallstones and bile from Japanese patients. Contrast media were not used at the Department of Surgery, Maharaj Nakorn Chiang Mai Hospital and Siriraj Hospital (Bangkok) in Thailand for patients with cholelithiasis.

The comparison of the amount of iodine in gallstones and bile from the three areas, therefore, showed that the iodine content reflects iodine intake. Moreover, this comparative study of the iodine in gallstones and bile from patients living in the three areas revealed that the low level of iodine intake by adults living in Chiang Mai has continued from the start of gallstone formation until now, although iodized salt, iodized oil and iodated water have been distributed in Thailand since 1962, and remarkable results have been obtained[18].

We did not make an analysis of the chemical composition of the iodine in bile and gallstones in the present report.

From an investigation of the amounts of iodine in bile and gallstones, we found that the low iodine condition of Chiang Mai people over a long period has continued to the present. Furthermore, in spite of diligent research into endemic goiter, almost without exception, the primary cause has been identified as iodine deficiency[19]. It is known that goiter caused by iodine deficiency is more widespread among Chiang Mai residents than among Japanese and Bangkok residents. We, therefore, compared the amount of PBIs in the three areas.

The amount of PBI in Chiang Mai residents was clearly smaller than in Bangkok residents. The amount of iodine in cholesterol stones and bile, and PBI of patients living in Bangkok were greater than those of Japanese and Chiang Mai residents. We showed that these amounts reflected the iodine intake of residents.

To avoid artifacts, it was recommended that blood samples for determination of the parameters of thyroid function should not be collected within 10 days of the application of the contrast medium (Biliscopin) we used[20]. The shortest period between the injection of this medium and operation was 2 weeks, but the mean PBI value in Japanese patients was significantly greater than that in healthy Japanese people. It was reported that the determination of PBI is invalidated for several weeks after the administration of Pheniodol[16]. Our result agreed with this report, although the contrast medium we used differed from this medium.

Our results indicate that the iodine intake condition of residents in Chiang Mai has been poor in the past and still is at the present. This evidently low iodine intake causes a low level of PBI in sera. This low iodine intake produces goiter in some people.

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การศึกษาเปรียบเทียบปริมาณไอโอดีนในนิ่วถุงน้ำดีและน้ำดีของผู้ป่วยชาวญี่ปุ่นและผู้ป่วยชาวไทยในจังหวัดเชียงใหม่และกรุงเทพมหานคร

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คณะผู้วิจัยได้ทำการวัดปริมาณไอโอดีนในนิ่วถุงน้ำดีและน้ำดีของผู้ป่วยชาวญี่ปุ่น และผู้ป่วยชาวไทยในจังหวัดเชียงใหม่และกรุงเทพมหานคร โดยวิธี neutron activation analysis ผลการศึกษาพบว่า ค่าเฉลี่ยของปริมาณไอโอดีนในนิ่วถุงน้ำดีทั้ง 3 ชนิด (cholesterol, pigment และ rare) และในน้ำดีของผู้ป่วยชาวเชียงใหม่ มีปริมาณน้อยกว่าผู้ป่วยที่พำนักที่เมืองคาวาซากิและกรุงเทพมหานคร แสดงให้เห็นถึงว่าผู้ป่วยชาวเชียงใหม่มีการรับประทานไอโอดีนปริมาณต่ำ ตั้งแต่เริ่มมีการก่อเกิดนิ่วถุงน้ำดี จนถึงช่วงเวลาที่มีการผ่าตัดนิ่ว รวมทั้งมีการรับประทานไอโอดีนปริมาณต่ำเมื่อมีการเก็บรวบรวมน้ำดี นอกจากนั้นยังพบว่าระดับปริมาณไอโอดีนที่เกาะกับโปรตีน (PBI) ในน้ำเหลืองของกลุ่มตัวอย่างชาวเชียงใหม่ซึ่งมีการรับประทานไอโอดีนปริมาณต่ำเป็นระยะเวลานาน มีค่าน้อยกว่าผู้ป่วยชาวกรุงเทพมหานครซึ่งรับประทานไอโอดีนปริมาณปกติ ส่วนปริมาณ PBI ของกลุ่มตัวอย่างชาวเชียงใหม่ทั้งผู้ป่วยคอพอก กลุ่มตัวอย่างที่มีสุขภาพดี และผู้ป่วยนิ่วถุงน้ำดี พบว่ามีค่าใกล้เคียงกัน

คำสำคัญ : นิ่วถุงน้ำดี, น้ำดี, ปริมาณไอโอดีน, ชาวญี่ปุ่น, ชาวไทย

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