Clinical Biochemistry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Rapid inductively coupled plasma mass spectrometry method to determine iodine in amniotic fluid, breast milk and cerebrospinal fluid

Yutong Zou[a,1], Danchen Wang[a,1], Songlin Yu[a,1], Xinqi Cheng[a], Liangyu Xia[a], Yicong Yin[a], Shaowei Xie[a], Qian Cheng[a], Ling Qiu[a,*], Xiaolan Lian[b,*]

[a] Department of Clinical Laboratory, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Science, Beijing 100730, China
[b] Department of Endocrinology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Science, Beijing 100730, China

ARTICLE INFO

Keywords:
ICP-MS
Iodine
Amniotic fluid
Breast milk
CSF

ABSTRACT

Background: Given that both insufficient and excess maternal iodine have adverse consequences such as poor cognitive performance, delayed physical development and increased fetal and infant mortality, the determination of maternal iodine status is very important. In this study, we established and verified a method involving inductively coupled plasma-mass spectrometry (ICP-MS) technology for the rapid determination of the amniotic fluid iodine concentration (AFIC), breast milk iodine concentration (BMIC) and cerebrospinal fluid (CSF) iodine concentration (CSFIC).

Method: Amniotic fluid, breast milk and CSF were collected from residual samples at Peking Union Medical College Hospital (PUMCH). The linearity, detection limit, precision, recovery, carryover and matrix effect of the testing method using ICP-MS technology were thoroughly evaluated according to the EP-10-A2 evaluation protocol approved by the Clinical and Laboratory Standards Institute (CLSI) guidelines. Furthermore, we evaluated the AFIC, BMIC and CSFIC distributions among clinical patients from PUMCH.

Results: The correlation coefficient (r) was higher than 0.99 (0.995–1.000). The limit of detection (LOD) was 0.233 μg/L, and the limit of quantification (LOQ) was 0.778 μg/L. For amniotic fluid, breast milk and CSF, the assay repeatabilities were 1.5%–1.8%, 1.9%–4.0% and 1.8%–4.0%, respectively, and the within-laboratory coefficient of variations (CV%) over five days were 3.3%–9.2%, 7.2%–8.0% and 3.2%–7.8%, respectively. The recovery rates ranged from 97.7% to 109.8%. Moreover, the median concentrations of iodine in the amniotic fluid, breast milk and CSF of the patients from PUMCH were 176.3 μg/L, 136.0 μg/L, and 81.8 μg/L, respectively.

Conclusion: A rapid, stable and accurate method that incorporates ICP-MS technology for the determination of iodine concentration was established for amniotic fluid, breast milk and CSF in this study.

1. Introduction

Iodine, an important trace element, is necessary for the synthesis of thyroid hormones (THs), which are essential for normal growth, development and metabolism [1]. Iodine deficiency is the largest single reason for preventable brain damage worldwide [2], and iodine deficiency disorders can affect individuals throughout their entire lifespans, especially during pregnancy. In 2011, approximately 1.8 billion individuals (28.5%) worldwide had inadequate iodine intake [3], and maternal iodine intake was insufficient in China [4]. The demand for iodine increases by 50% in pregnancy, and pregnant women are therefore more vulnerable to iodine insufficiency [5]. Iodine insufficiency can lead to endemic cretinism, spontaneous abortion, preterm delivery and stillbirth or adversely affect offspring development, with potentially lifelong consequences [6,7]. For the fetus, an adequate supply of iodine from the mother is particularly important during the second trimester of pregnancy and continues to be important in children up to 3 years of age [2]. When the iodine supply is inadequate,

Abbreviations: AFIC, amniotic fluid iodine concentration; BMIC, breast milk iodine concentration; CSF, cerebrospinal fluid; CSFIC, cerebrospinal fluid iodine concentration; UIC, urine iodine concentration; ICP-MS, inductively coupled plasma-mass spectrometry; CV, coefficient of variation; LOD, limit of detection; LOQ, limit of quantification; THs, thyroid hormones; PUMCH, Peking Union Medical College Hospital; CLSI, Clinical and Laboratory Standards Institute; SD, standard deviation

* Corresponding authors.
E-mail addresses: lingqiubj@163.com (L. Qiu), lianxl@pumch.cn, lianxl@pumch.com (X. Lian).
[1] These authors contributed equally to this article.

https://doi.org/10.1016/j.clinbiochem.2020.03.009
Received 15 December 2019; Received in revised form 20 February 2020; Accepted 16 March 2020

congenital abnormalities, perinatal mortality or irreversible mental retardation can occur [8]. Therefore, there is an urgent need to monitor and evaluate maternal iodine concentrations.

Although the WHO recommends using the median urine iodine concentration (UIC) as a biomarker for the assessment of maternal iodine status [2], previous studies have reported controversial results [9,10]. In utero, the fetus directly uses THs synthesized by the mother during the first 20 weeks of gestation [11] and then obtains iodine from the mother to produce THs independently of the mother, and these THs are also stored in the fetal thyroid to partly support the demand for THs after birth [12]. Thus, the amniotic fluid iodine concentration (AFIC) can be a direct or better index than the maternal UIC to represent the fetal iodine status. Additionally, the breastfed infant is more vulnerable to iodine deficiency because they completely depend on the iodine supply of his mother [13]. Some studies have noted that the mammary gland can change the fractional uptake of circulating iodine when dietary consumption varies, especially in iodine-sufficient regions [14], which means that some pregnant women could be overtreated due to their low UICs even if they can actually supply enough iodine to their infants via breast milk. Excessive intake can also cause disorders for both mothers and children, such as the Wolff–Chaikoff effect [15] and autoimmune thyroiditis [16]. Therefore, the breast milk iodine concentration (BMIC) is considered as a more sensitive and accurate measurement for the maternal iodine status and the amount they can supply for their children [17]. Although there is no research that clearly indicates the role that iodine in cerebral spinal fluid (CSF) plays in the human body, we still pay attention to this index. Because the substances secreted and emanated from tissues can be readily accessible in body fluids [18], the cerebrospinal fluid iodine concentration (CSFIC) may be closely associated with not only adjacent tissues but also whole-body functions [19]. It was also reported that iodine can induce inflammation by regulating the expression of several proteins such as IL-17 [20], therefore, CSFIC may reflect abnormalities in the human body, especially inflammation of the brain.

Several methods are commonly used to determine iodine concentrations. The Sandell–Kolthoff (S–K) method is recommended as the routine and standard method for iodine monitoring, and widely used in hundreds of laboratories. Even if an automated method involving routine biochemical analyzers has been developed in recent years, all methods based on the S–K principle have obvious limitations, such as the requirement for a high temperature, the long digestion time, and the release of toxic products [21]. Additionally, an ion-selective electrode method and high-performance liquid chromatography were developed for the determination of free iodine, but these methods are also complicated, and incomplete iodine extraction can lead to a low recovery [22]. Due to its higher accuracy, precision and lower detection limit, inductively coupled plasma-mass spectrometry (ICP-MS) has recently been considered to be the best way to simultaneously quantify many elements in biological fluids [23], and the gold standard for the determination of low iodine concentrations in complex matrices such as breast milk [24].

To date, only a few studies have focused on the establishment of methods to determine the BMIC [25,26], and no studies have been conducted to identify methods to determine the AFIC or CSFIC. Because the method using ICP-MS technology has been developed and applied in the clinical laboratory of PUMCH [27], we aimed to establish and evaluate a very rapid testing method using ICP-MS technology for the determination of the AFIC, BMIC and CSFIC in this study.

2. Materials and methods

2.1. Machines and materials

The analysis was performed using an iCAP-Q ICP-MS, assisted by the ASX-520 CETAC Automatic Sampling Instrument (Thermo Scientific, Waltham, MA). Additionally, the Sorvall ST16R Centrifuge was purchased from Thermo Scientific. The ICP-MS equipment was tuned before sampling, and the collision-kinetic energy discrimination (KED) mode was used to monitor the signals at 127I and 185Re. Some detailed parameters of the ICP-MS equipment are as follows: plasma power, 1550 W; nebulizer gas flow (Ar), 1 L/min; spray chamber temperature, 2.7 °C; CCT1 flow (He), 4.8 mL/min; and KED, 3 V.

Standard potassium iodide (KI, purity: 99.6%, batch number: 100194-200502) and internal standard rhenium (Re, 10^6 μg/L, in 10% hydrochloric acid medium, batch number: 14040372) were purchased from the National Research Center for Certified Reference Materials of China. Pure isopropyl alcohol (batch number: 182060) and pure ammonia solution (batch number: 711706) were purchased from Fisher Scientific (Pittsburgh, PA). Tuning solution (with 1 μg/L lithium, cobalt, uranium and indium in 2% HNO_3 and 0.5% HCl) was purchased from Thermo Scientific. Ultrapure deionized water was produced by a Millipore Advantage Water Purifier (Billerica, MA) in our laboratory.

We poured 30 mL isopropanol and 1 mL ammonia solution (14 mmol/L) into a clean plastic bottle, and ultrapure deionized water was added to 2 L at a constant volume. The prepared 1.5% isopropanol and 7 mmol/L ammonia solution was used as the diluent in this method. With the weighing method, standard KI and the diluent were weighed accurately and concentrated to 10 mg/L reserved solution by a densitometer. The solution was divided into aliquots, sealed and cryopreserved at −80 °C. Before every testing session, it was gradually diluted to 1 μg/L, 5 μg/L, 10 μg/L, 25 μg/L, 50 μg/L and 100 μg/L with the diluent as a standard solution for the calibration curve. With the three-way valve, Re was diluted to 20 μg/L with the diluent as an internal standard solution to correct the matrix effect and stability of plasma between samples and standard solutions. Method blank samples were prepared by mixing 500 μL ultrapure water with 4.5 mL diluent. The 7 μmol/L hydrous ammonium diluted with ultrapure deionized water, as the washing solution, could effectively eliminate the memory effect of iodine in this study [27].

2.2. Sample collection

All samples were collected from the residuals of patient samples in the clinical laboratory of PUMCH, and mixed into several pooled fluids of different iodine concentrations. According to the distribution of iodine in patients, we obtained pooled amniotic fluid with three different concentrations, pooled breast milk with two different concentrations and pooled CSF with four different concentrations. These pooled samples were stored at 4 °C, and all measurements were finished within one week. Before each analysis, all samples and controls were equilibrated to room temperature (25 °C) and thoroughly mixed. Furthermore, 53 amniotic fluid and matched plasma samples, which were drawn from the same person within one day, and 150 CSF and matched serum samples were collected from the clinical laboratory in PUMCH.

2.3. Preparation and analysis

Two hundred microliters of amniotic fluid, CSF samples or control solutions of two different concentrations were directly transferred into a clean 10-mL plastic tube and mixed with 1.8 mL diluent, resulting in a 10-fold dilution. Before dilution, breast milk samples were stored at 4 °C to spontaneously split into two layers, and 200 μL aqueous fractions were drawn and diluted in the same way. If the test result was higher than the upper limit of the linear range, the sample was additionally diluted and retested. Then, the tubes were centrifuged at 1500 rpm/min for 3 min to remove the precipitate.

We used an internal standard method to quantify substances. With the concentration of the standard solution as the X-axis and the corrected response intensity as the Y-axis, the linear equation was obtained. Then, the actual concentration of the sample could be obtained by introducing the corrected strength into the equation. Before each measurement, standard curves were redrawn. The final concentration

was the average of three repeated measurements, corrected by calibration curve and multiplied by a dilution factor. It took 1.56 min to analyze a sample, including 40 s for reading, 30 s for suction and 60 s for washing, which meant that approximately 150 samples could be measured within eight hours.

2.4. Method validation

Linearity evaluation was carried out with polynomial regression of the calibrator concentrations on the theoretical peak area ratios of the target substance and the internal standard. The linearity was considered to be satisfactory when the R value was higher than 0.99. The LOD and LOQ were defined as 3 times and 10 times the standard deviation (SD) of blank samples, respectively, multiplied by the slope of the regression curve [28].

Precision was evaluated by analyzing all pooled samples for five successive days, and each pooled sample was analyzed five times per day according to the CLSI EP15-A3 guidelines. Due to the lack of certified reference materials, accuracy was evaluated by the calculation of recovery. Recovery was calculated by spiking 100 μL pooled human fluids with 100 μL calibrators of two different concentrations and comparing the iodine concentrations after subtracting the value of the initial pooled samples with that of the added calibrators. The accuracy was considered to be satisfying if the recovery was within 90%–110%.

After measuring a high-concentration sample (H), a reagent blank was tested in triplicate as L_1, L_2 and L_3. The carryover rate was defined as L_1 minus L_3 divided by H minus L_3. The background signal of iodine in the diluent and the Re in both the diluent and samples were measured to evaluate the interference of the reagent with the samples.

2.5. Method application

Furthermore, to evaluate the distribution of iodine in patients from PUMCH, we analyzed matched amniotic fluid and plasma from 53 pregnant women, as well as matched CSF and serum from 150 clinical patients in the clinical laboratory of PUMCH. Since methods for the measurement of iodine in urine, serum and breast milk have been established and developed in our laboratory, we directly obtained and evaluated all BMIC results during from 2015 to 2019 from the Hospital Information System (HIS) and Laboratory Information System (LIS) of PUMCH. We also collected and measured matched serum and plasma samples from 40 patients who had blood drawn on the same day in the clinical laboratory of PUMCH to evaluate the consistency between serum and plasma samples.

This study was reviewed and approved by the Ethics Committee of PUMCH of the Chinese Academy of Medical Sciences (S-K766).

2.6. Statistical analysis

Excel 2010 (Microsoft Inc., Redmond, WA, USA) and SPSS 20.0 software (IBM Inc., Armonk, NY, USA) were used for analyses. The Kolmogorov-Smirnov test was applied to evaluate the distribution. Normally distributed data were presented as the means ± SDs, and non-normally distributed data were presented as the medians (quartiles). The Pearson or Spearman rank correlation (r) was used to assess the correlations between two measurements. A nonparametric test was applied for comparisons across different groups, and differences were considered statistically significant when the p-values were < 0.05.

3. Results

3.1. Linearity and LOD/LOQ

Excellent linearity was observed in this study. All R-values were higher than 0.99 (0.995–1.000) with the standard concentration ranging from 1 μg/L to 100 μg/L, which is equivalent to 10–1000 μg/L in undiluted samples. The LOD was 0.233 μg/L, and the LOQ was 0.778 μg/L, which are sensitive enough for clinical application.

Table 1
The precision of the ICP-MS method.

	Mean ± SD (μg/L)	Repeatability (%)	Within-laboratory CV (%)
amniotic $fluid_L$	58.3 ± 5.4	1.8	9.2
amniotic $fluid_M$	280.2 ± 9.8	1.5	3.3
amniotic $fluid_H$	783.2 ± 24.7	1.6	3.3
$lactic_L$	145.6 ± 11.0	1.9	7.2
$lactic_H$	185.9 ± 15.6	4.0	8.0
CSF_L	5.8 ± 0.5	4.0	7.8
CSF_{M1}	48.1 ± 1.5	2.0	3.3
CSF_{M2}	174.0 ± 6.0	2.1	3.2
CSF_H	5373.5 ± 176.6	1.8	3.4

3.2. Precision and accuracy

The evaluation of precision is shown in Table 1. The repeatability was 1.5%–1.8%, 1.9%–4.0% and 1.8%–4.0%, and the within-laboratory coefficient of variation (CV%) over the period of five days was 3.3%–9.2%, 7.2%–8.0% and 3.2%–7.8% for amniotic fluid, breast milk and CSF, respectively. As shown in Table 2, the recovery rates were 99.3% and 101.9% for amniotic fluid, 109.8% and 109.0% for breast milk, and 97.7% and 101.8% for CSF, which represented satisfactory accuracy and implied that the use of Re as an internal standard could compensate for the possible ion suppression or strengthening from the matrix. Furthermore, two levels of NIST SRM 3668 were analyzed to evaluate and verify the accuracy of this method for the determination of urinary and serum iodine in our previous study [27]. Also, a method comparison with the classic S–K principle-based method was conducted. Regression analysis showed a correlation of 0.984 with a slope of 1.0419 and an intercept of –7.2069. The CUSUM test and Bland–Altman plots also suggested fair consistency between the two methods, which implied the good accuracy of this method using ICP-MS technology in this study.

3.3. Carryover and matrix effect

Respectively, the carryover rates were 0.046% (0.018%–0.062%), 0.068% (0.052%–0.088%) and 0.010% (0.001%–0.017%) for amniotic fluid, breast milk and CSF, which were negligible for clinical application. The iodine content in the diluent was 0.454 μg/L, and the Re contents in the diluent, amniotic fluid, breast milk and CSF samples were 0.19%, 0.07%, 0.13% and 0.00% of the internal standard, which would not interfere with clinical measurements. Furthermore, the memory effect was also evaluated and deemed negligible in our previous study [27].

Table 2
The recovery of the ICP-MS method.

Analytes	Added calibrator (μg/L)	Mean (μg/L)	SD	Recovery (%)	Bias (%)
Amniotic fluid	50	49.67	0.42	99.3	0.66
	100	101.88	0.89	101.9	−1.88
Breast milk	100	109.80	1.63	109.8	−9.80
	200	217.90	4.38	109.0	−8.95
CSF	100	97.69	9.65	97.7	2.31
	200	203.63	4.73	101.8	−1.81

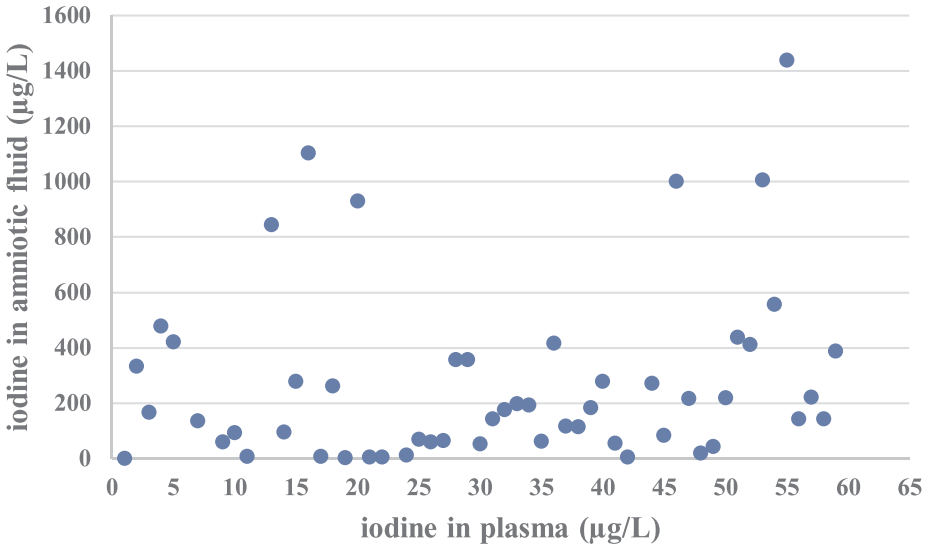

Fig. 1. Correlation of iodine levels in amniotic fluid and plasma The figure shown iodine concentrations in amniotic fluid and matched plasma of 53 pregnant women. Spearman correlation analysis calculated r = 0.174 and p = 0.214.

3.4. Clinical application

The median AFIC of 53 pregnant women (age: 35 ± 5 years) in Beijing was 176.3 μg/L (range: 61.4 μg/L–372.3 μg/L), while the median iodine concentration of matched plasma was 77.2 μg/L (range: 69.8 μg/L–83.5 μg/L). The correlation between the iodine content of amniotic fluid and that of plasma was weak (r = 0.174; p = 0.214) (Fig. 1). Unlike the stable distribution of plasma iodine, the individual variation of iodine in amniotic fluid was very large, which indicated that the level of iodine accessible to the fetus was notably different among different individuals and needed to be monitored.

The BMIC distribution was evaluated in 547 lactating women (age: 34 ± 4 years) for five consecutive years in PUMCH using data from the HIS and LIS. The median BMIC was 136.0 μg/L, and the values ranged from 89.0 μg/L to 222.0 μg/L. There was no significant difference between the different years or age groups, while the iodine distribution of hyperthyroidism patients was significantly higher than that of hypothyroidism patients (median: 185.0 μg/L vs 129.5 μg/L, p = 0.018). Similar to the AFIC distribution, the individual variation of iodine in breast milk was also large.

As shown in Fig. 2, the median CSFIC of 150 patients (age: 43 ± 19 years), including 62 males and 88 females without thyroid diseases, from PUMCH was 81.8 μg/L (range: 22.3 μg/L–306.6 μg/L), while the median iodine concentration of matched serum was 59.2 μg/L (range: 46.7 μg/L–93.1 μg/L). The correlation between CSFIC and iodine in serum was weak (r = 0.192; p < 0.05). The individual variation in iodine in CSF was also wider than that in serum iodine.

Furthermore, matched serum and plasma samples from 40 patients from PUMCH were analyzed. Since the serum and plasma iodine distribution was normal, the Pearson correlation was calculated. With r equal to 0.988, the consistency between the two types of samples was deemed excellent (Fig. 3).

4. Discussion

In this study, we established and evaluated a very rapid and accurate method using ICP-MS technology by diluting samples with an ammonia solution for the determination of iodine in amniotic fluid, breast milk and CSF. Linearity, LOD/LOQ, precision, recovery, carryover and matrix effects were thoroughly evaluated and verified, and the whole preparation and analysis of this method was maneuverable, time-effective and safe. However, due to the lack of certified reference materials mainly for amniotic fluid and CSF, the accuracy of this method was evaluated in a less reliable way.

Using Re as an internal standard, the possible ion suppression or strengthening from the matrix could have been compensated for. However, there are other studies using different elements, such as tellurium, germanium and antimony, as internal standards, and different studies had different results [26,29]. Since the stability of Re as an internal standard for the determination of iodine in this ICP-MS method has been found not only in this study but also in its long-term application in the clinical laboratory of PUMCH, we still chose it as our internal standard. Notably, further studies need to be conducted to explore the best choice for the determination of the concentrations of different elements using different methods.

As shown in our previous study and another study [26,27], the autosampler wash station and the uptake tubing/nebulizer/spray chamber were two significant areas showing memory effects within the ICP-MS. With 7 μmol/L hydrous ammonium diluted with ultrapure deionized water for washing for one minute between every sample, the memory effect of iodine in the autosampler wash station and the pipeline system could be effectively eliminated. The quarter bend and the cone were also regularly cleaned with disposable dust removal paper dipped with the diluent or ultrasonic cleaning equipment to eliminate memory effects and possible contaminations such as carbon. Furthermore, high-purity Ar (0.8 L/min, Shiyuan Jingye, China) was used for plasma generation and nebulization, and to purge the samples before every analysis to remove the volatile carbon. Instrument checking and maintenance were regularly conducted by professional engineers.

To our knowledge, few studies have focused on iodine in breast milk, and none have focused on iodine in amniotic fluid or CSF. In this research, we not only established a rapid and accurate method using ICP-MS technology for the determination of the AFIC, BMIC and CSFIC, but also evaluated their distribution and emphasized the importance of monitoring and measuring them. Some cross-sectional studies have reported inconsistencies between BMIC and UIC in lactating women [9,10], and this result was also found in this study. Compared with the stable distribution of iodine in serum and plasma, the wider distribution of the AFIC, BMIC and CSFIC may show increased sensitivity and accuracy for the determination of iodine insufficiency or excess and other associated disorders, such as endoplasmic reticulum stress, which can induce the overexpression of inflammatory factors [30]. Additionally, as the main source of iodine for fetuses and infants, both amniotic fluid and breast milk can directly reflect iodine status, and effective treatment can be provided in a timely manner. In addition, the UIC can be affected by many factors, such as changes in intake, and can vary in a

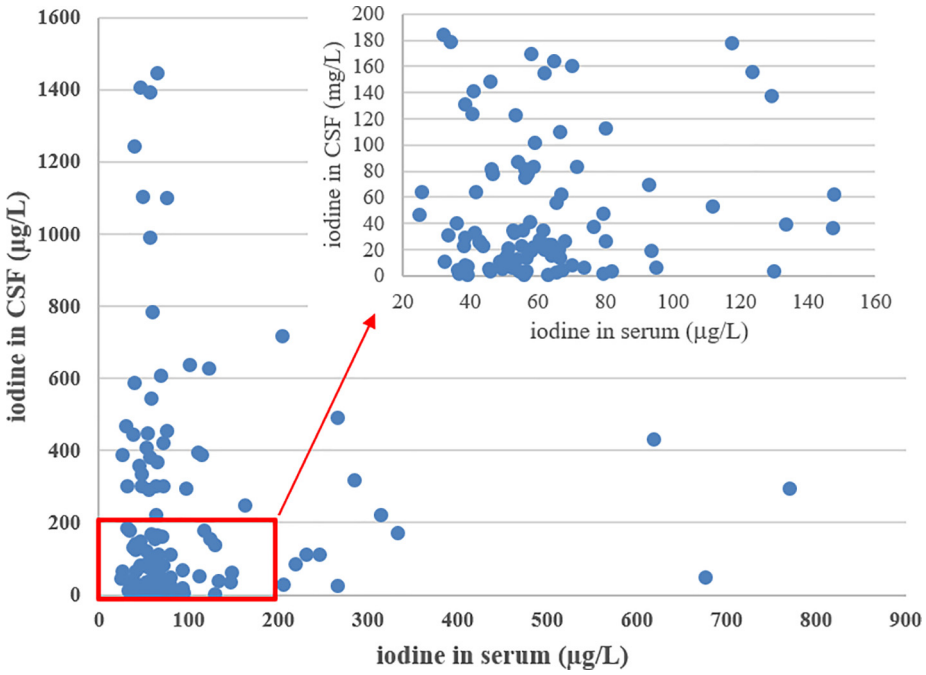

Fig. 2. Correlation of iodine levels in CSF and serum CSF: cerebrospinal fluid. The figure shown iodine concentrations in CSF and matched serum of 150 patients without thyroid diseases. Spearman correlation analysis calculated r = 0.192 and p < 0.05.

short time, even if creatinine measurements were used to correct the results. Therefore, our study suggested that all three indexes could better reflect the disorders of iodine in the human body, and that AFIC and BMIC could be better indexes to monitor the concentration of iodine in both mothers and their offspring.

There were also limitations in our study. As a simpler pre-preparation method, we centrifuged and diluted the samples prior to analysis, which could lead to some iodine remaining adhered to the organic portion of the samples [31]. We did not evaluate the concentration difference between the supernatant fluid and the whole sample in this study. A previous study [26] showed that the iodine concentrations in the fatty fraction of breast milk (145 ± 48 g/L) were considerably higher than those in the aqueous fraction (88.5 ± 2.1 g/L), which meant that the determination of the iodine concentration in breast milk in this study was not the same as the actual concentration. However, the iodine determination in the aqueous fraction was quite stable, which suggested its ability to represent the concentration of the whole sample. The method using ICP-MS technology to determine the iodine concentration in breast milk has been applied in the clinical laboratory of PUMCH and appears fairly related to clinical features. Furthermore, amniotic fluid, breast milk and CSF are all complex matrices consisting of many bioactive components and nutrients. With the direct dilution method using an ammonia solution and Re as the internal standard, whether it is enough to correct some non-spectral interferences requires further evaluation and verification.

In conclusion, a very rapid and accurate method using ICP-MS technology was established to determine the iodine concentration in amniotic fluid, breast milk and CSF. Of note, a larger continuous sample should be included in future studies to evaluate the clinical efficacy of the method using ICP-MS technology and the iodine concentrations in

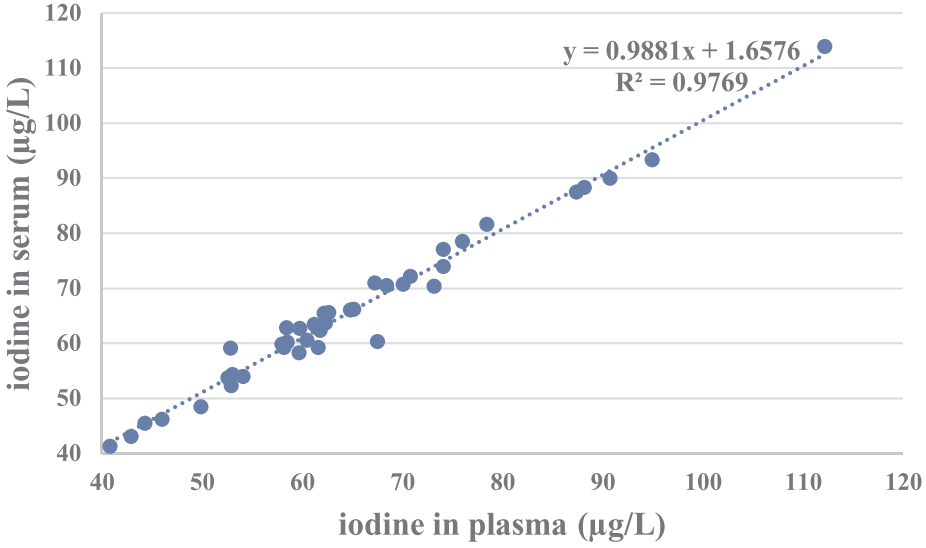

Fig. 3. Correlation of iodine levels in serum and plasma. The figure shown iodine concentrations in serum and matched plasma of 40 patients from clinical laboratory. Pearson correlation analysis calculated $r = 0.988$, and regression equation was $y = 0.9881x + 1.6576$, with $R^2 = 0.9769$.

amniotic fluid, breast milk and CSF in Chinese people.

Funding

This work was funded by research grants from the National Natural Science Foundation of China (81702060) (http://www.nsfc.gov.cn/) and the Key Research and Development Program of Ningxia (2018BFG02010).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2020.03.009.

References

[1] M.B. Zimmermann, P.L. Jooste, C.S. Pandav, Iodine-deficiency disorders, Med. J. 372 (2008) 1251–1262.
[2] Organization WH, UNICEF 2001 Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers. Geneva, Switzerland, WHO, Department of Nutrition for Health and Development: 2nd ed.
[3] M. Andersson, V. Karumbunathan, M.B. Zimmermann, Global iodine status in 2011 and trends over the past decade, J. Nutr. 142 (4) (2012) 744–750.
[4] G. Mao, W. Zhu, M. Zhe, Y. Wang, X. Wang, X. Lou, Z. Wang, Iodine deficiency in pregnant women after the adoption of the new provincial standard for salt iodization in Zhejiang Province, China, BMC Pregnancy Childbirth 18 (1) (2018) 313.
[5] M.B. Zimmermann, The importance of adequate iodine during pregnancy and infancy, World Rev Nutr Diet 115 (2016) 118–124.
[6] M.B. Zimmermann, Iodine deficiency, Endocr Rev 30 (4) (2009) 376–408.
[7] M.B. Zimmermann, The effects of iodine deficiency in pregnancy and infancy, Paediatr Perinat Epidemiol 26 (Suppl 1) (2012) 108–117.
[8] M. Fereja, S. Gebremedhin, T. Gebreegziabher, M. Girma, B.J. Stoecker, Prevalence of iodine deficiency and associated factors among pregnant women in Ada district, Oromia region, Ethiopia: a cross- sectional study, BMC Pregnancy Childbirth 18 (1) (2018) 257.
[9] M.J. Costeira, P. Oliveira, S. Ares, G.M. de Escobar, J.A. Palha, Iodine status of pregnant women and their progeny in the Minho Region of Portugal, Thyroid 19 (2) (2009) 157–163.
[10] M. Andersson, I. Aeberli, N. Wüst, A.M. Piacenza, T. Bucher, I. Henschen, M. Haldimann, M.B. Zimmermann, The Swiss iodized salt program provides adequate iodine for school children and pregnant women, but weaning infants not receiving iodine-containing complementary foods as well as their mothers are iodine deficient, J. Clin. Endocrinol. Metab. 95 (12) (2010) 5217–5224.
[11] D. Glinoer, The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status, Best Pract. Res. Clin. Endocrinol. Metab. 18 (2) (2004) 133–152.
[12] F. Azizi, P. Smyth, Breastfeeding and maternal and infant iodine nutrition, Clin. Endocrinol. (Oxf) 70 (5) (2009) 803–809.
[13] H.M. Mulrine, S.A. Skeaff, E.L. Ferguson, A.R. Gray, V.J. Pierre, Breast-milk iodine concentration declines over the first 6 mo postpartum in iodine-deficient women, Am. J. Clin. Nutr. 92 (4) (2010) 849–856.
[14] S. Dold, M.B. Zimmermann, A. Aboussad, M. Cherkaoui, Q. Jia, T. Jukic, Z. Kusic, A. Quirino, Z. Sang, T.O. San Luis, E. Vandea, M. Andersson, Breast milk iodine concentration is a more accurate biomarker of iodine status than urinary iodine concentration in exclusively breastfeeding women, J. Nutr. 147 (4) (2017) 528–537.
[15] W.R. Heymann, Potassium iodide and the wolff-chaikoff effect: relevance for the dermatologist, J. Am. Acad. Dermatol. 42 (3) (2000) 490–492.
[16] W. Teng, Z. Shan, X. Teng, H. Guan, Y. Li, D. Teng, Y. Jin, X. Yu, C. Fan, W. Chong, F. Yang, H. Dai, Y. Yu, J. Li, Y. Chen, D. Zhao, X. Shi, F. Hu, J. Mao, X. Gu, R. Yang, Y. Tong, W. Wang, T. Gao, C. Li, Effect of iodine intake on thyroid diseases in China, N. Engl. J. Med. 354 (26) (2006) 2783–2793.
[17] P. Nazeri, H. Dalili, Y. Mehrabi, M. Hedayati, P. Mirmiran, F.J. Azizi, Breast milk iodine concentration rather than maternal urinary iodine is a reliable indicator for monitoring iodine status of breastfed neonates, Biol. Trace Elem. Res. 185 (1) (2018) 71–77.
[18] Shao C, Li M, Li X, Wei L, Zhu L, Yang F, Jia L, Mu Y, Wang J, Guo Z, Zhang D, Yin J, Wang Z, Sun W, Zhang Z, Gao Y 2011 A Tool for Biomarker Discovery in the Urinary Proteome: A Manually Curated Human and Animal Urine Protein Biomarker Database. Mol Cell Proteomics 10 (11):M111.010975.
[19] M. Zhao, Y. Yang, Z. Guo, C. Shao, H. Sun, Y. Zhang, Y. Sun, Y. Liu, Y. Song, L. Zhang, Q. Li, J. Liu, M. Li, Y. Gao, W. Sun, A comparative proteomics analysis of five body fluids: plasma, urine, cerebrospinal fluid, amniotic fluid and saliva, Proteomics Clin. Appl. 12 (6) (2018) e1800008.
[20] N. Figueroa-Vega, M. Alfonso-Pérez, I. Benedicto, F. Sánchez-Madrid, R. González-Amaro, M. Marazuela, Increased circulating pro-inflammatory cytokines and Th17 lymphocytes in Hashimoto's thyroiditis, J. Clin. Endocrinol. Metab. 95 (2) (2010) 953–962.
[21] G. Giovacchini, L. Giovanella, A. Haldemann, U. Staub, F.G. Füchsel, P. Koch, Potentiometric measurement of urinary iodine concentration in patients with thyroid diseases with and without previous exposure to non-radioactive iodine, Clin. Chem. Lab. Med. 53 (11) (2015) 1753–1760.
[22] L.H. Pacquette, A.M. Levenson, J.J. Thompson, Determination of total iodine in infant formula and nutritional products by inductively coupled plasma/mass spectrometry: single-laboratory validation, J. AOAC Int. 95 (1) (2012) 169–176.
[23] Jean-Pierre Goullé, L. Mahieu, J. Castermant, Metal and metalloid multi-elementary ICP-MS validation in whole blood, plasma, urine and hair: reference values, Foren. Sci. Int. 153 (1) (2005) 39–44.
[24] L.H. Pacquette, A.M. Levenson, J.J. Thompson, D. Dowell, Total iodine in infant formula and nutritional products by inductively coupled plasma/mass spectrometry: first Action. 14, J. AOAC Int. 96 (4) (2012) 798–801.
[25] S. Dold, J. Baumgartner, C. Zeder, A. Krzystek, J. Osei, M. Haldimann, M.B. Zimmermann, M. Andersson, Optimization of a new mass spectrometry method for measurement of breast milk iodine concentrations and an assessment of the effect of analytic method and timing of within-feed sample collection on breast milk iodine concentrations, Thyroid 26 (2) (2016) 287–295.
[26] D. Huynh, S.J. Zhou, R. Gibson, L. Palmer, B. Muhlhausler, Validation of an optimized method for the determination of iodine in human breast milk by inductively coupled plasma mass spectrometry (ICPMS) after tetramethylammonium hydroxide extraction, J. Trace Elem. Med. Biol. 29 (2015) 75–82.
[27] S. Yu, Y. Yin, Q. Cheng, J. Han, X. Cheng, Y. Guo, D. Sun, S. Xie, L. Qiu, Validation of a simple inductively coupled plasma mass spectrometry method for detecting urine and serum iodine and evaluation of iodine status of pregnant women in Beijing, Scand. J. Clin. Lab Invest. 78 (6) (2018) 501–507.
[28] P.W.J.M. Boumans, Measuring detection limits in inductively coupled plasma emission spectrometry using the "SBR—RSDB approach"—I. A tutorial discussion of the theory, Spectrochim. Acta Part B Atomic Spectrosc. 46 (1991) 431–445.
[29] P.A. Fecher, I. Goldmann, A. Nagengast, Determination of iodine in food samples by inductively coupled plasma mass spectrometry after alkaline extraction, J. Anal. Atomic Spectrom. 13 (9) (1998) 977–982.
[30] X. Chen, H. Huang, B. Liang, J. Zhou 2018 Abnormal Iodine Nutrition-Induced ER Stress Upregulates MCP-1 Expression Through P38/MAPK Signaling Pathway in Thyroid Cells. Biol. Trace Elem Res. Dec. 11.
[31] D.R. Novo, J.E. Mello, F.S. Rondan, A.S. Henn, P.A. Mello, M.F. Mesko, Bromine and iodine determination in human saliva: Challenges in the development of an accurate method, Talanta 191 (2019) 415–421.