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Thyroglobulin as a Biomarker of Iodine Deficiency: A Review

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Background: Thyroglobulin, produced exclusively by the thyroid gland, has been proposed to be a more sensitive biomarker of iodine status than thyrotropin or the thyroid hormones triiodothyronine and thyroxine. However, evidence on the usefulness of thyroglobulin (Tg) to assess iodine status has not been extensively reviewed, particularly in pregnant women and adults.

Summary: An electronic literature search was conducted using the Cochrane CENTRAL, Web of Science, PubMed, and Medline to locate relevant studies on Tg as a biomarker of iodine status. Since urinary iodine concentration (UIC) is the recommended method to assess iodine status in populations, only studies that clearly reported both Tg and UIC were included. For the purpose of this review, a median Tg $<13\,\mu g/L$ and a median UIC $\geq 100\,\mu g/L$ (UIC $\geq 150\,\mu g/L$ for pregnant women) were used to indicate adequate iodine status. We excluded studies conducted in subjects with either known thyroid disease or those with thyroglobulin antibodies. The search strategy and selection criteria yielded 34 articles of which nine were intervention studies. The majority of studies (six of eight) reported that iodine-deficient pregnant women had a median Tg $\geq 13\,\mu g/L$. However, large observational studies of pregnant women, including women with adequate and inadequate iodine status, as well as well-designed intervention trials that include both Tg and UIC, are needed. In adults, the results were equivocal because iodine-deficient adults were reported to have median Tg values of either <13 or $\geq 13\,\mu g/L$. Only studies in school-aged children showed that iodine-sufficient children typically had a median Tg $<13\,\mu g/L$. Some of the inconsistent results may be partially explained by the use of different methodological assays and failure to assess assay accuracy using a certified reference material.

Conclusions: These data suggest that Tg does hold promise as a biomarker of iodine deficiency. However, it is associated with limitations. A median Tg cutoff of $13\,\mu g/L$ warrants further investigation, particularly in adults or pregnant women, as there is a lack of both observational and intervention studies in these groups.

Introduction

Iodine is needed by the thyroid gland to produce thyroid hormones required for normal growth and development (1). Insufficient iodine intake causes iodine deficiency, which affects millions of people worldwide (2). Iodine deficiency is most commonly assessed by measuring urinary iodine concentration (UIC) because approximately 90% of dietary iodine is excreted in the urine (3). Due to large intra- and interindividual variation, UIC cannot be used to assess iodine status in individuals and is only appropriate for groups (4). A median UIC $<100\,\mu g/L$ in children and nonpregnant adults indicates iodine deficiency (5). Since UIC only assesses recent iodine intake (i.e., days) (5), a low UIC in a single urine sample does not necessarily indicate iodine deficiency in that individual (4). In addition to UIC, other measures of iodine status include thyroid volume, thyrotropin (TSH), triiodothyronine (T3), and thyroxine (T4); each of these indices has limitations. Thyroid volume reduces gradually (i.e., months to years) in previously iodine-deficient subjects (6). TSH, T3, and T4 concentrations typically fall within the normal range in mildly iodine-deficient populations of school-aged children and adults (7,8) such as those who live in developed countries such as the United States, the United Kingdom, Australia, and New Zealand. Another biomarker of iodine status sensitive to an intermediate change (i.e., weeks to months) in iodine intake would be useful.

Thyroglobulin (Tg) plays an important role in the synthesis of thyroid hormones T3 and T4 (9). It is a glycoprotein comprising two 330 kDa protein chains synthesized in the thyrocyte (10). After synthesis, Tg is transported and stored in the follicular colloid of the thyrocyte (11). In the follicular lumen, the tyrosine residues of Tg undergo iodination to

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produce mono- (MIT) and di-iodotyrosines (DIT) catalyzed by thyroid peroxidase (12) and hydrogen peroxide (13). Subsequent coupling of these iodotyrosines produces T3 and T4 (14,15). Tg is pinocytosed into the thyroid cell (16) and undergoes proteolysis by lysosomes to release T3 and T4 (17), which are then secreted into the bloodstream (18).

When iodine intake is insufficient, low circulating levels of T4 stimulate the release of thyrotropin-releasing hormone from the pituitary gland, which subsequently increases the production of TSH. In addition to increasing the synthesis and proteolysis of Tg, TSH also stimulates the growth and division of the follicular cells, which causes the thyroid gland to enlarge (i.e., goiter) (19). In iodine deficiency, an increased amount of Tg is released into the blood (20), which is positively correlated with thyroid volume (21). For example, healthy adults have a mean Tg concentration ranging from 5 to 14 μg/L (22–27). In contrast, adults with endemic goiter have a mean Tg ranging from 94 to 208 μg/L (28–30). Recently, experts attending a National Institutes of Health workshop (31) recommended that Tg be used in the evaluation of iodine status.

The most common use of Tg is to monitor the treatment of patients with differentiated thyroid cancer (DTC) (32). Several review articles have focused on Tg monitoring in patients with DTC (11,33,34) or the performance of different assays used for monitoring DTC (35,36). The evidence on the usefulness of Tg in patients with DTC is well established. However, data on the effectiveness of Tg to assess iodine status in healthy populations is scarce. This review will report on: first, the analytical issues of Tg methods; second, observational studies measuring Tg to assess iodine status in healthy populations of pregnant women, newborns, children, and adults; and third, intervention studies investigating the effect of iodine supplementation on Tg in populations of pregnant women, newborns, children, and adults. This information will be used to determine if Tg can be used as a biomarker to assess iodine status.

Search Strategy

We conducted an electronic literature search using the Cochrane CENTRAL, Web of Science, PubMed, and Medline (OvidSP) to locate relevant studies published in English between January 1960 and October 2013 using Tg as a biomarker of iodine status. We used the following combined keywords: serum thyroglobulin, thyroglobulin, blood, children, infants, adults, pregnant women, pregnancy, maternal iodine status, iodine status, iodine deficiency, iodine insufficiency, iodine sufficiency, and iodine supplementation. We also located additional studies from references in the retrieved articles. Since UIC is the recommended biomarker of iodine status in populations (5), only studies that clearly report both Tg and UIC were included. We excluded studies conducted in subjects with either known thyroid disease or those with thyroglobulin antibodies (TgAb) because such subjects can have falsely low or high Tg that are not caused by insufficient iodine intake. The search resulted in 34 articles (i.e., 38 studies) being selected (Table 1). Of these, nine were randomized controlled trials, two were nonrandomized controlled trials, three were cohort observational studies, 23 were cross-sectional studies (10 multicenter), and one was a monitoring report of iodization programs that included a measurement before the introduction of iodized salt to a measurement after the introduction of iodized salt. In order to investigate the consistency of the relationship between iodine status as determined by UIC and Tg more clearly, for those studies that reported this information for more than one group, we considered each of these groups separately (i.e., one study of pregnant women and their newborns (37); one study of pregnant women and adults (38); one study of children and adults (30); three studies of children living in different regions (39) or countries (40,41); and seven studies of adults living in different regions (21,25,42–44) or countries (45,46)).

Discussion

Methods to measure Tg concentration

Tg can be measured using either immunometric assay (IMA) or radioimmunoassay (RIA) (35). Of the 34 articles measuring Tg (Table 1), the predominant Tg assay used was RIA (27%), followed by various IMAs, including immunoluminometric assay (22%), immunochemiluminescence assay (21%), immunoradiometric assay (12%), fluoroimmunoassay (10%), enzyme-linked immunosorbent assay (3%), electrochemiluminescence immunoassay (3%), and not reported (3%). Only one article (21) measured Tg using two different types of assays. A dried blood spot method using fluoroimmunoassay (FIA) (40) has been developed by Zimmermann *et al.* to assess Tg in children (5). Though Tg obtained from a dried blood spot was well correlated with serum samples ($r = 0.98$, $p < 0.0001$) in healthy children ($n = 29$) (47), this relationship has yet to be validated in populations of adults including pregnant women. Furthermore, the dried blood spot method has not been reproduced in other laboratories.

Studies of Tg using RIA were first published in the 1960s. Several of these early studies (48–50) reported that Tg was undetectable in some healthy participants. For example, a small study conducted by Hjort *et al.* (48) used a RIA with a limit of detection (LoD) of 50 μg/L and found that Tg was undetected in all 12 healthy subjects, indicating that these subjects would likely have had Tg concentrations $\leq$50 μg/L. In contrast, Torrigiani *et al.* (49) detected Tg in 60–70% of healthy subjects ($n = 111$) when they used a RIA with a LoD of 10 μg/L; van Harle *et al.* (50) detected Tg in 74% of healthy subjects ($n = 95$) using a RIA with a LoD of 1.6 μg/L. Therefore, early RIAs had a relatively poorer functional sensitivity compared with first-generation Tg assays (0.5–1.0 μg/L) developed in the 1980s (51,52) and second-generation Tg assays ($\leq$0.1 μg/L) in use since the early 2000s (53,54); studies using first-generation Tg assays (21,55) did not report undetectable Tg in any healthy subjects.

Tg has been reported to be method dependent (56–58), and the interassay variation can vary between 43% and 65% in healthy subjects (35,57,59). To overcome interassay variation and allow for comparisons between studies, a certified Tg reference material (i.e., CRM-457) has been produced as a quality-control material for assay standardisation (60). Some but not all types of Tg assays have been standardized against CRM-457 in-house by the manufacturers (61). However, Tg CRM-457 only reduces interassay variation by 14–27% (59). It is suggested that this is because current Tg assays are unable to identify the heterogeneity of Tg epitopes (52,62). Of

Table 1. Types of Tg and TgAb Assays in Studies Assessing UIC and Tg in Various Population Groups

Studies	*Year*	*Tg assay*	*TgAb assay*
Pregnant women			
Observational			
Pedersen *et al*. (38)[a]	1988	RIA	RIA
Laurberg *et al*. (76)	1994	Yes (NR)	NA
Eltom *et al*. (78)	2000	RIA	NA
Costeira *et al*. (79)	2010	RIA	RIA
Brucker-Davis *et al*. (74)	2012	IRMA	NA
Raverot *et al*. (75)	2012	IRMA	NA
Andersen *et al*. (37)[b]	2013	ILMA	RIPA
Brough *et al*. (77)	2013	ICMA	AA
Intervention			
Liesenkötter *et al.* (80)	1996	RIA	NA
Nøhr *et al*. (81)	2000	ILMA	RIPA
Santiago *et al*. (82)	2013	ICMA	NA
Newborns			
Observational			
Andersen *et al*. (37)[b]	2013	ILMA	RIPA
Intervention in pregnancy			
Pedersen *et al.* (85)	1993	ICMA	Tg recovery
Glinoer *et al.* (86)	1995	RIA	RIA
Children			
Observational			
Simsek *et al*. (39)	2003	ICMA	NA
Zimmermann *et al*. (40)[c]	2006	FIA	RIA
Bayram *et al*. (30)[d]	2009	RIA	RIA
Skeaff *et al*. (73)	2012	RIA	NA
Skeaff and Lonsdale-Cooper (55)	2013	ECLIA	NA
Zimmermann *et al*. (41)	2013	FIA	RIA
Intervention			
Benmiloud *et al.* (89)	1994	ILMA	NA
Zimmermann *et al*. (47)	2003	FIA	RIA
Zimmermann *et al.* (40)[c]	2006	FIA	NA
Gordon *et al*. (64)	2009	RIA	RIA
Adults			
Observational			
Fenzi *et al.* (25)	1985	IRMA	HA
Gutekunst *et al*. (45)	1986	ILMA	NA
Pedersen *et al*. (38)[a]	1988	RIA	RIA
Hintze *et al*. (90)	1991	ELISA	RIA
Laurberg *et al*. (46)	1998	ILMA	RIPA
Knudsen *et al*. (44)	2001	ILMA	RIA
Thomson *et al*. (91)	2001	RIA	NA
Rasmussen *et al*. (43)	2002	ILMA	RIA
Teng *et al*. (42)	2006	ICMA	ICMA
Bayram *et al*. (30)[d]	2009	RIA	RIA
Vejbjerg *et al*. (21)	2009	ILMA & FIA	RIA & FIA
Cahoon *et al*. (72)	2013	ICMA	RIA & ICMA
Intervention			
Thomson *et al*. (63)	2009	ICMA	ICMA
Soriguer *et al*. (92)	2011	IRMA	RIA

[a]Included pregnant women and adults.
[b]Included pregnant women and newborns.
[c]Counted as one article.
[d]Included children and adults.

AA, agglutination assay; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; FIA, fluoroimmunoassay; HA, hemagglutination assay; ICMA, immunochemiluminescence assay; ILMA, immunoluminometric assay; IRMA, immunoradiometric assay; NA, not assessed; NR, not reported; RIA, radioimmunoassay; RIPA, radioimmunoprecipitation assay; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; UIC, urinary iodine concentration.

34 articles measuring Tg (Table 1), only four (40,41,63,64) used Tg CRM-457 as an external quality control.

Another issue with regard to the measurement of Tg is the presence of TgAb. When a RIA is used, a subject positive for TgAb will most likely have a higher Tg value, while IMA tends to lower Tg in TgAb-positive subjects (33,65). Thus, subjects who have a positive test for TgAb should be excluded from the results if Tg is used as a biomarker of iodine status in a population. In adults, studies (66–69) have found that 3–13% of adults have TgAb. However, in children, the prevalence of TgAb is lower (70,71), and Zimmermann *et al.* (47) suggest that screening for TgAb in this age group is not necessary. Twenty-two of 34 studies measured TgAb prior to Tg measurement (Table 1). Of these, the predominant TgAb assay used was a RIA (58%), followed by the radioimmunoprecipitation assay (14%), immunochemiluminescence assay (12%), Tg recovery (5%), hemagglutination assay (5%), agglutination assay (5%), and FIA (2%). Only two articles (21,72) measured TgAb using two different types of TgAb assays.

In a large multicenter study of healthy children aged 5–14 years, Zimmermann *et al.* reported a reference range for Tg of 4–40 μg/L as determined by FIA (40). This is similar to reference ranges reported for adults of 3–40 μg/L using both RIA and IMA methods (65,68). We did not identify any consistent effects of age or sex on Tg. Only one study (73) reported that Tg decreased with advancing age. In 1994, the WHO/ICCIDD/UNICEF suggested that a median Tg concentration <10 μg/L indicates adequate iodine status in populations of school-age children. However, in 2007, the WHO/ICCIDD/UNICEF, although acknowledging that Tg could be used an indicator of iodine status, did not provide a cutoff for Tg. More recently, Zimmermann *et al.* (41) conducted a large multicenter study of children ($n=2512$) from 12 countries with varying iodine status, and suggest that a median Tg concentration <13 μg/L and/or <3% of Tg values >40 μg/L be used as a biomarker of adequate iodine status in children and, with caution, in adults. To date, the cutoff of 13 μg/L and/or <3% of Tg values >40 μg/L has not been examined in younger children or pregnant women. Because no studies have reported the percentage of Tg values >40 μg/L in populations, for the purpose of this review, a median Tg <13 μg/L and a median UIC ≥ 100 μg/L (UIC ≥ 150 μg/L for pregnant women) were used to indicate adequate iodine status.

Pregnant women

Eight observational studies measuring Tg in iodine-deficient pregnant women aged between 15 and 46 years were identified (Table 2). Six of eight studies (37,38,74–77) reported that iodine-deficient pregnant women (either first, second, or third trimester, or at delivery) had a median Tg ≥ 13 μg/L (range 16–67 μg/L). Two of the eight studies (78,79) assessed Tg concentration in iodine-deficient women throughout their pregnancy (i.e., in each trimester); in one study (79), a median Tg <13 μg/L was observed in all three trimesters, and in one study (78), a Tg ≥ 13 μg/L was reported in the first and third trimesters, but it was <13 μg/L in the second trimester. Although six of eight studies (37,38, 74,75,77,79) collected information on the use of iodine supplements in pregnancy, of these, only one study (37) reported that the Tg concentration of women taking iodine supplements was significantly lower compared with women who did not take supplements (i.e., difference of ~ 15 μg/L). We are unaware of any published studies of pregnant women with adequate iodine status that include measures of both UIC and Tg.

Three intervention studies investigating the effect of iodine supplementation on Tg in iodine-deficient pregnant women were identified (Table 3). One of the studies (80) assessed Tg concentration in the first trimester before supplementation and then again at two weeks postpartum; one study (81) assessed Tg in the first and third trimesters; and one study (82) assessed Tg in all three trimesters and again 12–24 weeks postpartum. Tg concentrations in women in the first trimester (i.e., at baseline before supplementation) ranged from 13 to 25 μg/L, and postpartum, in women that had received any type of additional iodine (i.e., supplements or iodized salt), Tg ranged from 8 to 18 μg/L. Of the two studies with postpartum data (80,82), only one study (80) reported that women taking iodine supplementation in pregnancy had a postpartum median Tg <13 μg/L. However, the interpretation of these findings is confounded by differences in study designs, including a lack of a placebo group, relatively small sample sizes ($n=66$–131), varying levels and types of supplemental iodine (iodized salt or supplements containing 150–300 μg iodine per day), duration of follow-up (2–24 weeks postpartum), and use of different Tg assays.

In summary, it appears that the majority studies typically report that iodine-deficient pregnant women have a median Tg ≥ 13 μg/L. Furthermore, iodine supplementation does not consistently decrease Tg below this cutoff either during pregnancy or postpartum, although this may reflect inadequate supplementation, as UIC did not reach recommended cutoffs. More large observational studies of pregnant women, including women with adequate and inadequate iodine status, as well as good intervention trials that include both Tg and UIC, are required before conclusions can be drawn about the usefulness of Tg as a biomarker of iodine status in pregnancy. Another consideration is whether Tg in pregnancy needs to be trimester specific, as is suggested for thyroid hormones such as TSH (83) and T4 (84).

Newborns

Three studies that measured Tg in cord blood from newborns were identified (Tables 4 and 5). Two of the three studies (85,86) were supplementation trials of mothers during pregnancy. The Tg concentration of newborns born to mothers receiving a placebo or who did not take supplements in pregnancy ranged from 62 to 113 μg/L, while in the newborns of mothers who took iodine supplements, Tg ranged from 31–65 μg/L. The usefulness of measuring Tg in newborn cord blood is questionable. A more commonly used and relatively accessible biomarker to assess iodine status in newborns is neonatal TSH collected by heel prick two to three days after birth (5).

Children

Six observational studies measuring Tg in children aged between 5 and 14 years were identified (Table 4). Four studies (30,39,41,73) found that iodine-deficient children had a median Tg ≥ 13 μg/L (range 13–59 μg/L), while two studies

Table 2. Observational Studies Measuring Tg in Relation to Iodine Status in Pregnant Women

Authors	Age (years)[a]; n[b]; country	Trimesters	UIC[c] (μg/L)	Tg[c] (μg/L)	Findings	Comments
Pedersen *et al.* (38)	21–38; $n=20$; Denmark	3rd	52[d]	67	Suggested high Tg might be due to an increase in iodine intake in pregnancy	Women did not take iodine supplements.
Laurberg *et al.* (76)	NR; $n=20$; Denmark, Sweden, and Iceland	At term	Denmark 39 Sweden 78 Iceland 118	Denmark 29.7 Sweden 15.9 Iceland 15.9	Women living in Denmark had a significantly higher median Tg than those living in Sweden and Iceland ($p<0.05$)	No data on supplement use
Eltom *et al.* (78)	20–40; $n=48$; Sweden and Sudan	1st, 2nd, and 3rd	*Trimesters*: 1st 2nd 3rd Swedish 89 89 76 Sudanese 38 25 38	*Trimesters*: 1st 2nd 3rd Swedish 15.5 10.5 18.0 Sudanese 27.5 25.0 30.0	Sudanese women had a significantly higher median Tg than the Swedish women in the 1st ($p<0.05$), 2nd ($p<0.001$), and 3rd trimesters ($p<0.01$).	Women were followed throughout pregnancy; no data on supplement use
Costeira *et al.* (79,93)[e]	29.9; $n=118$; Portugal	1st, 2nd and 3rd trimester, and 1 year PP	*Trimester* 1st 65 2nd 57 3rd 70 1 year PP 40	*Trimester* 1st 11.0 2nd 11.0 3rd 12.7 1 year PP 9.7	Tg in 1st and 2nd trimester increased from 11 to 13 μg/L in 3rd trimester	Women were followed throughout pregnancy; they did not take iodine supplements
Brucker-Davis *et al.* (74)	18–40; $n=110$; France	1st	116	17.4	Tg was not correlated with UIC	Women did not take iodine supplements
Raverot *et al.* (75)	15.3–45.7; $n=228$; France	1st, 2nd, and 3rd	*Trimester* 1st 69 2nd 91 3rd 91	*Trimester* 1st 16.6 2nd 15.7 3rd 16.2	Tg in the 1st, 2nd, or 3rd trimesters were not significantly different ($p>0.05$)	Women did not take iodine supplements
Andersen *et al.* (37)	27.3; $n=140$; Denmark	At term	No supplements NR Supplements NR All 41[f]	No supplements 29.3[6] Supplements 14.0[6] All 22.9[6]	Women taking supplements (i.e., 150 μg I/day) had a significantly lower Tg than those not taking supplements ($p<0.001$)	
Brough *et al.* (77)	31; $n=70$; New Zealand	3rd trimester or breast-feeding for >3 weeks	3rd trimester 85 PP 74	3rd trimester 15.9 PP 13.9	Tg was not correlated with UIC in women in the 3rd trimester and at PP	70% pregnant women and 36% breastfeeding women used iodine supplements ranging from 100 to 150 μg I/day

[a]Range used unless mean reported.
[b]Only subjects with no known thyroid disease or negative for TgAb were included.
[c]Median used unless mean or geometric mean reported.
[d]UIC reported as μg/g creatinine.
[e]Tg was reported in Costeira *et al.* (79); UIC and the data on supplement use were reported in Costeira *et al.* (93). These two studies were counted as one study (79).
[f]Geometric mean.
I, iodine; PP, postpartum.

TABLE 3. INTERVENTION STUDIES INVESTIGATING THE EFFECT OF IODINE SUPPLEMENTATION ON TG IN PREGNANT WOMEN

Authors	*Age (years)*[a]*; country*	*Study design*[b]	*Group*[c]	*UIC (μg/L)*[d]				*Tg (μg/L)*[d]				*Findings*	*Comments*
Liesenkötter *et al.* (80)	21–40; Germany	Women ($n=108$) randomized to receive either iodine supplements (300 μg I/day) or no iodine until 0.5 months PP		*1st trimester*[e]	*0.5 months PP*[e]			*1st trimester*[g]	*0.5 months PP*[g]			Women taking iodine supplements did not have a significantly lower Tg in the 1st trimester and 0.5 months PP	Unequal group sizes (38 women in iodine supplemented group while 70 women in no iodine group); 14 women had goiter previously
			0 μg	55	50[f]			16.6	13.5				
			300 μg	49	105			16.5	8.3				
Nøhr *et al.* (81)	18–35; Denmark	Women ($n=66$) randomized to receive a vitamin and mineral tablet with 0 (placebo) or 150 μg I daily until 9 months PP		*Trimesters*				*Trimesters*				Women taking supplements had a significantly lower Tg than women taking placebo in the 3rd trimester ($p=0.001$)	All women were thyroid peroxidase antibody-positive; PP data for Tg was available from a figure only
				1st	3rd			1st	3rd				
			0 μg	51	53			17.1	19.4				
			150 μg	51[g,h]	105			18.0[f,g]	14.1				
Santiago *et al.* (82)	31; Spain	Women ($n=131$) randomized to receive either IS, 200 μg, or 300 μg I daily until 3–6 months PP		*Trimesters*[g]			*3–6 months PP*	*Trimesters*[g]			*3–6*[g] *months PP*	There was no significant difference in Tg within groups ($p=0.13$) or between groups ($p=0.21$)	All pregnant women were not iodine supplemented before enrolling in the study; 32% of pregnant women took IS at least 1 year before their pregnancy
				1st	2nd	3rd		1st	2nd	3rd			
			IS	145	130	144	NA	21.3	22.7	22.1	16.7		
			200 μg	117	177	166	NA	25.4	21.6	24.8	14.9		
			300 μg	137	222	212	NA	13.0	8.4	13.9	18.1		

[a]Range used unless mean reported.
[b]Only subjects with no known thyroid disease or negative for thyroglobulin antibody were included.
[c]Actual quantity of iodine from supplement; Liesenkötter *et al.* (80) and Santiago *et al.* (82) used iodine supplements in the form of KI.
[d]Median used unless mean reported.
[e]UIC reported as μg/g creatinine.
[f]Estimated value from a figure.
[g]Mean.
[h]Estimated value from a table.
IS, iodized salt; KI, potassium iodide.

TABLE 4. OBSERVATIONAL STUDIES MEASURING TG IN RELATION TO IODINE STATUS IN NEWBORNS, CHILDREN, AND ADULTS

Authors	Age (years)[a]; n[b]; country	UIC[c] (μg/L)		Tg[c] (μg/L)		Findings	Comments
Newborns							
Andersen *et al.* (37)	Newborns; $n=140$; Denmark	No supplements Supplements All	— — 44[d]	No supplements Supplements All	61.6[d] 31.1[d] 50.0[d]	Infants of mothers taking iodine supplements of 150 μg I/day had a significantly lower Tg than infants born to mothers not taking supplements ($p<0.001$)	A lag period (i.e., 5 days) between the collection of urine from infant and cord blood samples
Children							
Simsek *et al.* (39)	8–10; $n=727$; Turkey	*Urban*[e] Düzce Bolu *Rural* Yiğilca Mudurnu Akçakoca Gerede	 96 108 13 46 71 75	*Urban*[e] Düzce Bolu *Rural* Yiğilca Mudurnu Akçakoca Gerede	 10.9 8.4 59.1 27.2 14.2 12.8	Severely iodine deficient children had a significantly lower Tg than children with mild to moderate iodine deficiency and iodine sufficient children ($p<0.001$); Tg was negatively correlated with urinary iodine ($r=-0.27$, $p<0.001$).	
Zimmermann *et al.* (40)	5–14; $n=710$; 5 countries	*Countries:* Bahrain Peru South Africa China Switzerland All	 177 161 266 234 130 198	*Countries:* Bahrain Peru South Africa China Switzerland All	 19.3 11.6 18.4 13.3 11.2 14.5	Purpose of this study was to determine the Tg reference interval of children (i.e., 4–40 μg/L). Of the five countries, children from three countries had high Tg despite being iodine sufficient	
Bayram *et al.* (30)	10–14; $n=109$; Turkey	51[e]		49.9[e]		Nongoitrous children had a significantly lower Tg than goitrous children ($p<0.001$); Tg was negatively correlated with urinary iodine ($r=-0.611$, $p<0.05$)	
Skeaff *et al.* (73)	5–14; $n=1153$; New Zealand	*Age (years)* 5–7 8–10 11–14 All	 63 67 75 68	*Age (years)* 5–7 8–10 11–14 All	 16.2 12.5 11.1 12.9	Iodine sufficient children had a significantly lower Tg than iodine deficient children ($p<0.001$)	
Skeaff and Lonsdale-Cooper (55)	8–10; $n=147$; New Zealand	113		10.8		UIC indicated adequate iodine status but Tg indicated mild iodine deficiency, suggesting that the children still had thyroid enlargement	Correction factor of 0.588 used to adjust for intraassay variation in Tg values between ECLIA and RIA method

(*continued*)

TABLE 4. (CONTINUED)

Authors	Age (years)[a]; n[b]; country	UIC[c] (μg/L)		Tg[c] (μg/L)		Findings	Comments
Zimmermann *et al.* (41)	6–12; $n=2512$; 12 countries	*Countries:*		*Countries[d]:*		Tg followed a U-shaped curve from severely deficient to excessive iodine intake as assessed by UIC	
		Morocco	16	Morocco	25.5		
		Tajikistan	52	Tajikistan	10.9		
		Switzerland	137	Switzerland	10.5		
		Philippines	154	Philippines	13.1		
		Bahrain	178	Bahrain	18.0		
		Peru	197	Peru	11.5		
		Croatia	205	Croatia	11.3		
		China	235	China	12.6		
		Indonesia	235	Indonesia	9.8		
		Paraguay	257	Paraguay	13.6		
		South Africa	282	South Africa	18.6		
		Tanzania	338	Tanzania	17.6		
		All	151	All	13.3		
Adults							
Fenzi *et al.* (25)	38.8; $n=840$; Italy	Endemic goiter	44[e,f]	Endemic goiter	49.9[e]	Adults living in an iodine sufficient area had a significantly lower Tg than adults living in an endemic goiter area ($p<0.01$); Tg was negatively correlated with urinary iodine ($r=-0.185$, $p=0.001$)	
		Iodine sufficient	88[e,f]	Iodine sufficient	9.5[e]		
Gutekunst *et al.* (45)	≥17; $n=1291$; Germany and Sweden	Germany	63[g]	Germany	43.0	German adults had a significantly lower Tg than Swedish adults ($p<0.0001$)	
		Sweden	141[g]	Sweden	21.2		
Pedersen *et al.* (38)	22–37; $n=20$; Denmark	42[g]		32.5			Six adults were positive for TgAb but were not included in Tg results
Hintze *et al.* (90)	60–97; $n=286$; Germany	64[g]		8.9		Adults with no goiter had a significantly lower median Tg than adults with goiter ($p<0.001$)	
Laurberg *et al.* (46)	66–70; $n=523$; Denmark and Iceland	Denmark	38	Denmark	15.5	In Denmark (Jutland), 14.2% adults living had Tg >50 μg/L; while in Iceland, 3.4% adults had Tg >50 μg/L	Differences in Tg between adults living Denmark and Iceland not reported
		Iceland	150	Iceland	9.5		
Knudsen *et al.* (44)	18–65; $n=3759$; Denmark	Copenhagen	68	Copenhagen	11.3	Adults living in Copenhagen had a significantly lower Tg than adults living in Aalborg ($p<0.001$)	Adults included those who were taking iodine supplements.
		Aalborg	53	Aalborg	15.2		

(*continued*)

TABLE 4. (CONTINUED)

Authors	Age (years)[a]; n[b]; country	UIC[c] (μg/L)			Tg[c] (μg/L)			Findings	Comments
Thomson *et al.* (91)	18–49; $n=233$; New Zealand	54			5.1			Tg was negatively correlated with UIC ($r=-0.210$, $p=0.003$)	
Rasmussen *et al.* (43)	18–65; $n=4649$; Denmark	Copenhagen		68	Copenhagen		11.5	Adults living in Copenhagen had a significantly lower Tg than adults living in Aalborg ($p<0.001$); Tg was negatively correlated with iodine intake	Adults included pregnant women (1.3%) and lactating women (1.8%)
		Aalborg		53	Aalborg		15.4		
Teng *et al.* (42)	14–95; $n=3761$; China		*Baseline*	*5 years*		*Baseline*	*5 years*	Adults living in Zhangwu city had a significantly lower Tg than adults living in Huanghua and Pangshan cities at baseline ($p<0.001$) and 5 years ($p<0.001$)	
		Panshan	103	97	Panshan	7.7	11.7		
		Zhangwu	375	350	Zhangwu	6.0	9.1		
		Huanghua	615	635	Huanghua	6.4	10.2		
Bayram *et al.* (30)	28.7; $n=109$; Turkey	31[e]			68.9[e]			Adults with no goiter had a significantly lower Tg than adults with goiter ($p<0.001$)	
Vejbjerg *et al.* (21)	18–65; $n=4649$; Denmark		IS			IS		Adults living in Copenhagen and Aalborg had a significantly lower Tg after introduction of mandatory iodization of salt ($p<0.001$)	This study included two cross-sectional samples
			Before	*After*		*Before*	*After*		
		Copenhagen	61	99	Copenhagen	11.5	9.1		
		Aalborg	45	86	Aalborg	15.4	9.3		
Cahoon *et al.* (72)	10–33; $n=7890$; Belarus	NR			UIC (μg/L)			Adults with UIC 100–2120 μg/L had a significantly lower median Tg than subjects with UIC of 50–100, 20–50, and 0–20 μg/L ($p<0.001$)	
					0–20		12.1		
					20–50		9.7		
					50–100		8.0		
					100–2120		6.6		

[a]Range used unless mean reported.
[b]Only subjects with no known thyroid disease or negative for TgAb.
[c]Median used unless mean or geometric mean reported.
[d]Geometric mean.
[e]Mean.
[f]UIC reported as urinary iodine excretion (μg/day).
[g]UIC reported as μg/g creatinine.

TABLE 5. INTERVENTION STUDIES INVESTIGATING THE EFFECT OF IODINE SUPPLEMENTATION ON TG IN NEWBORNS, CHILDREN, AND ADULTS

Authors	Age (years)[a]; country	Study design[b]	UIC (μg/L)[c]		Tg (μg/L)[c]		Findings	Comments
Newborns								
Pedersen *et al.* (85)	Newborns; Denmark	Data obtained from infants ($n=54$) born to mothers who were randomized to receive either 200 μg I/day or no iodine supplement	0 μg 200 μg	27 64	0 μg 200 μg	67 38	Infants of mothers supplemented with 200 μg I/day had a significantly lower Tg than infants born to mothers not taking supplements ($p=0.005$)	A lag period (i.e., 5 days) between the collection of urine from infants and cord blood samples
Glinoer *et al.* (86)	Newborns; Belgium	Data obtained from infants ($n=180$) born to mothers who were randomized to receive either 131 μg I/day, 131 μg + 100 μg L-T4, or placebo	0 μg 131 μg 131 μg+L-T4	43[d] 77[d] 80[d]	0 μg 131 μg 131 μg+L-T4	113[d] 65[d] 52[d]	Infants of mother supplemented with 131 μg I and 131 μg I+L-T4 had a significantly lower Tg than infants of mothers taking placebo ($p<0.001$)	Cord blood used
Children								
Benmiloud *et al.* (89)	6–11; Algeria	Children ($n=169$) randomized to receive either a single dose of iodized poppy seed oil orally (120, 240, 480, or 960 mg I) or intramuscular injection of 480 mg I for 150–395 days		*Baseline* / *5 months*		*Baseline* / *5 months*	All groups of children had a decrease in Tg after 5 months	The study only reported Tg values for baseline and 5 months
			Orally					
			120 mg	27 / 41		98.5 / 31.0		
			240 mg	25 / 99		98.5 / 22.0		
			480 mg	25 / 109		175.0 / 24.0		
			960 mg	25 / 132		77.0 / 14.0		
			Injection					
			480 mg	27 / 1185		62.0 / 12.0		
Zimmermann *et al.* (47)	6–15; Morocco	Children ($n=377$) received IS for 12 months		*Baseline* / *Months* 5 / 12		*Baseline* / *Months* 5 / 12	Children had a significantly lower Tg after using IS for 12 months ($p<0.001$)	
				17 / 181 / 165		24.5 / 6.2 / 4.4		
Zimmermann *et al.* (40)	5–14; Morocco	Children ($n=86$) received IS for 10 months		*Baseline* / *Months* 5 / 10		*Baseline* / *Months* 5 / 10	Children had a significantly lower Tg after using IS for 10 months ($p<0.001$)	
				12 / 74 / 102		49.0 / 13.0 / 8.0		
Gordon *et al.* (64)	10–13; New Zealand	Children ($n=184$) randomized to receive either placebo or 150 μg I tablet daily for 28 weeks		*Baseline* / *7 months*		*Baseline* / *7 months*	Children taking iodine tablets had a significantly lower Tg after 7 months ($p<0.001$)	Main outcome was cognition
			0 μg	62 / 81		15.2 / 11.6		
			150 μg	66 / 145		16.5 / 8.5		

(*continued*)

TABLE 5. (CONTINUED)

Authors	*Age (years)*[a]*; country*	*Study design*[b]		*UIC (μg/L)*[c]		*Tg (μg/L)*[c]		*Findings*	*Comments*
Adults									
Thomson *et al.* (63)	60–80; New Zealand	Adults ($n = 100$)		*Baseline*[e]	*3 months*[e]	*Baseline*[e]	*3 months*[e]	Both groups taking iodine supplements had a significantly lower Tg after 3 months compared to baseline ($p < 0.01$)	
		randomized to receive	0 μg	49	44	14.4	14.0		
		either placebo, 100 μg	Se	45	44	15.4	15.2		
		Se, 80 μg I, or 100 μg	80 μg	33	71	21.2	15.4		
		Se + 80 μg I daily for 12 weeks	Se + 80 μg	63	84	17.3	14.7		
Soriguer *et al.* (92)	34.9; Spain	A cross-over study of		*Baseline*[d,f]	*2 months*[d,f]	*Baseline*[d]	*2 months*[d]	There was no difference in Tg between the groups after supplementation	A cross-over study with 1 month washout; adults recruited were regular users of IS
		adults ($n = 30$)	100 μg	192	233	3.9	0.8		
		randomized to 100,	200 μg	140	230	7.6	8.8		
		200, or 300 μg I/day	300 μg	201	377	6.8	4.0		

[a]Range used unless mean reported.
[b]Only subjects with no known thyroid disease or negative for TgAb.
[c]Median used unless mean or geometric mean reported.
[d]Mean.
[e]Geometric mean.
[f]UIC reported as urinary iodine excretion (μg/day).
Se, selenium.

(40,41) reported that iodine-sufficient children also had a median Tg ≥13 μg/L (range 13–19 μg/L). Four of six studies (39–41,55) reported that children with adequate iodine status had a median Tg <13 μg/L. However, one study (39) reported that iodine-deficient children had a median Tg <13 μg/L. The study by Zimmermann *et al.* (41) included 2512 children from 12 countries with severe iodine deficiency (i.e., median UIC <20 μg/L), mild iodine deficiency (i.e., median UIC 50–99 μg/L), adequate iodine status (i.e., median UIC 100–299 μg/L), and iodine excess (i.e., median UIC ≥300 μg/L). It showed that median Tg appeared to follow a U-shaped curve with the nadir at an UIC of 100–300 μg/L. When iodine intake is very high, excess iodide transiently inhibits the activity of thyroid peroxidase and proteolysis of Tg, which subsequently reduces the synthesis and secretion of thyroid hormones (i.e., the Wolff–Chaikoff effect) (87). However, when prolonged excess iodine intake occurs, Tg could increase because the thyroid gland fails to escape from the Wolff–Chaikoff effect (88). Nonetheless, close examination of data reported by Zimmermann *et al.* (41) suggests that the relationship between UIC and Tg is highly variable. It is not known, however, how much of this variability is associated with UIC and/or Tg because a single UIC can be confounded by the hydration status, dietary intake, and diurnal variation (4).

Four intervention studies investigating the effect of iodine supplementation on Tg in iodine-deficient children aged 5–14 years for a duration of 5–12 months were identified (Table 5). Three of the four studies (40,47,64) were more than six months long, and reported that median Tg decreased significantly and fell below 13 μg/L when UIC increased from <100 to ≥100 μg/L. The remaining study (89) included five treatment groups but not a control group, was only five months long, and had fewer children in each group. In the three groups where the children became iodine sufficient, Tg was <13 μg/L in only one group.

The majority of observational and intervention studies in school children appear to support the 13 μg/L cutoff proposed by Zimmermann *et al.* (41) to assess iodine status in this age group. However, the relationship between UIC and Tg is not always consistent, suggesting that Tg alone should not be used to assess iodine status in this group.

Adults

Twelve observational studies measuring Tg in adults aged between 18 and 97 years were identified (Table 4). Seven studies (21,25,30,38,43,45,46) showed that iodine deficient adults had a median Tg ≥13 μg/L (range 16–69 μg/L), while only one study (45) reported that iodine-sufficient adults had a median Tg ≥13 μg/L. However, 8 of 12 studies (21,25,42–44,72,90,91) reported that adults who were categorized as iodine deficient had a median Tg <13 μg/L. One of these studies (42) included adults with iodine excess (i.e., median UIC ≥300 μg/L) who, in contrast to the findings of Zimmermann *et al.* (41) in schoolchildren, had a median Tg <13 μg/L.

Two intervention studies investigating the effect of iodine supplementation on Tg in adults were identified (Table 5). One study included iodine-sufficient middle-aged adults supplemented with additional iodine for 8–12 weeks (92); at baseline, the median Tg was <13 μg/L, which decreased, but not significantly, after supplementation. Another study of older adults (60–80 years) (63) who were moderately iodine deficient reported a median Tg ≥13 μg/L at baseline. Although iodine status improved, the subjects remained mildly iodine deficient, which likely explains that, although Tg concentration significantly decreased after supplementation, it remained ≥13 μg/L.

Based on these observational studies, it is difficult to conclude that the Tg cutoff of 13 μg/L suggested by Zimmermann *et al.* (41) for children can be used as a biomarker of iodine status in adults. Furthermore, there are no randomized placebo-controlled trials in adults that have shown an improvement in iodine status (indicated by an increase in baseline UIC from <100 to ≥100 μg/L) results in a concomitant fall in Tg concentration from ≥13 to <13 μg/L.

Summary and Conclusions

Tg does hold promise as a biomarker of iodine deficiency. However, it is also associated with limitations. The variety of methods used to analyze Tg makes it difficult to compare studies. It would be helpful if studies that measured Tg standardized their assays with CRM-457. Furthermore, particularly in adult populations, subjects should be screened for TgAb. Despite these problems, the studies included in this review support the use of Tg as a biomarker of iodine status in school children using the <13 μg/L cutoff as suggested by Zimmermann *et al.* (41). However, it is not possible to draw conclusions regarding the efficacy of Tg in adults because the data are equivocal, while there are no studies of pregnant women with adequate iodine status that also include data on Tg concentration. In particular, few intervention studies have investigated the diagnostic performance of Tg assays and its clinical relevance in assessing iodine status in healthy populations. Well-designed randomized placebo-controlled trials are required to investigate further the effect of iodine supplementation on Tg in mild to moderately iodine-deficient populations, particularly in adults and pregnant women.

Author Disclosure Statement

The authors declare that they have no conflict of interest.

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