CLINICAL STUDY

Impact of protein energy malnutrition on thyroid size in an iodine deficient population of Gujarat (India): is it an aetiological factor for goiter?

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Abstract

Objective: To assess the severity of protein energy malnutrition (PEM) in iodine deficient subjects and to assess the impact of PEM on thyroid size.

Methods: 1002 subjects (530 school-aged children and 472 adults) were assessed for PEM by direct anthropometric measurements of height, weight, triceps skinfold (TSF) thickness, mid upper arm circumference (MUAC) and thigh circumference (TC), and derived indices of body surface area (BSA), body mass index (BMI), and Z-scores for weight-for-age (WAZ), height-for-age (HAZ), and weight-for-height (WHZ). Severity of PEM was based on the World Health Organization (WHO) criteria and the threshold on the Waterlow classification. Thyroid size was measured by ultrasonography to determine the thyroid volume (TV). Linear regression analysis was performed between TV and anthropometric parameters.

Results: Children had severe PEM as evident from the WHO percentage prevalence of stunting ($\text{HAZ} < -2\text{SD}$) = 64% (where $< -2\text{SD}$ is the Z-score deficit), wasting ($\text{WHZ} < -2\text{SD}$) = 43%, underweight ($\text{WAZ} < -2\text{SD}$) = 82% and $\text{BMI} < 16 \text{ kg/m}^2$ = 90%. Waterlow classification showed that children were either stunted or wasted, or stunted and wasted, or stunted and obese. Nearly 100% (529/530) of the children had goiter as evidenced from enlarged TV-for-BSA when compared with the WHO reference. There was a weak but statistically significant ($P < 0.05$) positive correlation between TV and BSA, weight, height, MUAC, TC and HAZ but a negative correlation between TV and WHZ, BMI and TSF ($r = -0.1$ – 0.2).

Adults had PEM as evident from $\text{BMI} < 18.5 \text{ kg/m}^2$ in 54% subjects. Median MUAC = 22.7 cm reveals prolonged severe PEM. Eighty-two percent had enlarged TV ($> 20 \text{ ml}$). There was a significant ($P = 0.01$) negative correlation between TV and MUAC.

Conclusions: (i) The severity of acute (wasting) and chronic (stunting) PEM is very high in Gujarati children. They are stunted or wasted, or stunted and wasted, or stunted and obese. Gujarati adults are thin with low protein and fat reserves. (ii) Anthropometric parameters showed a significant ($P < 0.001$) correlation ($r = 0.1$ – 0.2) with thyroid size. (iii) Higher prevalence of goiter may be due to macro-nutrient malnutrition (PEM) in the face of micro-nutrient malnutrition (iodine deficiency disorders, IDD).

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Introduction

The possibility that factors other than iodine deficiency contribute to the production of endemic goiter was perceived as early as 1924 (1). Of the world's undernourished people more than half live in India. Because of the high cost of animal protein and constraints imposed by caste and religious norms, most Indians are vegetarians and depend greatly on pulses. The commonly encountered nutritional disorders are protein

energy malnutrition (PEM), and vitamin A, iron and iodine deficiencies (IDD). Although IDD is a specific nutritional disorder due to deficiency of the micro-nutrient iodine, the effects of generalized PEM on the expression and severity of IDD, in particular goiter, remains to be elucidated (2).

We have previously reported that in Gujarat (Western India) mild to moderate IDD persists (median urinary iodine $56 \mu\text{g/l}$), but the prevalence of goiter (100%) was greater than expected for the degree of

Table 1 Classification for assessing severity of malnutrition by percentage prevalence ranges of three indicators among children under 5 years of age.

Z-score < -2SD	Indicator	Low	Medium	High	Very high
Height-for-age	Stunting	<20	20–29	30–39	≥40
Weight-for-age	Underweight	<10	10–19	20–29	≥30
Weight-for-height	Wasting	<5	5–9	10–14	≥15

Data taken from (6).

iodine deficiency (3). We found that almost all children were goitrous by using ultrasonography and speculated that other factors such as concomitant goitrogen intake or the effects of PEM as evidenced from low body mass index (BMI) might be significant contributors to the greater than expected prevalence of goiter in this population (3). If PEM was a significant factor then apart from its effects on increasing thyroid size, it would further compromise thyroid hormone homeostasis.

The principle aim of the present study was to determine the relative contribution of PEM as determined by direct and derived anthropometric indices on thyroid size in the mild to moderate iodine deficient school-aged children and adult population of Gujarat, India.

Subjects and methods

A total of 1002 subjects having mild to moderate iodine deficiency (based on determination of urinary iodine in all subjects) were included in the study. The characteristics of these subjects, methods of selection and geography of the endemia have been reported previously (3, 4).

There were 530 children aged 6–15 years and 472 adults aged 16–83 years from the Baroda and Dang districts of Gujarat State. The detailed results of their iodine status as indicated by outcome indicators (clinical and biochemical), age, sex, geographical distribution and data on diet have been reported elsewhere (3, 4). Serum thyroxine levels were not measured in our subjects due to their poor sensitivity, but blood spot thyrotropin (TSH) was measured in all subjects (3, 4). A thorough clinical examination was carried out to discover stigmata of malnutrition such as xerophthalmia, Bitot’s spots and skin changes and these were recorded. PEM was assessed by direct anthropometric measurements of height, weight, mid upper arm circumference (MUAC), thigh circumference (TC) and triceps skinfold (TSF) thickness and derived indices like body surface area (BSA), body mass index (BMI), arm muscle area (AMA) and arm fat area (AFA). AMA measures lean body mass whereas AFA reflects the subcutaneous adipose tissue.

World Health Organization (WHO) classification for PEM

Z-score deficits (< -2SD) were calculated for height-for-age (HAZ), weight-for-age (WAZ) and weight-for-height (WHZ) for all children (5). These deficits give rise to three indicators of PEM, stunting, underweight and wasting respectively, that classify the severity of PEM by the percentage prevalence ranges (6) (Table 1). Wasting is the preferred indicator for thinness in children. These reference ranges, however, are only for children less than 5 years of age (6).

Figure 1 Waterlow classification. A, C, D and F: stunted or wasted. B: stunted and wasted. E: obese. Wasting: lean condition due to acute nutritional problems. Stunting: reduced linear growth due to chronic nutritional problems.

Waterlow classification (combination of HAZ and WHZ indices)

This classification combines each of the derived indices as a global plot to determine the relative distribution of normal and abnormal anthropometry (Fig. 1) (7). Thus the Waterlow classification presents an overview of the thresholds of malnutrition in a population and divides them into one of six groups (A to F) as shown in the legend for Fig. 1.

Thyroid volumes (TV)

In schoolchildren the thyroid glands were classified as 'normal' or 'enlarged' using the 97th percentile of the WHO reference values as cut off (8). In adults, TV > 20 ml was considered as enlarged (9).

Statistical methods

Proportion, mean, standard deviation and median (with interquartile range) have been used to describe the data, as appropriate. Statistical analysis was performed using SPSS version 6.1.2. Thyroid volume was logarithmically transformed and the Kolmogorov-Smirnov test was used to verify normality of the transformed data. Differences in thyroid volume and

other nutritional parameters between districts were tested using the Mann-Whitney test. *t*-tests were used to test for gender differences in anthropometric and clinical parameters. Linear regression analysis was used to test for association between thyroid volume and PEM variables. The Bonferroni method was used to correct the significance levels for multiple comparisons.

Results

Subjects (adults and children) had no clinical signs of vitamin A deficiency. However as previously reported they were mild to moderately iodine deficient (3, 4).

Prevalence of PEM and goiter

Children PEM as assessed by the three indicators of stunting, wasting and underweight was highly prevalent in both the Baroda and Dang districts. Sixty four percent (339/530) of children had stunted growth, 57% (273/481) had wasting and 82% (434/530) were underweight.

Eighty percent had BMI values less than 15 kg/m² thereby indicating that the total body fat content was less than 5% of body-weight. As BMI is an important index for thinness in children over 10 years of age, its frequency distribution as shown in Fig. 2 is only used

Figure 2 BMI frequency distribution for Gujarati children aged >10 to 15 years.

Table 2 Anthropometric parameters and thyroid volume in children.

Parameter	Mean $\pm$ s.d.	Median (IQR)	Mean $\pm$ s.d.	Median (IQR)	P value
<i>Dang</i> (n = 412)		<i>Girls</i> (n = 219)		<i>Boys</i> (n = 193)	
WAZ	-2.4 $\pm$ 0.6	-2.5 (-2.8 : -2.1)	-2.4 $\pm$ 0.6	-2.5 (-2.8 : -2)	0.48
HAZ	-2.3 $\pm$ 1	-2.4 (-2.8 : -1.6)	-2.1 $\pm$ 1	-2.3 (-2.7 : -1.5)	0.15
WHZ	-1.9 $\pm$ 0.8	-2.0 (-2.4 : -1.4)	-2 $\pm$ 0.9	-2 (-2.5 : -1.5)	0.68
TSF (mm)*	8 $\pm$ 2	7.5 (6.5 : 9)	6 $\pm$ 1.7	6 (5 : 7)	0.0001
MUAC (cm)*	16.3 $\pm$ 1.7	16 (15 : 17)	16.2 $\pm$ 1.5	16 (15 : 17)	0.52
TC (cm)*	30.6 $\pm$ 2.8	30.5 (29 : 32)	31.5 $\pm$ 3	31.5 (30 : 33.5)	0.0001
BMI (kg/m ²)*	13.9 $\pm$ 5.4	13.2 (12 : 14)	13.5 $\pm$ 2.4	13.2 (12.6 : 14)	0.33
TV (ml)	29.7 $\pm$ 12.5	27 (23 : 34)	32 $\pm$ 10	30 (25 : 36)	0.01
<i>Baroda</i> (n = 118)		<i>Girls</i> (n = 28)		<i>Boys</i> (n = 90)	
WAZ	-2.3 $\pm$ 0.7	-2.3 (-2.8 : -2.3)	-2.5 $\pm$ 0.7	-2.5 (-2.9 : -2.2)	0.24
HAZ	-3.9 $\pm$ 3	3.4 (-5.4 : -2.0)	-3.3 $\pm$ 2.2	-2.5 (-5 : -2)	0.16
WHZ	-1.4 $\pm$ 4.4	0 (-1.2 : 2.1)	0.29 $\pm$ 3.4	-0.9 (-2.0 : 1.7)	0.17
TSF (mm)*	9.6 $\pm$ 3.7	9 (7 : 11)	8.1 $\pm$ 2.9	7 (6 : 9)	0.02
MUAC (cm)*	18.1 $\pm$ 2.9	17 (16 : 20)	17.1 $\pm$ 2.3	17 (16 : 18.4)	0.07
TC (cm)*	33.3 $\pm$ 6.7	32 (30 : 36.6)	32.6 $\pm$ 4.5	32 (29 : 35.5)	0.53
BMI (kg/m ²)*	18.5 $\pm$ 8	16 (13 : 20)	16.5 $\pm$ 5	14 (13 : 18.6)	0.13
TV (ml)	27.1 $\pm$ 10	30.7 (19 : 34)	25 $\pm$ 13	22 (14 : 35)	0.41

P value indicates significant gender difference for each parameter; *indicates significant P value (<0.001) for district as mentioned in the text. IQR, Interquartile range.

for children in the age range of 11–15 years. This figure shows that a few children had BMI values greater than 19 kg/m². These children were from the Baroda district and were severely stunted (HAZ < -2SD) accounting for the high BMI. Using BMI alone may be misleading in these circumstances.

Table 2 shows the detailed results of anthropometric and clinical parameters used to assess nutritional

status and thyroid size. Dang children were more malnourished than Baroda children as evidenced by BMI, weight, height, MUAC, TC and TSF thickness ($P < 0.001$).

The Waterlow classification showed that only a few children were normal and the rest were either stunted or wasted, or both wasted and stunted, or obese and stunted. There was a very strong correlation ($r = 0.6$) between wasting and stunted (Fig. 3).

Goiter by ultrasonography was seen in almost 100% (529/530) of children compared with the WHO TV-for-BSA reference and in 97% (515/530) of children compared with the WHO TV-for-age reference.

There was no relation of thyroid volume to iodine intake as seen from urinary iodine (UI) on the one hand and different ranges of WHZ on the other hand due to the interplay of multiple factors and goiter in all the children (Table 3). A bimodal relation between thyroid volume and WHZ is evident.

Adults Table 4 shows the detailed results of anthropometric and clinical parameters used to assess nutritional status and thyroid size in adults. Fifty four

Figure 3 Waterlow classification of studied children. N: normal. A, C, D and F: stunted or wasted. B: stunted and wasted. E: obese.

Table 3 Thyroid volume (ml) in children according to their iodine excretion and Z-score weight-for-height (WHZ) index.

WHZ	Urinary iodine (μ g/l)			
	<50	51–100	101–300	Total
<-3	29.75	23.99	26.98	27.44
-2 to -3	28.35	29.37	29.33	28.92
-1 to -2	29.19	30.68	35.97	30.96
>-1	26.65	26.15	27.8	26.85

Table 4 Anthropometric parameters and thyroid volume in adults.

	Mean $\pm$ s.d.	Median (IQR)	Mean $\pm$ s.d.	Median (IQR)	P value
<i>Dang</i> (n = 80)		<i>Women</i> (n = 55)		<i>Men</i> (n = 25)	
BMI (kg/m ²)	17.2 $\pm$ 2.7	16 (15.6 : 18.3)	18 $\pm$ 2	17.9 (17 : 18.8)	0.17
BSA (m ²)	1.3 $\pm$ 0.1	1.3 (1.23 : 1.36)	1.46 $\pm$ 0.1	1.45 (1.4 : 1.5)	0.0001
TSF (mm)	8.3 $\pm$ 3.0	8.5 (6 : 10.5)	8.1 $\pm$ 2.9	8 (5 : 10)	0.76
MUAC (cm)	21 $\pm$ 1.9	21 (20 : 22)	23 $\pm$ 2.4	22.5 (22 : 24)	0.001
TC (cm)	38.7 $\pm$ 4.4	39 (36 : 41)	39.5 $\pm$ 2.9	39.5 (37.5 : 42)	0.36
TV (ml)	50 $\pm$ 25	46 (39 : 59)	51 $\pm$ 15	47 (39 : 60)	0.87
<i>Baroda</i> (n = 392)		<i>Women</i> (n = 172)		<i>Men</i> (n = 220)	
BMI (kg/m ²)	20.3 $\pm$ 4.6	19 (17 : 22.6)	18.8 $\pm$ 3.4	18 (16 : 20.7)	0.0001
BSA (m ²)	1.4 $\pm$ 0.14	1.4 (1.3 : 1.5)	1.5 $\pm$ 0.14	1.5 (1.4 : 1.6)	0.0001
TSF (mm)	11.7 $\pm$ 4.5	11 (9 : 14.5)	7.8 $\pm$ 2.9	7 (6 : 10)	0.0001
MUAC (cm)	23 $\pm$ 3.5	23 (20.5 : 25)	23.2 $\pm$ 2.9	23 (21.5 : 24.5)	0.94
TC (cm)	40.7 $\pm$ 6.8	40 (36 : 45)	40 $\pm$ 5.5	40 (36 : 43)	0.31
TV (ml)	33.5 $\pm$ 16	30 (21 : 42)	35.5 $\pm$ 16	36.4 (21 : 46)	0.23

P value indicates significant gender difference for each parameter.
IQR, Interquartile range.

percent had PEM (mild to severe) as evidenced by BMI values less than 18.5 kg/m². Thus Gujarati adults are thin with low protein and fat reserves as evidenced from their lower MUAC, AMA, AFA and TSF values. Figure 4 shows the frequency distribution of BMI with

some overweight subjects found only in the Baroda district (BMI > 25 kg/m²). Enlarged thyroid volume (>20 ml) was found in 388/472 subjects (82.2%). More females had goiter (by ultrasound) and more had goiter grade 2 (5 women and 2 men). Thyroid

Figure 4 BMI frequency distribution in adults aged >15 years from Dang and Baroda districts. BMI range <15.0 = very severe malnutrition with total body fat <5% of body-weight. BMI range 15.1 to 16.0 = severe malnutrition. BMI range 16.1 to 17.0 = moderate malnutrition. BMI range 17.1 to 18.4 = mild malnutrition. BMI range 18.5 to 24.9 = normal.

ultrasound revealed 100% goiter prevalence in the Dang and 77% in the Baroda districts. Median thyroid volume was 46.8 ml in Dang and 32.7 ml in Baroda ($P < 0.001$).

Regression analysis

In children, there was a weak but statistically significant ($P < 0.05$) positive correlation between TV and the variables BSA, weight, height, MUAC, TC, and HAZ (stunting) ($r = 0.17, 0.11, 0.2, 0.11, 0.14, 0.15$ respectively). All these indices are directly or indirectly related to growth in children hence the expected positive correlation.

A weak but statistically significant ($P < 0.05$) negative correlation ($r = -0.14$) between TV and the variables TSF and WHZ was seen.

When the logarithmic transformation of TV (LN-TV) was considered, LN-TV showed a weak ($r = -0.11$) but significant ($P = 0.009$) correlation with BMI. It also showed a significant correlation with HAZ ($r = 0.35, P = 0.0003$) and WHZ ($r = -0.16, P = 0.0003$).

In adults, there was a weak ($r = -0.1$) but statistically significant ($P < 0.05$) negative correlation between TV and MUAC as well as AMA, in other words the poorer the protein nutrition the larger the thyroid size. There was no correlation between TV and other anthropometric parameters like weight, height, BMI, BSA and TC. When the logarithmic transformation of TV (LN-TV) was considered, LN-TV showed a weak but statistically significant ($P = 0.008$) correlation with age, TC, MUAC and TSH ($r = -0.20, -0.12, -0.12, 0.36$ respectively).

The best fitting multivariate linear regression models for thyroid volume using backward elimination for children and adults are published elsewhere (3, 4).

Discussion

The present study shows that PEM was highly prevalent in mild to moderately iodine deficient school-children and adults of Gujarat (Western India). Thyroid enlargement was, in part, related to the degree of PEM in children independent of the effect of iodine deficiency (Table 3). Our study thus highlights the complex interplay of nutritional factors that influence the clinical expression of endemic goiter and potentially other iodine deficiency disorders.

The degree of PEM found in this population group by the three indicators stunting, underweight and wasting indicates severe PEM in Gujarat (6). On a population basis, such high levels of stunting have previously been associated with poor socioeconomic conditions and endemic goiter in a rural population (10). This study highlights not only the importance of addressing the fundamental importance of iodine supplementation, but also the importance of addressing nutritional intake in general.

The mechanism of goiter in the setting of PEM is probably multi-factorial. In PEM children, negatively charged iodide is less efficiently absorbed against the electrochemical gradient requiring energy (11). Iodine concentration of the thyroid gland decreases due to depressed iodide clearance and uptake in PEM (12). Thus PEM indirectly results in alterations in iodine metabolism that may lead to thyroid hyperplasia and further reduces circulating thyroid hormone levels. Secondly, PEM may contribute to goitrogenesis directly through the lack of substrate availability, in particular the lack of essential amino acids such as tyrosine (13). These substrate deficiencies are probably exaggerated as subjects consumed a narrow, homogenous vegetarian diet with pulses as the main source of protein. The detection of the amino acid profile in seed proteins has revealed low levels of tyrosine and phenylalanine in the white-coloured seed coat accession compared with the WHO (1991) requirement pattern (14).

Previous studies have shown that the best predictors of thyroid size in normal iodine sufficient children are BSA, weight, height and age whereas WAZ, HAZ and WHZ are less predictive of thyroid volume (15). These authors did not measure other anthropometric parameters of nutrition such as MUAC, TC and TSF. Positive correlation between thyroid weight measured scintigraphically and the ratio of thyroid gland weight to BSA has also been shown (16). The Gujarati children showed the expected positive correlation ($r = 0.12-0.20, P < 0.05$) of thyroid size to variables such as BSA, weight, height and HAZ. The mid upper arm and thigh circumferences in children, but not in adults, were also positively related to thyroid size. The correlation of these growth-determined variables to thyroid volume was less than that found in an iodine sufficient population due to greater thyroid size in the studied population. A stronger positive correlation can be expected in normal iodine sufficient Indian children (17, 18).

By contrast, thyroid size was larger in children who exhibited more severe features of PEM. A negative correlation between TV and variables such as BMI, TSF and WHZ (wasting which is the preferred index for thinness in children) was found. These findings were independent of the degree of iodine deficiency, and indicate that PEM is one of the determinants of thyroid size.

Recent studies have shown that nutritional biochemical markers such as thyroxine binding pre albumin (TBPA) show a good relation to WAZ and HAZ scores (19), i.e. TBPA may be a useful marker to assess the effects of nutrition on thyroid size.

Adults also showed a very high prevalence of PEM as evidenced by the prevalence of low BMI (a critical situation) in the population. Almost 54% of the population had BMI values less than 18.5 kg/m^2 (Fig. 4) (6). There was a negative correlation between TV and MUAC and AMA, indicating a relationship

between markers of prolonged protein deficiency and thyroid size.

The greatest public health concern of the present findings is the potential impact of PEM not on the development of goiter *per se*, but the effects on brain development of the fetus and neonate. Although not measured directly, the study findings would support the notion that PEM would further compromise thyroid hormone homeostasis, which would potentiate the impact on fetal and neonatal brain development.

In summary, the present study conducted in subjects with severe PEM in the setting of iodine deficiency has demonstrated that there may be an impact of PEM on thyroid volume as measured by ultrasonography. The study highlights the complex interplay of nutritional factors that determine thyroid size and thus thyroid hormone homeostasis.

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