Section: General Medicine

Original Research Article

PREVALENCE AND PATTERN OF THYROID DYSFUNCTION IN PREDIABETES AND ITS ASSOCIATION WITH OBESITY AND DYSLIPIDAEMIA: A HOSPITAL-BASED CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Prediabetes and thyroid dysfunction are both common in South India and are mechanistically linked through insulin resistance. Data describing the burden, pattern and cardiometabolic correlates of thyroid dysfunction specifically within prediabetic populations remain limited, particularly from iodine-sufficient regions of India. **Objectives:** To determine the prevalence and pattern of thyroid dysfunction among adults with prediabetes, to describe its association with age, sex, obesity, dyslipidaemia and hypertension, and to consider the implications for population-level screening policy.

Materials and Methods: A hospital-based cross-sectional study was conducted in the Department of General Medicine, Government Medical College, Kozhikode, over one year (January–December 2016). Adults meeting American Diabetes Association criteria for prediabetes (fasting plasma glucose 100–125 mg/dL and/or HbA1c 5.7–6.4%) were enrolled; those on drugs affecting thyroid function, with prior thyroid ablation, pregnancy, or chronic hepatic or renal disease were excluded. Serum free triiodothyronine, free thyroxine and thyroid-stimulating hormone were measured by electrochemiluminescence immunoassay, alongside anthropometry, blood pressure and fasting lipid profile. Associations were assessed by the chi-square test with Yates' continuity correction and Fisher's exact test, with unadjusted odds ratios and 95% confidence intervals; trend across body mass index categories was tested by the Cochran–Armitage test. All effect estimates are unadjusted; individual participant records were not retrievable, so multivariable adjustment could not be undertaken.

Results: Among 316 prediabetic adults (mean age 47.5 years; 53.2% male), thyroid dysfunction was present in 126 (39.9%). The pattern was overwhelmingly hypothyroid: subclinical hypothyroidism in 84 (26.6%) and overt hypothyroidism in 26 (8.2%), together accounting for 87.3% of all abnormalities, with hyperthyroidism in only 16 (5.1%). Prevalence was higher in women than men (51.4% versus 29.8%; odds ratio 2.49, 95% CI 1.56–3.98) and in those aged over 60 years (64.3% versus 34.6%; odds ratio 3.40, 95% CI 1.86–6.22). A graded relationship with adiposity was evident, prevalence rising from 20.9% in those of normal weight to 53.1% in the overweight and 63.6% in the obese (Cochran–Armitage test for trend $p < 0.001$). Thyroid dysfunction was strongly associated with raised total cholesterol (odds ratio 5.04, 95% CI 3.06–8.28) and raised triglycerides (odds ratio 4.69, 95% CI 2.86–7.69), but not with LDL cholesterol or hypertension.

Conclusion: Two in five adults with prediabetes in this iodine-sufficient South Indian setting had an abnormal thyroid profile, predominantly subclinical hypothyroidism. Female sex, age above 60 years specifically rather than advancing age generally, adiposity and atherogenic dyslipidaemia clustered with thyroid dysfunction. Given that India has an estimated 136 million adults with prediabetes, universal thyroid screening of this population is not affordable, and these findings delineate the subgroups in which risk-stratified case-finding is likely to be most productive. Because thyroid status was determined from a single unconfirmed measurement, and because treatment of subclinical hypothyroidism yields limited clinical benefit, any screening proposal requires formal cost-effectiveness evaluation against universal and no-screening strategies before adoption into public health practice.
Keywords: Prediabetic state; Thyroid diseases; Hypothyroidism; Obesity; Dyslipidaemias; Prevalence; India.

INTRODUCTION

Prediabetes is an intermediate state of dysglycaemia carrying substantial risk of progression to type 2 diabetes mellitus (T2DM) and associated with vascular injury in its own right. The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) national survey estimated the weighted prevalence of prediabetes in India at 15.3% against 11.4% for diabetes, with prediabetes exceeding diabetes in most states.[1] Kerala, where the present study was conducted, has among the highest recorded burdens of both dysglycaemia and thyroid disease in the country.

Thyroid hormone and insulin act on overlapping metabolic pathways. Thyroid hormone opposes insulin action in the liver while acting synergistically with insulin in skeletal muscle and adipose tissue, and disturbance of either axis perturbs the other. Community-based data show a graded rise in thyroid dysfunction across the spectrum of glucose tolerance, from 7.6% in normoglycaemia to 9.3% in prediabetes and 11.6% in established T2DM, with subclinical hypothyroidism predominating.[2] Prospectively, raised thyroid-stimulating hormone (TSH) is associated with a 17% higher risk of incident T2DM, and low free triiodothyronine and free thyroxine with 40% and 33% higher risks respectively.[3] Subclinical hypothyroidism is independently associated with the metabolic syndrome, with a pooled odds ratio of 1.28 across nearly eighty thousand participants.[4]

The relationship with adiposity is equally well documented and appears bidirectional. Obesity is accompanied by higher TSH, higher free triiodothyronine and altered deiodinase activity in adipose tissue, and the prevalence of subclinical hypothyroidism is higher in obese than in non-obese individuals.[5] Mendelian randomisation indicates that the causal arrow runs at least partly from adiposity to thyroid function rather than the reverse, since genetically predicted body mass index raises TSH whereas genetically predicted TSH does not alter body mass index.[6] Metabolic syndrome has correspondingly been shown to predict incident thyroid disease in meta-analysis.[7]

Hypothyroidism also disturbs lipid metabolism, reducing LDL receptor expression and hepatic lipase activity and thereby raising total and LDL cholesterol and triglycerides; levothyroxine replacement reverses much of this derangement in overt and, to a smaller degree, subclinical disease.[8,9] Hypothyroidism-associated dyslipidaemia is now recognised as a modifiable contributor to hepatic steatosis and cardiovascular risk.[10] Since prediabetic individuals already carry an atherogenic lipid profile, coexisting thyroid dysfunction is of potential clinical consequence in this group.

Despite these mechanistic links, most published series describe thyroid dysfunction in established diabetes rather than in prediabetes, and Indian data from iodine-sufficient regions are sparse. The present study was therefore undertaken to determine the prevalence and pattern of thyroid dysfunction among adults with prediabetes in North Kerala, and to characterise its relationship with age, sex, obesity, dyslipidaemia and hypertension. The relationship between thyroid dysfunction and parental history of diabetes in the same cohort is reported separately.

MATERIALS AND METHODS

Study design and setting

This hospital-based observational cross-sectional study was conducted in the Department of General Medicine, Government Medical College, Kozhikode, Kerala, over one year from January to December 2016. Reporting follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cross-sectional studies.

Participants

The sampling frame comprised adult attendants and relatives accompanying patients admitted to the medical wards. This group was selected to provide access to community-dwelling adults who were not themselves acutely ill, thereby avoiding the confounding influence of non-thyroidal illness on thyroid function tests. Individuals older than 18 years were screened by fasting plasma glucose and glycated haemoglobin, and those meeting the 2016 American Diabetes Association criteria for prediabetes —

fasting plasma glucose 100–125 mg/dL and/or HbA1c 5.7–6.4% — were eligible.

Exclusion criteria were established diabetes mellitus or use of antidiabetic medication; treatment with corticosteroids, amiodarone, lithium or antithyroid drugs; previous thyroidectomy or radioactive iodine therapy; pregnancy or lactation; chronic renal or hepatic disease; and refusal of consent. A total of 316 participants meeting these criteria were enrolled.

Measurements

A structured proforma recorded demographic details, symptoms suggestive of thyroid dysfunction, drug and comorbidity history, family history and menstrual history. Height, weight, body mass index (BMI) and blood pressure were measured, and complete general and systemic examination performed. BMI was categorised by World Health Organization Asia-Pacific cut-offs as normal (18.5–22.9 kg/m²), overweight (23.0–27.5 kg/m²) or obese (>27.5 kg/m²). Hypertension was defined by an existing diagnosis or by blood pressure meeting contemporary diagnostic thresholds at examination.

Serum free thyroxine (FT4), free triiodothyronine (FT3) and TSH were estimated by electrochemiluminescence immunoassay. Reference intervals applied were TSH 0.27–4.2 µU/mL, FT3 2.0–4.4 ng/mL and FT4 0.93–1.7 ng/mL. Fasting lipid profile, renal function and liver function tests were performed in the institutional central laboratory. Lipid abnormalities were categorised using conventional thresholds: total cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL and LDL cholesterol ≥129 mg/dL. The lipid panel recorded in the study proforma comprised total cholesterol, triglycerides and LDL cholesterol; high-density-lipoprotein cholesterol was not recorded, and the protocol does not document whether LDL cholesterol was assayed directly or derived by calculation.

Thyroid dysfunction was classified into four mutually exclusive categories: overt hypothyroidism (TSH >4.2 µU/mL with FT3 <2.0 ng/mL and FT4 <0.93 ng/mL); subclinical hypothyroidism (TSH >4.2 µU/mL with FT3 and FT4 within the reference interval); overt hyperthyroidism (TSH <0.27 µU/mL with FT3 >4.4 ng/mL and FT4 >1.7 ng/mL); and subclinical hyperthyroidism (TSH <0.27 µU/mL with FT3 and FT4 within the reference interval). Participants with all three indices within reference limits were classified as euthyroid. Thyroid status was determined from a single blood sample; confirmatory repeat testing was not performed.

Statistical analysis

Data were analysed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies and percentages, continuous variables as mean ± standard deviation. Associations between categorical variables were tested by the Pearson chi-square test, with the Yates-corrected statistic and Fisher's exact test reported for two-by-two comparisons. Unadjusted odds ratios with 95% confidence intervals were derived from contingency tables by the Woolf logit method. The ordered relationship between BMI category and thyroid dysfunction was assessed by the Cochran–Armitage test for trend. A two-sided p value below 0.05 was considered nominally significant.

All effect estimates presented are unadjusted. Multivariable logistic regression, which would have identified independent correlates among the mutually intercorrelated variables of age, sex, adiposity and lipid indices, could not be performed: the study was completed in 2016 and the individual participant records are no longer retrievable, leaving only the aggregate cross-tabulations from which the present analyses are derived. Adjusted estimates cannot be recovered from marginal contingency tables, since these do not contain the joint distribution of covariates. The odds ratios reported must therefore be read as measures of association observed in the data, not as independent effects, and this constraint is treated as a principal limitation of the study rather than as a matter of analytical preference.

One structural feature of the analysis merits explicit statement, because it bounds the effect of a known limitation. The study protocol defined overt hypothyroidism as requiring both free triiodothyronine and free thyroxine to be subnormal, whereas standard endocrine practice requires only a subnormal free thyroxine with raised thyroid-stimulating hormone, free triiodothyronine being frequently preserved until disease is advanced. This non-standard definition will have classified some genuinely overt cases as subclinical. However, the outcome variable in every association analysis reported here is the binary presence or absence of thyroid dysfunction of any kind. Reclassification under the conventional criterion moves participants between the subclinical and overt hypothyroid categories but cannot move any participant into or out of the thyroid dysfunction group as a whole. The denominator of 126 is therefore invariant to the definition used, and all associations reported in Tables 3 to 5 and Figures 2 to 4 are unaffected. Only the internal breakdown presented in Table 2 would alter, in the direction of a higher overt and correspondingly lower subclinical count.

Several correlates were examined without a formally pre-specified primary outcome; under Bonferroni correction for the seven univariable comparisons reported, a threshold of p = 0.007 would apply, which the associations with sex, age, BMI, total cholesterol and triglycerides all meet, while those with LDL cholesterol and hypertension do not.

Ethical considerations

The protocol was approved by the Institutional Ethics Committee of Government Medical College, Kozhikode. Written informed consent was obtained from every participant after explanation of the purpose and implications of the study. Participants found to have thyroid dysfunction were referred for clinical evaluation and management.

RESULTS

Characteristics of the cohort

Three hundred and sixteen adults with prediabetes were studied. Age ranged from 23 to 66 years with a mean of 47.5 years; the largest single band was 41–50 years (98 participants, 31.0%), and only 13 participants (4.1%) were aged 30 years or younger. There were 168 men (53.2%) and 148 women (46.8%). Mean HbA1c was 5.9 ± 0.19%, all values lying within the prediabetic range. Overweight or obesity was present in 168 participants (53.2%), hypertension in 173 (54.7%) and raised total cholesterol in 164 (51.9%). Cohort characteristics are shown in Table 1.

Table 1: Baseline characteristics of the study population (N = 316)

Characteristic	n	%
Age group (years)		
18–30	13	4.1
31–40	65	20.6
41–50	98	31.0
51–60	84	26.6
>60	56	17.7
Sex		
Male	168	53.2
Female	148	46.8
Body mass index (kg/m²)		
18.5–22.9 (normal)	148	46.8
23.0–27.5 (overweight)	113	35.8
>27.5 (obese)	55	17.4
Cardiometabolic parameters		
Hypertension	173	54.7
Total cholesterol ≥200 mg/dL	164	51.9
Triglycerides ≥150 mg/dL	110	34.8
LDL cholesterol ≥129 mg/dL	140	44.3
Family history of type 2 diabetes		
Present (one or both parents)	158	50.0
Absent	158	50.0

LDL, low-density lipoprotein. Percentages are of the whole cohort.

Prevalence and pattern of thyroid dysfunction

Thyroid dysfunction was identified in 126 of 316 participants, an overall prevalence of 39.9%. The pattern was overwhelmingly hypothyroid. Subclinical hypothyroidism was the commonest single abnormality, affecting 84 participants (26.6% of the cohort and 66.7% of all abnormal results), followed by overt hypothyroidism in 26 (8.2% and 20.6% respectively). Hypothyroidism of any degree therefore accounted for 110 of the 126 abnormalities (87.3%). Hyperthyroidism was uncommon, comprising subclinical hyperthyroidism in 12 participants (3.8%) and overt hyperthyroidism in only 4 (1.3%). Mean TSH among those with thyroid dysfunction was 6.24 µU/mL. The distribution is set out in Table 2 and illustrated in Figure 1.

Table 2: Prevalence and pattern of thyroid dysfunction (N = 316)

Thyroid function category	n	% of cohort (N = 316)	% of those with dysfunction (n = 126)
Euthyroid	190	60.1	—
Subclinical hypothyroidism	84	26.6	66.7
Overt hypothyroidism	26	8.2	20.6
Subclinical hyperthyroidism	12	3.8	9.5
Overt hyperthyroidism	4	1.3	3.2
All hypothyroidism	**110**	**34.8**	**87.3**
All hyperthyroidism	**16**	**5.1**	**12.7**
Any thyroid dysfunction	**126**	**39.9**	**100**

Percentages in the final column are of the 126 participants with thyroid dysfunction. Totals may differ from the sum of components by 0.1% owing to rounding.

Thyroid dysfunction in relation to age and sex

Prevalence varied significantly across age bands (2 × 5 chi-square p = 0.001). The clearest signal was in the oldest group: 36 of 56 participants aged over 60 years (64.3%) had thyroid dysfunction, against 90 of 260 (34.6%) aged 60 years or younger, an unadjusted odds ratio of 3.40 (95% CI 1.86–6.22; p < 0.001). Prevalence in the intermediate bands was comparatively flat, at 30.8% for those aged 31–40 years, 34.7% for 41–50 years and 35.7% for 51–60 years, so the relationship with age was better described as a marked excess above 60 years than as a smooth gradient. The youngest band showed an apparently high prevalence of 46.2%, but this rests on

only 6 cases among 13 participants and should not be over-interpreted.

The association with sex was strong and consistent. Thyroid dysfunction affected 76 of 148 women (51.4%) but only 50 of 168 men (29.8%), an unadjusted odds ratio of 2.49 (95% CI 1.56–3.98; $\chi^2 = 15.30$, $p < 0.001$). Findings by age and sex are presented in Table 3 and Figure 2.

Table 3: Thyroid dysfunction according to age group, sex and body mass index

Variable	Thyroid dysfunction, n (%)	Euthyroid, n (%)	Total	p value
Age group (years)				
18–30	6 (46.2)	7 (53.8)	13	
31–40	20 (30.8)	45 (69.2)	65	
41–50	34 (34.7)	64 (65.3)	98	
51–60	30 (35.7)	54 (64.3)	84	
>60	36 (64.3)	20 (35.7)	56	**0.001**
Sex				
Male	50 (29.8)	118 (70.2)	168	
Female	76 (51.4)	72 (48.6)	148	**<0.001**
Body mass index (kg/m²)				
18.5–22.9 (normal)	31 (20.9)	117 (79.1)	148	
23.0–27.5 (overweight)	60 (53.1)	53 (46.9)	113	
>27.5 (obese)	35 (63.6)	20 (36.4)	55	**<0.001**

p values are from the Pearson chi-square test across all categories of each variable. The p value for body mass index refers to the 2 × 3 comparison; the Cochran–Armitage test for trend across ordered categories also gave p < 0.001.

Thyroid dysfunction in relation to adiposity

A graded relationship with adiposity was evident. Thyroid dysfunction was present in 31 of 148 participants of normal weight (20.9%), 60 of 113 who were overweight (53.1%) and 35 of 55 who were obese (63.6%). The overall association was highly significant ($\chi^2 = 43.31$, df = 2, $p < 0.001$), and the Cochran–Armitage test confirmed a significant linear trend across the ordered categories ($p < 0.001$). Comparing participants with BMI ≥23 kg/m² against those of normal weight gave an unadjusted odds ratio of 4.70 (95% CI 2.85–7.77). Mean BMI among those with thyroid dysfunction was 25.01 kg/m². This was the steepest gradient observed for any variable examined and is shown in Figure 3.

Thyroid dysfunction in relation to lipids and blood pressure

Associations with the lipid profile were selective rather than uniform. Raised total cholesterol showed the strongest association of any variable in the study: 94 of 164 participants with total cholesterol ≥200 mg/dL (57.3%) had thyroid dysfunction, against 32 of 152 (21.1%) with values below that threshold, an unadjusted odds ratio of 5.04 (95% CI 3.06–8.28; $p < 0.001$). Mean total cholesterol among those with thyroid dysfunction was 222 mg/dL. Raised triglycerides showed a comparable association, thyroid dysfunction affecting 70 of 110 participants with triglycerides ≥150 mg/dL (63.6%) versus 56 of 206 (27.2%) below that level, an unadjusted odds ratio of 4.69 (95% CI 2.86–7.69; $p < 0.001$); mean triglycerides in the thyroid dysfunction group was 167.4 mg/dL.

By contrast, LDL cholesterol showed no association whatever: 54 of 140 participants with LDL ≥129 mg/dL (38.6%) had thyroid dysfunction, against 72 of 176 (40.9%) below that threshold (odds ratio 0.91, 95% CI 0.58–1.43; $p = 0.673$). The dissociation between total cholesterol, which was strongly associated, and LDL cholesterol, which was not, is unexpected given that LDL constitutes the major component of total cholesterol, and is considered further in the Discussion. Hypertension likewise showed no significant association, affecting 72 of 173 hypertensive participants (41.6%) versus 54 of 143 normotensive participants (37.8%) (odds ratio 1.17, 95% CI 0.75–1.85; $p = 0.486$). These results appear in Table 4, with all effect estimates summarised in Table 5 and displayed in Figure 4.

Table 4: Thyroid dysfunction according to lipid parameters and hypertension

Variable	Thyroid dysfunction, n (%)	Euthyroid, n (%)	Total	p value
Total cholesterol (mg/dL)				
<200	32 (21.1)	120 (78.9)	152	
≥200	94 (57.3)	70 (42.7)	164	**<0.001**
Triglycerides (mg/dL)				
<150	56 (27.2)	150 (72.8)	206	
≥150	70 (63.6)	40 (36.4)	110	**<0.001**
LDL cholesterol (mg/dL)				
<129	72 (40.9)	104 (59.1)	176	
≥129	54 (38.6)	86 (61.4)	140	**0.673**
Hypertension				
Absent	54 (37.8)	89 (62.2)	143	
Present	72 (41.6)	101 (58.4)	173	**0.486**

LDL, low-density lipoprotein. p values are from the Pearson chi-square test.

Table 5: Summary of unadjusted associations with thyroid dysfunction

Correlate	Unadjusted odds ratio	95% confidence interval	p value
Female sex (vs male)	2.49	1.56–3.98	<0.001
Age >60 years (vs ≤60 years)	3.40	1.86–6.22	<0.001
BMI ≥23 kg/m² (vs normal)	4.70	2.85–7.77	<0.001
Total cholesterol ≥200 mg/dL	5.04	3.06–8.28	<0.001
Triglycerides ≥150 mg/dL	4.69	2.86–7.69	<0.001
LDL cholesterol ≥129 mg/dL	0.91	0.58–1.43	0.673
Hypertension	1.17	0.75–1.85	0.486

BMI, body mass index; LDL, low-density lipoprotein. Odds ratios are unadjusted, derived from two-by-two contingency tables by the Woolf logit method.

Clinical features

Symptoms were non-specific and, with the exception of fatigability, infrequent. Among the 110 participants with hypothyroidism, fatigability was reported by 64 (58.2%) and bradycardia recorded in 39 (35.5%); constipation was noted in 12 (10.8%), weight gain in 11 (10.1%), hair loss in 7 (6.0%) and cold intolerance in only 4 (3.2%). Among the 16 participants with hyperthyroidism, fatigability was again commonest (12 participants), followed by palpitations (8), weight loss (7) and heat intolerance (3). Symptom frequency did not differ materially between younger participants (18–50 years) and those over 60 years, save for a modest excess of fatigability in the elderly that may reflect age itself rather than thyroid status. The clinical profile is shown in Table 6.

Table 6: Clinical features among participants with thyroid dysfunction

Clinical feature	n	% of subgroup
Hypothyroidism (n = 110)		
Fatigability	64	58.2
Bradycardia	39	35.5
Constipation	12	10.8
Weight gain	11	10.1
Loss of hair	7	6.0
Cold intolerance	4	3.2
Hyperthyroidism (n = 16)		
Fatigability	12	75.0
Palpitations	8	50.0
Weight loss	7	43.8
Heat intolerance	3	18.8

Percentages are of the relevant subgroup. Fatigability was the only feature reported by a majority of participants in either subgroup; the remaining features were infrequent and none is specific to thyroid disease.

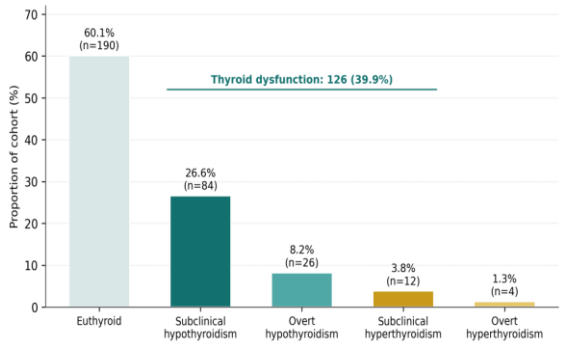

Figure 1: Distribution of thyroid function categories in the study population

Hypothyroid categories account for 110 of the 126 abnormal results (87.3%).

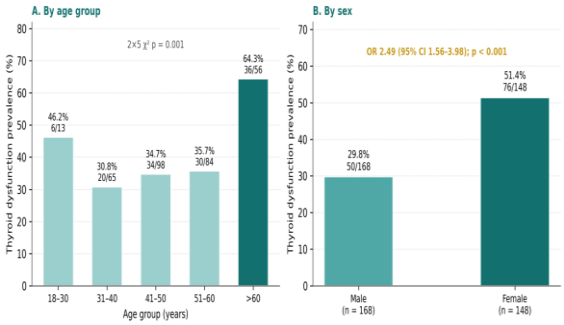

Figure 2: Prevalence of thyroid dysfunction by age group and sex

CI, confidence interval; OR, odds ratio. Panel A: prevalence by age band, with the >60 year group highlighted. Panel B: prevalence by sex.

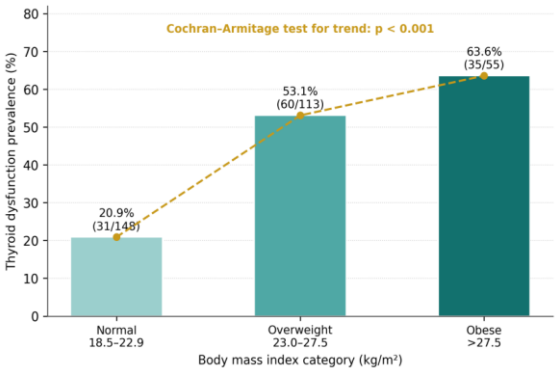

Figure 3: Prevalence of thyroid dysfunction across body mass index categories

Body mass index categorised by World Health Organization Asia-Pacific cut-offs. The dashed line indicates the trend across ordered categories.

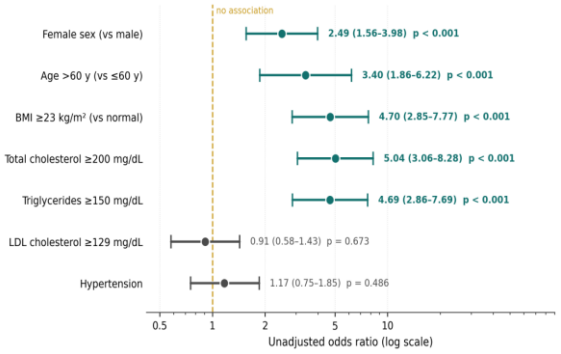

Figure 4: Unadjusted odds ratios for correlates of thyroid dysfunction in prediabetes

BMI, body mass index; CI, confidence interval; LDL, low-density lipoprotein. Horizontal bars represent 95% confidence intervals; the dashed vertical line marks an odds ratio of 1. Estimates are unadjusted.

DISCUSSION

This study of 316 prediabetic adults in North Kerala found an abnormal thyroid profile in two of every five participants, with subclinical hypothyroidism the dominant abnormality and hyperthyroidism distinctly uncommon. Thyroid dysfunction clustered with female sex, age above 60 years, adiposity and atherogenic dyslipidaemia, while showing no relationship with LDL cholesterol or hypertension. The strength of the gradients across BMI categories and lipid thresholds was considerably greater than that of most associations reported in this literature, and the pattern of which variables were and were not associated is itself informative.

Prevalence in context

The observed prevalence of 39.9% substantially exceeds the 9.3% reported among prediabetic individuals in a community-based Chinese survey,[2] and the 19.3% reported among 608 prediabetic subjects in the Tehran Thyroid Study.[11] It also exceeds the 19.6% reported for the general population of Kerala. Three factors probably contribute, in ascending order of likely importance. First, the sampling frame comprised attendants of hospitalised patients rather than a random community sample, favouring selection of individuals with existing health concerns. Second, Kerala is iodine-sufficient with a high documented background burden of thyroid disorders, and Indian series consistently report higher rates than East Asian ones; a recent Indian case-control study similarly found raised TSH significantly commoner in prediabetic individuals than in matched controls.[12] Third, and most consequential, thyroid status here was determined from a single blood sample. Contemporary practice requires confirmation of an isolated raised TSH on a repeat specimen after six to twelve weeks, since a substantial proportion of such values normalise spontaneously. Because subclinical hypothyroidism constituted 84 of the 126 abnormalities, the absence of confirmatory retesting is likely to have inflated the estimate appreciably, and the figure is best read as the prevalence of a single abnormal thyroid profile rather than of confirmed thyroid disease. The relative pattern — subclinical hypothyroidism predominant, overt hyperthyroidism rarest — is nonetheless robust to this limitation and accords closely with international data.[2,3]

Age and sex

The excess in women, at more than double the odds seen in men, is consistent with the established female preponderance of autoimmune thyroid disease and with previous reports in dysglycaemic populations. The age relationship deserves more careful statement than it is usually given. Prevalence was essentially flat between 31 and 60 years and rose steeply only above 60 years, so the finding is a threshold effect rather than the smooth gradient sometimes described. This distinction matters for case-finding: if the excess is concentrated above 60 years, a screening rule keyed to that threshold would be more efficient than one applying a continuous age weighting. The apparently high prevalence in the 18–30 year band rests on 13 participants and 6 events, and no weight should be placed on it.

Adiposity

The gradient across BMI categories — from 20.9% in normal-weight participants to 63.6% in the obese — was the steepest observed in this study and is consistent with a substantial body of evidence. Obese individuals show higher TSH and free triiodothyronine, reduced TSH receptor expression and altered deiodinase activity in adipose tissue, and a higher prevalence of subclinical hypothyroidism than non-obese individuals.[5] Higher TSH is associated with greater visceral and hepatic fat even within the euthyroid range.[13] Importantly, Mendelian randomisation indicates that genetically predicted BMI raises TSH whereas genetically predicted TSH does not alter BMI,[6] suggesting the causal arrow runs predominantly from adiposity to thyroid function rather than the reverse. A cross-sectional design such as ours cannot adjudicate

direction, but this evidence tempers any inference that the thyroid abnormality caused the obesity, and cautions against the common clinical assumption that weight gain in a prediabetic patient signals underlying hypothyroidism.

The lipid findings, including a discrepancy

The associations with total cholesterol and triglycerides are biologically coherent. Hypothyroidism reduces LDL receptor expression and hepatic lipase activity, raising total cholesterol and triglycerides, and levothyroxine replacement reverses much of this derangement.[8,9] A cross-sectional study from Syria similarly found total cholesterol, LDL and triglycerides all lowest in euthyroid participants and progressively higher in subclinical and overt hypothyroidism.[14]

Against that background, the absence of any association with LDL cholesterol requires explicit examination rather than silent omission. LDL constitutes the major fraction of total cholesterol, so a strong association with the latter (odds ratio 5.04) alongside a null association with the former (odds ratio 0.91) is internally difficult to reconcile.

The most probable explanation is methodological and concerns how LDL cholesterol was determined. The study proforma records total cholesterol, triglycerides and LDL cholesterol but not high-density-lipoprotein cholesterol, and does not state whether LDL was assayed directly or calculated. This distinction matters. If LDL was calculated by the Friedewald equation, which assumes a fixed 5:1 ratio of triglyceride to very-low-density-lipoprotein cholesterol, then systematic misestimation is expected in this cohort: although the classical caution concerns triglycerides above 400 mg/dL, discordance between Friedewald-derived and reference LDL values becomes appreciable above 150 mg/dL,[16] a range occupied by a substantial proportion of these prediabetic participants. Misestimation concentrated in the participants most likely to have thyroid dysfunction would blur a true gradient toward the null, which is what was observed. If instead LDL was measured directly by homogeneous assay, this explanation does not apply and the null result requires a different account. Because the derivation method was not documented, we cannot determine which situation obtains, and we therefore report the finding as observed without claiming to have explained it.

Resolving the question would require recalculating LDL cholesterol by an equation that handles raised triglycerides better — the Martin–Hopkins equation, which substitutes an adjustable for the fixed ratio, or the Sampson–National Institutes of Health equation, which estimates very-low-density-lipoprotein cholesterol by multiple least-squares regression and remains accurate to triglyceride concentrations of 800 mg/dL.[17,18] Both equations require high-density-lipoprotein cholesterol, which was not measured in this study, so neither recalculation is possible here. This is a concrete methodological lesson for subsequent work in this population rather than a deficiency that can be remedied retrospectively.

Two further considerations bear on interpretation. Dichotomisation of LDL at 129 mg/dL discards information and reduces power, so a genuine but modest gradient could have been obscured. And a pooled analysis of 69,006 participants from sixteen international cohorts found lipid levels broadly similar across subclinical thyroid dysfunction categories,[15] indicating that lipid associations in subclinical disease are considerably less consistent than the mechanistic literature alone would suggest. Since subclinical hypothyroidism constituted two-thirds of the abnormalities in this cohort, a muted or absent LDL signal is not in itself implausible.

The null association with hypertension is unsurprising and consistent with the same pooled analysis, which found blood pressure largely independent of subclinical thyroid status.[15]

Clinical features

The symptom data carry a clear practical message. Apart from fatigability, classical hypothyroid symptoms were rare — cold intolerance in 3.2%, hair loss in 6.0%, weight gain in 10.1% — and fatigability itself is among the least specific symptoms in medicine, affecting more than one in five middle-aged adults in general population surveys.[19] Symptom-based case-finding would therefore have missed the great majority of participants identified biochemically here. This accords with population-based evidence that patients with biochemical subclinical hypothyroidism report no more thyroid-related symptoms than euthyroid controls,[20] and that symptom scores perform poorly for identifying hypothyroidism in older people.[21] The implication is that if thyroid dysfunction is to be detected in prediabetic adults, it must be sought biochemically in defined risk groups rather than pursued on clinical suspicion.

Clinical implications

The public health arithmetic is the decisive consideration here. With a national prediabetes prevalence of 15.3%, India has of the order of 136 million adults in this state.[1] Adding a thyroid function test for every one of them is not a feasible proposition for any health system, and the practical question is therefore not whether thyroid dysfunction is common in prediabetes — our data indicate that it is — but whether a defensible rule exists for deciding whom to test. Our data delineate candidate criteria: prediabetic women, adults over 60 years, and those who are overweight, obese or dyslipidaemic. In the obese subgroup nearly two-thirds had an abnormal thyroid profile, a yield high enough to make targeted testing worth evaluating seriously.

Three cautions temper that conclusion, and each is material at population scale. First, the candidate criteria are strongly intercorrelated: older women are more often obese and dyslipidaemic, so a rule combining all of them may add little over the best single criterion. Because the present analysis is unadjusted, it cannot determine which of these

criteria carry independent information, and a rule combining all of them may perform no better than the best single criterion; establishing this is a prerequisite for any screening proposal. Second, detection is not in itself a benefit. Randomised evidence shows that levothyroxine in subclinical hypothyroidism confers no clinically relevant improvement in quality of life or thyroid-related symptoms, and current guidance recommends against treating most adults with the condition.[22,23] Since subclinical hypothyroidism accounted for two-thirds of the abnormalities found here, a screening programme built on this yield would identify many people for whom no beneficial intervention exists. Third, because these abnormalities were not confirmed on repeat testing, a proportion would have resolved spontaneously, so the true yield of confirmed disease is lower than the figures reported.

The appropriate next step for policy is therefore not a screening recommendation but a formal economic evaluation: a decision-analytic model comparing risk-stratified case-finding against universal screening and against no screening, reporting incremental cost per confirmed case detected and per quality-adjusted life-year gained at Indian willingness-to-pay thresholds, and incorporating both the spontaneous resolution rate of unconfirmed subclinical hypothyroidism and the limited treatment benefit in that group. Only such an analysis can determine whether the associations reported here justify any change in practice at population level. We advance them as the empirical basis for that evaluation rather than as a recommendation in themselves.

Strengths and limitations

Strengths include a reasonably large sample for this literature, universal application of the same assay platform and thresholds, exclusion of participants taking drugs known to perturb thyroid indices, recruitment of individuals who were not themselves acutely ill, and complete lipid and anthropometric data on all participants.

The limitations are substantial. The cross-sectional design precludes any inference about temporality or causality; for adiposity and dyslipidaemia in particular, the direction of association cannot be established from these data. The most consequential limitation is the absence of multivariable adjustment. Age, sex, body mass index and lipid indices are strongly intercorrelated in this population — older women are more often obese and dyslipidaemic — so the association attributed to any one variable may be substantially attributable to the others. Because the individual participant records from this 2016 study are no longer retrievable and adjusted estimates cannot be reconstructed from marginal contingency tables, none of the correlates reported can be described as independent. Residual confounding by variables never measured, including smoking, alcohol intake, socioeconomic status, dietary iodine and physical activity, compounds this. Thyroid status rested on a single measurement without confirmatory retesting, almost certainly inflating the prevalence of subclinical hypothyroidism. The study protocol defined overt hypothyroidism as requiring both FT3 and FT4 to be subnormal, whereas conventional criteria require only a low FT4 with raised TSH; this will have shifted some genuinely overt cases into the subclinical category, and the proportions in Table 2 should be read with that in mind. As set out in the Methods, this misclassification does not affect any of the reported associations, whose outcome variable is the presence of thyroid dysfunction of any type. Participants were hospital attendants rather than a community sample, limiting generalisability. Prediabetes was defined without an oral glucose tolerance test, so those with isolated impaired glucose tolerance were not captured, and glutamic acid decarboxylase antibody and C-peptide were not measured, so latent autoimmune diabetes in adults could not be excluded. High-density-lipoprotein cholesterol was not measured, so the atherogenic dyslipidaemia characteristic of insulin resistance could not be fully described, non-HDL cholesterol and lipid ratios could not be computed, and LDL cholesterol could not be recalculated by contemporary equations. Whether LDL was assayed directly or calculated is not documented in the protocol. Lipids and body mass index were analysed as dichotomised categories rather than as continuous variables, which discards information and reduces statistical power. Waist circumference, a better index of visceral adiposity than BMI in South Asian populations, was not recorded. Reference intervals were manufacturer-derived rather than locally validated and were not age-specific — a material consideration given that the strongest age signal lay in the oldest group, where TSH distributions shift upward with age. Finally, data were collected in 2016, and symptoms were elicited by direct enquiry rather than by a validated instrument.

Future directions

Three extensions would materially advance this work. First, a prospective community-based cohort with confirmatory repeat thyroid-stimulating hormone measurement after six to twelve weeks, and with an oral glucose tolerance test at entry, would yield a defensible estimate of the burden of confirmed thyroid disease in prediabetes and permit assessment of incident rather than merely prevalent risk. Such a study should also record waist circumference, which better reflects visceral adiposity in South Asian populations than body mass index, measure high-density-lipoprotein cholesterol, and determine LDL cholesterol directly by homogeneous assay rather than by calculation.

Second, any risk-stratification rule for thyroid testing in prediabetes must be derived from a multivariable model in a dataset where individual records are available, and then validated in an independent cohort, with reporting of sensitivity, specificity and number needed to test at candidate thresholds. The associations described here identify candidate criteria for such a rule but cannot themselves constitute one.

This experience also underlines a general point about data stewardship: analyses that cannot be revisited because participant-level records have not been preserved impose a permanent ceiling on what a dataset can contribute, and prospective studies should plan for long-term retention of anonymised records from the outset.

Third, and most important for public health, the decision-analytic evaluation outlined above should be undertaken. Given the scale of the Indian prediabetic population and the limited benefit of treating subclinical hypothyroidism, the question of whether any thyroid screening strategy in prediabetes is cost-effective remains genuinely open, and answering it would be of greater practical value than further prevalence surveys.

CONCLUSION

Two in five adults with prediabetes in this North Kerala cohort had an abnormal thyroid profile, with subclinical hypothyroidism the dominant pattern and hyperthyroidism uncommon. Thyroid dysfunction was associated with female sex, age above 60 years specifically rather than with advancing age generally, increasing adiposity and raised total cholesterol and triglycerides, but not with LDL cholesterol or hypertension. Classical symptoms were infrequent and non-specific, so biochemical case-finding in defined risk groups is far more likely to be productive than clinical suspicion.

The population-level implication is the substantive one. India has of the order of 136 million adults with prediabetes, and universal thyroid screening of that population is not affordable under any plausible health budget. The subgroups identified here — prediabetic women, adults over 60 years, and those who are obese or dyslipidaemic — represent the rational starting point for a risk-stratified alternative. That alternative is not, however, yet justified by evidence. Because the present estimates are unadjusted, it remains unknown which of these characteristics carries independent predictive information. Because thyroid status rested on a single unconfirmed measurement, because a substantial proportion of unconfirmed subclinical hypothyroidism resolves spontaneously, and because treating subclinical hypothyroidism confers little demonstrable clinical benefit, the yield of such a programme in confirmed and treatable disease would be considerably lower than the prevalence figures suggest. A formal cost-effectiveness evaluation comparing risk-stratified case-finding with universal and with no screening is the necessary next step, and these findings are offered as the empirical basis for that evaluation rather than as a screening recommendation.

Declarations

Ethics approval and consent to participate: Approved by the Institutional Ethics Committee, Government Medical College, Kozhikode. Written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: NT conceived the study, collected and analysed the data and drafted the manuscript. KGSK supervised the clinical conduct of the study and critically revised the manuscript. SEK contributed to study design and data interpretation. SSN supervised the laboratory analyses, contributed to interpretation of the biochemical data and critically revised the manuscript. All authors read and approved the final manuscript.

Related publication: The relationship between parental history of type 2 diabetes mellitus and thyroid dysfunction in this same cohort is reported in a companion manuscript. The two analyses address distinct research questions and use different primary exposure variables; the shared cohort is disclosed here and in the accompanying cover letter.

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