Section: Miscellaneous

Original Research Article

PARENTAL HISTORY OF TYPE 2 DIABETES MELLITUS AS A PREDICTOR OF THYROID DYSFUNCTION IN PREDIABETIC ADULTS: A CROSS-SECTIONAL STUDY FROM NORTH KERALA

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ABSTRACT

Background: Prediabetes and thyroid dysfunction are both highly prevalent in South India and are linked through insulin resistance and shared genetic determinants. Type 2 diabetes mellitus (T2DM) is strongly heritable, with parental transmission the dominant mode. Whether a parental history of T2DM identifies prediabetic individuals who are also at heightened risk of thyroid dysfunction has not previously been examined. The objective is to examine, in an exploratory analysis, whether a history of T2DM among the parents of prediabetic adults is associated with the occurrence of thyroid dysfunction, and to describe the relationship between thyroid autoimmunity and thyroid dysfunction in this population.

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 aged over 18 years meeting American Diabetes Association criteria for prediabetes (fasting plasma glucose 100–125 mg/dL and/or HbA1c 5.7–6.4%) were consecutively enrolled. Participants on drugs affecting thyroid function, with prior thyroid ablation, pregnancy, or chronic hepatic or renal disease were excluded. Participants were stratified into two equal groups (n = 158 each) by the presence or absence of T2DM in one or both parents. Serum free triiodothyronine, free thyroxine and thyroid-stimulating hormone were measured by electrochemiluminescence immunoassay, and anti-thyroid peroxidase (anti-TPO) antibody by immunoenzymometric assay. Associations were tested by the chi-square test with Yates' continuity correction and by Fisher's exact test, with unadjusted odds ratios and 95% confidence intervals derived from the contingency tables. No multivariable adjustment was undertaken.

Results: Of 316 prediabetic adults (mean age 47.5 years; 53.2% male), thyroid dysfunction was present in 126 (39.8%), the commonest pattern being subclinical hypothyroidism (26.6%). Thyroid dysfunction was more frequent among those with a parental history of T2DM than among those without (45.6% versus 34.2%; unadjusted odds ratio 1.61, 95% CI 1.02–2.54). This difference was of borderline statistical significance and was sensitive to the test applied: uncorrected Pearson χ^2 yielded p = 0.039, whereas Yates' continuity correction yielded p = 0.051 and Fisher's exact test p = 0.051. The corresponding fragility index was 1, indicating that reclassification of a single participant would abolish nominal significance. A similar pattern was observed for hypothyroidism (41.1% versus 28.5%; unadjusted odds ratio 1.76, 95% CI 1.10–2.80; p = 0.018 uncorrected, p = 0.025 with continuity correction), whereas hyperthyroidism showed no relationship with parental history. Anti-TPO antibody positivity was

strongly associated with thyroid dysfunction (46.0% versus 10.0%; odds ratio 7.68, 95% CI 4.26–13.84; $p < 0.001$), the only association in the study that was robust to correction for multiple comparisons.

Conclusion: In this cross-sectional sample of prediabetic adults, a parental history of type 2 diabetes mellitus was associated with a modest excess of thyroid dysfunction, principally hypothyroidism. Because the estimates are unadjusted, the significance is borderline and the design precludes any inference about temporality or causality, these findings should be regarded as hypothesis-generating rather than as establishing family history as a screening criterion. Prospective cohort studies incorporating multivariable adjustment, confirmatory repeat thyroid testing and formal cost-effectiveness evaluation are required before any change in clinical practice can be contemplated.

Keywords: Prediabetic state; Thyroid diseases; Hypothyroidism; Medical history taking; Autoantibodies; India.

INTRODUCTION

Prediabetes is an intermediate state of dysglycaemia that carries a substantial risk of progression to overt type.[1,2] diabetes mellitus (T2DM) and is itself associated with microvascular and macrovascular injury. The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) national survey estimated the weighted prevalence of prediabetes in India at 15.3% and that of diabetes at 11.4%, with prediabetes exceeding diabetes in most states and being more frequent in rural than in urban populations.[1] The absolute number of Indian adults occupying this intermediate state therefore runs into hundreds of millions, and any screening strategy applied indiscriminately to all of them would be neither affordable nor sustainable. Risk stratification within the prediabetic population is consequently a practical necessity rather than an academic exercise.

Thyroid dysfunction is the second endocrine disorder that frequently accompanies dysglycaemia. Community-based data show a graded increase in the prevalence of thyroid dysfunction across the spectrum of glucose tolerance, from 7.6% in normoglycaemic individuals to 9.3% in prediabetes and 11.6% in established T2DM, with subclinical hypothyroidism the predominant abnormality.[2] A meta-analysis of prospective observational studies has demonstrated that elevated thyroid-stimulating hormone (TSH) is associated with a 17% higher risk of incident T2DM, while low free triiodothyronine and low free thyroxine confer 40% and 33% higher risks respectively, describing a J-shaped relationship with TSH and inverted-J-shaped relationships with the free hormones.[3] A large prospective cohort has similarly shown that individuals with elevated TSH carry a 15% excess risk of incident prediabetes.[4] Recent Indian data confirm that thyroid abnormalities, particularly raised TSH, are commoner in prediabetic individuals than in matched normoglycaemic controls.[5] The relationship is bidirectional and biologically plausible: thyroid hormone opposes insulin action in the liver while acting synergistically with insulin in skeletal muscle and adipose tissue, and subclinical hypothyroidism is independently associated with the metabolic syndrome and its components.[6,7]

Against this background, the heritability of T2DM is well established and unusually high. In a large family-based cohort with genomic correction of pedigree structure, the family-based heritability of T2DM was estimated at 65%, and the likelihood of parental transmission substantially exceeded that of sibling transmission (odds ratio 4.11 versus 1.65); a family history among first-degree relatives was far more informative than one among second-degree relatives (odds ratio 3.84 versus 0.59).[8] Crucially, thyroid function and glycaemic regulation are not genetically independent. Genome-wide association analysis of thyroid traits, followed by Mendelian randomisation, has shown that genetically determined TSH concentrations correlate with glycaemic levels, and that anti-thyroid peroxidase (anti-TPO) antibody status shares genetic architecture with later metabolic and cardiac disease.[9] The type 2 iodothyronine deiodinase (DIO2) Thr92Ala polymorphism, which governs intracellular conversion of thyroxine to triiodothyronine, has been repeatedly implicated in insulin resistance, body mass index and glycaemic control, and provides a candidate molecular substrate linking the two axes.[10,11]

If T2DM and thyroid dysfunction share heritable determinants, then a parental history of T2DM might mark not only the individual's risk of progressing to diabetes but also a coexisting predisposition to thyroid disease. Prediabetic adults are the natural population in which to test this proposition, because dysglycaemia is already present but antidiabetic pharmacotherapy — which itself influences thyroid indices — has not yet been introduced. An extensive review of the literature did not identify any study that has examined whether family history of diabetes predicts thyroid dysfunction within a prediabetic cohort. The present study was therefore undertaken as an exploratory investigation to examine whether a history of T2DM among the parents of prediabetic subjects is associated with the occurrence of thyroid dysfunction, and to characterise the contribution of thyroid autoimmunity to the thyroid abnormalities observed. Given the cross-sectional design, the intention was to generate rather than to test a hypothesis.

MATERIALS AND METHODS

Study design and setting: This was a hospital-based observational cross-sectional study conducted in the Department of General Medicine, Government Medical College, Kozhikode, Kerala, over a period of one year from January 2016 to December 2016. The report conforms to 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 during the study period. This group was chosen because it provides access to community-dwelling adults who are not themselves acutely ill, thereby avoiding the confounding effect of acute illness on thyroid function tests. Individuals aged over 18 years were screened by fasting plasma glucose and/or glycated haemoglobin, and those satisfying the 2016 American Diabetes Association criteria for prediabetes — fasting plasma glucose 100–125 mg/dL and/or HbA1c 5.7–6.4% — were considered eligible.

Participants were excluded if they had established diabetes mellitus or were receiving antidiabetic medication; were taking corticosteroids, amiodarone, lithium or antithyroid drugs; had undergone thyroidectomy or radioactive iodine therapy; were pregnant or lactating; had a history of chronic renal or hepatic disease; or declined consent. Eligible participants were interviewed regarding the presence of diabetes mellitus in one or both parents and were allocated to two groups on this basis: Group 1, parental history of T2DM present (n = 158), and Group 2, parental history absent (n = 158). The recruitment pathway is summarised in Figure 1.

Sample size: The sample size was calculated using the formula $n = 4pq/d^2$, taking p as the reported prevalence of prediabetes in Kerala. A total of 316 participants meeting the inclusion criteria were enrolled and analysed.

Measurements: A structured proforma was used to record 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 recorded, and a complete general and systemic examination was performed. Body mass index was categorised using World Health Organization Asia-Pacific cut-offs as normal (18.5–22.9 kg/m²), overweight (23.0–27.5 kg/m²) and obese (>27.5 kg/m²).

Serum free thyroxine (FT4), free triiodothyronine (FT3) and thyroid-stimulating hormone (TSH) were estimated by electrochemiluminescence immunoassay (ECLIA). Anti-thyroid peroxidase (anti-TPO) antibody was assayed by immunoenzymometric assay. The laboratory 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 tests and liver function tests were performed for all participants in the central laboratory of the institution. Ultrasonography of the thyroid was performed where clinically indicated.

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 the reference interval were classified as euthyroid.

Statistical analysis: Data were entered on a structured proforma and analysed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as frequencies and percentages and continuous variables as mean ± standard deviation. Associations between categorical variables were tested using the Pearson chi-square test; because several cell counts were modest and the primary comparison lay close to the conventional significance threshold, the chi-square statistic with Yates' continuity correction and Fisher's exact test are reported alongside the uncorrected value for every comparison. Unadjusted odds ratios with 95% confidence intervals were derived from the corresponding two-by-two contingency tables using the Woolf logit method. For the primary outcome, the fragility index — the number of participants whose reclassification from event to non-event would render the result non-significant — was calculated as an index of the robustness of the finding. A two-sided p value below 0.05 was taken as nominally statistically significant.

Two features of the analysis warrant explicit statement. First, all effect estimates presented are unadjusted; multivariable logistic regression accounting for age, sex and body mass index was not performed, and the odds ratios reported must therefore not be interpreted as independent effects. Second, five outcomes were examined without a formally pre-specified primary endpoint and without correction for multiplicity; under a Bonferroni threshold of 0.010 for five comparisons, only the association between anti-TPO antibody positivity and thyroid dysfunction would retain significance. The analyses relating to parental history should accordingly be read as exploratory.

The sample size of 316 was determined using the single-proportion formula $n = 4pq/d^2$, which estimates a prevalence rather than powering a two-group comparison. A post-hoc calculation indicates that detecting the observed difference of 45.6% versus 34.2% with 80% power at a two-sided alpha of 0.05 would require approximately 289 participants per group; the achieved power with 158 participants per group is therefore approximately 54%. The study is consequently underpowered for its principal

comparison, and this is acknowledged as a substantive limitation rather than presented as an incidental caveat.

Ethical considerations: The study protocol was approved by the Institutional Ethics Committee of Government Medical College, Kozhikode. All participants were counselled regarding the purpose, design and implications of the study, and written informed consent was obtained from each participant before enrolment. Participants found to have thyroid dysfunction were referred for appropriate clinical evaluation and management.

RESULTS

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
Parental history of type 2 diabetes mellitus		
Present (one or both parents)	158	50.0
Absent	158	50.0
Comorbidity and lipid profile		
Hypertension	173	54.7
Total cholesterol ≥200 mg/dL	164	51.9
Serum triglycerides ≥150 mg/dL	206	65.2
LDL cholesterol ≥129 mg/dL	140	44.3
Anti-TPO antibody positive	77	24.4

Anti-TPO, anti-thyroid peroxidase antibody; LDL, low-density lipoprotein. Percentages are of the total cohort of 316 participants.

Characteristics of the study population: Three hundred and sixteen prediabetic adults were enrolled and analysed. The age of participants ranged from 23 to 66 years, with a mean of 47.5 years. The largest single age band was 41–50 years, which accounted for 98 participants (31.0%), followed by 51–60 years with 84 participants (26.6%); only 13 participants (4.1%) were aged 30 years or below. There was a slight male preponderance, with 168 men (53.2%) and 148 women (46.8%). The mean HbA1c of the cohort was 5.9 ± 0.19%, all values falling within the prediabetic range of 5.7–6.4%. Overweight or obesity was present in 168 participants (53.2%), hypertension in 173 (54.7%) and hypertriglyceridaemia in 206 (65.2%). By design, 158 participants (50.0%) reported diabetes mellitus in one or both parents. The characteristics of the cohort are presented in [Table 1].

Overall prevalence and pattern of thyroid dysfunction: Thyroid dysfunction was detected in 126 of the 316 prediabetic participants, giving an overall prevalence of 39.8%. Hypothyroidism accounted for the overwhelming majority of abnormalities: subclinical hypothyroidism was present in 84 participants (26.6%) and overt hypothyroidism in 26 (8.2%), together comprising 110 of the 126 abnormal results (87.3%). Hyperthyroidism was distinctly uncommon, with subclinical hyperthyroidism in 12 participants (3.8%) and overt hyperthyroidism in only 4 (1.3%). Anti-TPO antibody was positive in 77 participants (24.4%) overall.

Thyroid dysfunction in relation to parental history of type 2 diabetes: Of the 158 participants with a parental history of T2DM, 72 (45.6%) had thyroid dysfunction, compared with 54 of the 158 participants (34.2%) without such a history — an absolute difference of 11.4 percentage points, corresponding to an unadjusted odds ratio of 1.61 (95% CI 1.02–2.54) and a relative risk of 1.33 (95% CI 1.01–1.76). The statistical significance of this difference was borderline and depended on the test applied. The uncorrected Pearson chi-square statistic was 4.28 (df = 1, p = 0.039); with Yates' continuity correction the statistic fell to 3.82 (p = 0.051), and Fisher's exact test gave p = 0.051. The fragility index was 1, indicating that the reclassification of a single participant in either group — for example, a single borderline TSH value or a single misreported parental history — would move the uncorrected p value above 0.05. The lower bound of the confidence interval likewise lies immediately adjacent to unity. The primary contingency table is presented in Table 2 and the recruitment and outcome pathway in Figure 1.

Table 2: Thyroid dysfunction in prediabetic adults according to parental history of type 2 diabetes mellitus

Parental history of type 2 diabetes mellitus	Thyroid dysfunction present, n (%)	Euthyroid, n (%)	Total
Present	72 (45.6)	86 (54.4)	158
Absent	54 (34.2)	104 (65.8)	158
Total	126 (39.8)	190 (60.2)	316

Uncorrected Pearson $\chi^2 = 4.28$, df = 1, p = 0.039; χ^2 with Yates' continuity correction = 3.82, p = 0.051; Fisher's exact test p = 0.051. Unadjusted odds ratio 1.61 (95% CI 1.02–2.54); relative risk 1.33 (95% CI 1.01–1.76); absolute risk difference 11.4 percentage points; fragility index 1.

When the pattern of thyroid dysfunction was examined in detail [Table 3], the excess associated with parental history appeared confined to hypothyroidism. Hypothyroidism of any degree was present in 65 participants (41.1%) in the group with a parental history and in 45 participants (28.5%) in the group without (uncorrected $\chi^2 = 5.58$, p = 0.018; with continuity correction p = 0.025), corresponding to an unadjusted odds ratio of 1.76 (95% CI 1.10–2.80). Considered separately, neither subclinical hypothyroidism (31.0% versus 22.2%; p = 0.075) nor overt hypothyroidism (10.1% versus 6.3%; p = 0.219) reached nominal significance, although both showed the same direction of effect and effect sizes of similar magnitude, which may reflect loss of statistical power on subdivision rather than a genuine difference between the two forms. Hyperthyroidism showed no association with parental history (4.4% versus 5.7%; p = 0.608), the point estimate lying on the opposite side of unity (odds ratio 0.77, 95% CI 0.28–2.11). It should be emphasised that none of these comparisons would retain significance under Bonferroni correction for the five outcomes examined.

Among the 126 participants who already had thyroid dysfunction, the relative distribution of hypothyroid and hyperthyroid patterns did not differ significantly by parental history ($\chi^2 = 1.34$, p = 0.247). Parental history therefore appears to influence whether thyroid dysfunction is present rather than which type of dysfunction occurs. The effect estimates for all outcomes are summarised in Table 4 and displayed graphically in [Figure 2].

Table 3: Distribution of thyroid function categories according to parental history of type 2 diabetes mellitus

Thyroid status	Parental history present (n = 158), n (%)	Parental history absent (n = 158), n (%)	Total (N = 316), n (%)
Euthyroid	86 (54.4)	104 (65.8)	190 (60.2)
Subclinical hypothyroidism	49 (31.0)	35 (22.2)	84 (26.6)
Overt hypothyroidism	16 (10.1)	10 (6.3)	26 (8.2)
Subclinical hyperthyroidism	5 (3.2)	7 (4.4)	12 (3.8)
Overt hyperthyroidism	2 (1.3)	2 (1.3)	4 (1.3)
All thyroid dysfunction	72 (45.6)	54 (34.2)	126 (39.8)

Percentages are calculated within each parental-history column. The overall distribution of thyroid function categories differed between the two groups principally through the hypothyroid categories.

Table 4: Unadjusted association between parental history of type 2 diabetes mellitus and thyroid outcomes

Outcome	Parental history present, n (%)	Parental history absent, n (%)	Odds ratio (95% CI)	p value
Any thyroid dysfunction	72 (45.6)	54 (34.2)	1.61 (1.02–2.54)	0.039
Hypothyroidism (overt + subclinical)	65 (41.1)	45 (28.5)	1.76 (1.10–2.80)	0.018
Subclinical hypothyroidism	49 (31.0)	35 (22.2)	1.58 (0.95–2.62)	0.075
Overt hypothyroidism	16 (10.1)	10 (6.3)	1.67 (0.73–3.80)	0.219
Hyperthyroidism (overt + subclinical)	7 (4.4)	9 (5.7)	0.77 (0.28–2.11)	0.608

CI, confidence interval. Odds ratios are unadjusted and were derived from two-by-two contingency tables using the Woolf logit method; p values are from the Pearson chi-square test.

Thyroid autoimmunity: Anti-TPO antibody positivity was strongly and highly significantly associated with the presence of thyroid dysfunction. Fifty-eight of the 126 participants with thyroid dysfunction (46.0%) were anti-TPO positive, compared with only 19 of the 190 euthyroid participants (10.0%) ($\chi^2 = 53.37$, p < 0.001), giving an odds ratio of 7.68 (95% CI 4.26–13.84) and a relative risk of 4.60 (95% CI 2.89–7.34). Notably, one in ten participants with entirely normal thyroid function tests nonetheless carried anti-TPO antibody, identifying a subgroup at risk of future thyroid failure despite currently normal biochemistry. These findings are presented in [Table 5 and Figure 3].

Table 5: Anti-thyroid peroxidase antibody status in relation to thyroid dysfunction

Anti-TPO antibody status	Thyroid dysfunction present (n = 126), n (%)	Euthyroid (n = 190), n (%)	Total (N = 316), n (%)
Positive	58 (46.0)	19 (10.0)	77 (24.4)
Negative	68 (54.0)	171 (90.0)	239 (75.6)

Pearson $\chi^2 = 53.37$, df = 1, p < 0.001. Odds ratio 7.68 (95% CI 4.26–13.84); relative risk 4.60 (95% CI 2.89–7.34).

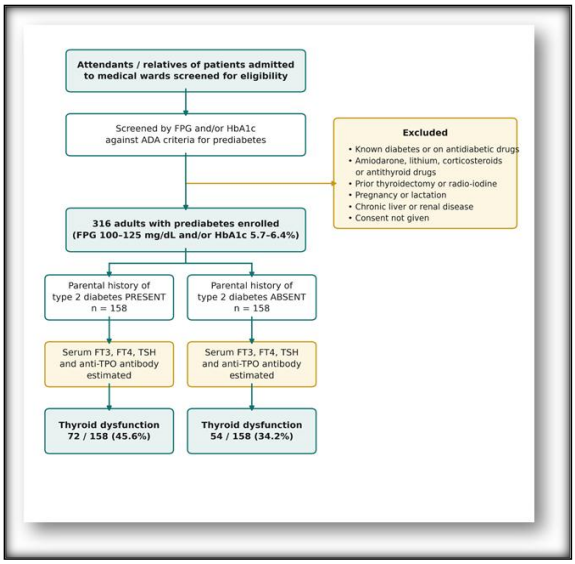

Figure 1: Flow of participants through the study

ADA, American Diabetes Association; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; TSH, thyroid-stimulating hormone.

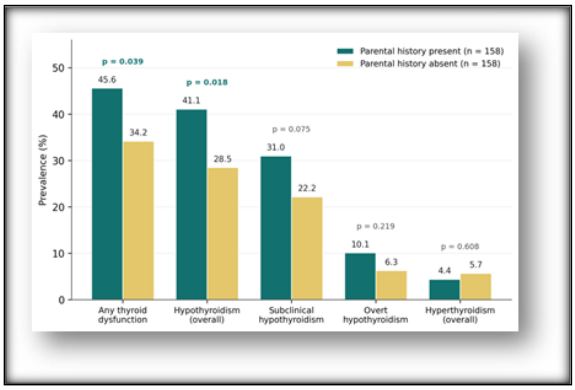

Figure 2: Prevalence of thyroid dysfunction and its subtypes according to parental history of type 2 diabetes mellitus

p values are from the Pearson chi-square test comparing the two parental-history groups for each outcome. The excess associated with parental history is confined to the hypothyroid categories.

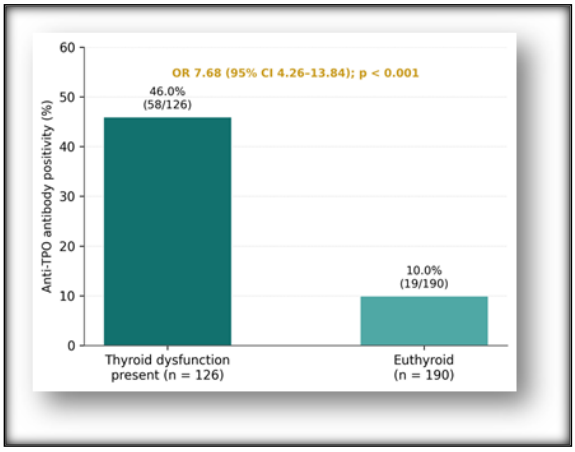

Figure 3: Anti-thyroid peroxidase antibody positivity in relation to thyroid function status

Anti-TPO, anti-thyroid peroxidase antibody; CI, confidence interval; OR, odds ratio.

DISCUSSION

The principal observation of this study is that among adults with prediabetes, those reporting a parental history of type 2 diabetes mellitus showed a higher prevalence of thyroid dysfunction than those without such a history — 45.6% against 34.2%, an unadjusted odds ratio of 1.61. To our knowledge this is the first report to examine family history of diabetes in relation to thyroid dysfunction specifically within a prediabetic population. The excess appeared attributable to hypothyroidism, with hyperthyroidism showing no relationship to parental history. Two qualifications must accompany this observation from the outset and govern the interpretation that follows. First, the association is of borderline statistical significance: it is nominally significant by uncorrected chi-square but not by Yates-corrected chi-square or Fisher's exact test, and its fragility index of 1 means that a single reclassified participant would abolish it. Second, and equally important, the estimate is entirely unadjusted; age, sex and body mass index are each independent determinants of thyroid dysfunction and may plausibly differ between the exposure groups, so the possibility that the association is wholly or partly confounded cannot be excluded from these data. The discussion that follows therefore concerns a candidate association meriting further examination, not an established one.

That said, the direction of the finding is at least biologically coherent rather than arbitrary. Hypothyroidism and dysglycaemia converge on insulin resistance, whereas thyrotoxicosis affects glucose homeostasis through a substantially different set of mechanisms; a signal confined to the hypothyroid categories is therefore the pattern that would be anticipated if the association were real. Coherence of this kind is a weak form of evidence and does not substitute for statistical robustness, but it does distinguish the present result from a purely chance finding among many tested associations.

The overall prevalence of thyroid dysfunction in this cohort, 39.8%, is considerably higher than the 9.3% reported among prediabetic individuals in a community-based Chinese survey.[2] and the figures reported from the Tehran Thyroid Study.[12] Three considerations account for much of this gap, and they should be weighed in ascending order of probable importance. First, the present study was hospital-based and drew on attendants of admitted patients rather than on a random community sample, so selection towards individuals with existing health concerns is likely. Second, Kerala is an iodine-sufficient region with a documented high background prevalence of thyroid disorders, and Indian series consistently report higher rates than East Asian ones. Third, and probably most consequential, thyroid status in this study was determined from a single

blood sample. Contemporary practice requires that an isolated elevation of TSH be confirmed on a repeat specimen after an interval of six to twelve weeks, since a substantial proportion of such values normalise spontaneously. Subclinical hypothyroidism accounted for 84 of the 126 abnormal results in this cohort, and the absence of confirmatory retesting is therefore likely to have inflated the reported prevalence appreciably. The figure of 39.8% should accordingly be read as the prevalence of a single abnormal thyroid profile rather than of confirmed thyroid disease. Recent Indian work supports this: a case-control study from Western Maharashtra found thyroid dysfunction, particularly raised TSH, to be significantly commoner in prediabetic individuals than in matched controls,[5] and a tertiary-care series reported thyroid dysfunction in 23.1% of patients with established T2DM.[13] The relative pattern we observed — subclinical hypothyroidism predominating at 26.6%, overt hyperthyroidism the rarest abnormality at 1.3% — is entirely consistent with these and with international data.[2,3]

If the association with parental history is genuine, several mechanisms might underlie it. These are offered as candidate explanations to be tested rather than as inferences supported by the present data, none of which speaks directly to mechanism. The most parsimonious is shared heritability. Family-based analyses place the heritability of T2DM at approximately 65% and identify parental transmission as the dominant route, with a substantially greater effect than sibling transmission.[8] If some of the loci conferring susceptibility to dysglycaemia also influence thyroid function, then parental history of diabetes becomes a crude but serviceable proxy for that shared genetic loading. Direct evidence for such overlap now exists: genome-wide association analysis of thyroid traits with Mendelian randomisation has demonstrated genetic correlation between TSH concentration and glycaemic levels, and between anti-TPO antibody status and later metabolic disease.[9] The DIO2 Thr92Ala polymorphism offers a specific candidate. This variant reduces the velocity of intracellular conversion of thyroxine to triiodothyronine and has been associated with insulin resistance, higher body mass index and poorer glycaemic control in several series, although its effects appear modest and are not consistently replicated across all phenotypes.[10,11]

A second, non-exclusive explanation is that insulin resistance itself — which is present in first-degree relatives of patients with T2DM long before dysglycaemia becomes detectable — mediates the association. Subclinical hypothyroidism is independently associated with the metabolic syndrome, carrying a pooled odds ratio of 1.28 across nearly eighty thousand participants, and with four of its five components.[6] In polycystic ovary syndrome, where insulin resistance is the central abnormality, subclinical hypothyroidism affects approximately one in five women and is accompanied by significantly higher HOMA-IR and fasting insulin.[14] Conversely, obesity at baseline predicts incident overt and subclinical hypothyroidism in prospective cohorts.[7] The relationship between the thyroid and glucose axes is thus reciprocal, and a family history that marks a heavier lifetime burden of insulin resistance could plausibly mark a heavier burden of thyroid dysfunction through this route rather than through any direct genetic link with the thyroid. The reciprocity of this relationship also permits an entirely inverted reading of the present data: hypothyroidism causes weight gain and insulin resistance, and may therefore have contributed to the prediabetic state rather than arising alongside it from a shared genetic origin. A cross-sectional design cannot distinguish between these possibilities, and neither should be presented as the more likely on the evidence available here.

The third mechanism is autoimmune. Anti-TPO positivity in our cohort was associated with a nearly eightfold increase in the odds of thyroid dysfunction, and this was by a wide margin the strongest association observed in the study. Almost half of all participants with thyroid dysfunction were antibody-positive, indicating that autoimmune thyroiditis, and not iodine deficiency, is the dominant aetiology in this iodine-sufficient population. Elevated anti-TPO titres have been reported to be commoner in patients with T2DM and visceral obesity,[15] and thyroid autoimmunity has been examined alongside dysglycaemia in prospective cohorts with mixed results.[16] Of clinical importance is our observation that 10% of biochemically euthyroid prediabetic participants were nonetheless anti-TPO positive: these individuals are, on the evidence of long-term community follow-up, at elevated risk of progressing to overt thyroid failure, and their identification is arguably the most actionable single finding in this dataset.

Any clinical implication must be framed with corresponding caution. Universal thyroid screening of every prediabetic adult in India is not a realistic proposition given the size of the affected population.[1] Parental history of diabetes, by contrast, costs nothing to elicit, requires no laboratory infrastructure, and is already recorded as part of routine diabetes risk assessment, which makes it an attractive candidate for stratification in principle. The present data are not, however, sufficient to support such a recommendation. An unadjusted odds ratio of 1.61 with a confidence interval reaching almost to unity, derived from a study powered at approximately 54% for its own primary comparison, establishes only that the hypothesis is worth testing properly. Whether a stratification of this magnitude would detect enough additional cases to justify its cost is an empirical question that requires a formal decision-analytic model, and it is entirely possible that an effect of this size would prove not to be cost-effective at prevailing Indian willingness-to-pay thresholds. We therefore advance family history as a hypothesis for evaluation in adequately powered prospective

work, and explicitly not as a criterion for immediate adoption in practice.

Strengths and limitations: The strengths of this study include a reasonably large sample by the standards of the literature on thyroid dysfunction in prediabetes, a balanced design with equal numbers in each exposure group, the exclusion of patients on drugs known to perturb thyroid indices, and the measurement of anti-TPO antibody in all participants rather than in a selected subgroup.

The limitations are substantial and are set out here in detail, since they materially constrain what may be inferred from the findings.

Design and temporality: The cross-sectional design permits no inference regarding causality or temporal sequence. Exposure and outcome were ascertained simultaneously, and it cannot be determined whether thyroid dysfunction preceded, followed or was independent of the metabolic state. As noted above, reverse causation — hypothyroidism promoting weight gain and insulin resistance and thereby contributing to prediabetes — remains an equally tenable reading of the same data. The study also cannot estimate incident risk, only prevalent burden.

Confounding and absence of multivariable adjustment: This is the most consequential analytical limitation. All effect estimates presented are unadjusted. Age, sex and body mass index are each established independent predictors of thyroid dysfunction, and each may plausibly be associated with parental history of diabetes; any of them could therefore confound the observed relationship. A multivariable logistic regression model with thyroid dysfunction as the dependent variable and parental history, age, sex and body mass index as covariates would be required to determine whether the association is independent, and no such model was fitted. Baseline characteristics were moreover tabulated for the cohort as a whole rather than stratified by exposure group, so the comparability of the two groups at baseline cannot be assessed from the data presented. Until adjusted estimates are available, the reported odds ratios must not be interpreted as independent effects.

Fragility of the primary finding and statistical power: The primary association is nominally significant by uncorrected chi-square ($p = 0.039$) but not by Yates-corrected chi-square or Fisher's exact test (both $p = 0.051$), and its fragility index is 1. The lower confidence limit of the odds ratio is 1.02. Five outcomes were examined without a pre-specified primary endpoint or adjustment for multiplicity, and none of the parental-history associations would survive Bonferroni correction. The study was additionally underpowered: approximately 289 participants per group would be required to detect the observed difference with 80% power, against the 158 per group available, giving an achieved power of approximately 54%. Taken together, these considerations mean the finding is suggestive and hypothesis-generating, and cannot be regarded as definitive.

Selection bias: Participants were attendants and relatives of patients admitted to medical wards rather than a randomly sampled community cohort. This sampling frame is likely enriched for individuals with a family history of chronic disease and for those with existing health concerns, and may therefore have skewed both the observed prevalence of thyroid dysfunction and the prevalence of the exposure itself. The comparison group of participants without parental diabetes, drawn from the same hospital-attendant frame, may not represent the general prediabetic population. Generalisability beyond a similar tertiary-care setting in North Kerala should not be assumed.

Recall and ascertainment bias: Family history of type 2 diabetes was obtained by participant report and was not verified against parental medical records or by direct parental screening. Self-reported family history is subject to recall error, and to error that may operate asymmetrically: participants whose parents died before the age at which diabetes typically manifests may be misclassified as unexposed, while participants already aware of a family history may be more health-literate and more likely to report accurately. Ascertainment was restricted to parents, so diabetes in siblings and in second-degree relatives — which contributes materially to familial risk — was not captured.

Diagnostic gaps in the definition of dysglycaemia: Prediabetes was defined by fasting plasma glucose and glycated haemoglobin without an oral glucose tolerance test. Participants with isolated impaired glucose tolerance and normal fasting glucose were therefore not identified, and only one pathophysiological subset of prediabetes was sampled; since impaired fasting glucose and impaired glucose tolerance differ in their relationship to thyroid hormone indices, this may have obscured or distorted the association under study. Glutamic acid decarboxylase antibody and C-peptide were not measured, so latent autoimmune diabetes in adults could not be excluded. This omission is not trivial in the present context: thyroid autoimmunity is over-represented in latent autoimmune diabetes,[17] and the inadvertent inclusion of even a small number of such individuals could generate an apparent association between familial dysglycaemia and thyroid dysfunction through a mechanism entirely distinct from the one proposed.

Measurement limitations: Thyroid status was determined from a single blood sample without confirmatory repeat testing, which as discussed above is likely to have inflated the prevalence of subclinical hypothyroidism. The diagnostic criterion applied for overt hypothyroidism required both free triiodothyronine and free thyroxine to be subnormal, whereas conventional criteria require only a low free thyroxine with raised thyroid-stimulating hormone; because free triiodothyronine is often preserved in early overt disease through compensatory deiodination, some genuinely overt cases may have been classified as subclinical. Laboratory reference

intervals were manufacturer-derived rather than locally validated and were not age-specific, and the anti-TPO positivity threshold was not separately established for this population. No genotyping was performed, so the genetic mechanisms discussed remain wholly inferential. Finally, data were collected during 2016, and secular changes in the metabolic profile of the source population since that time cannot be excluded.

Future directions: Four specific extensions of this work are required before the hypothesis advanced here can be either accepted or discarded, and they are presented in the order in which they should logically be undertaken.

First, a prospective longitudinal cohort design is essential. A cohort of prediabetic adults stratified at baseline by family history, followed with serial thyroid function testing at fixed intervals and with every abnormal thyroid-stimulating hormone value confirmed on a repeat specimen after six to twelve weeks, would establish whether parental diabetes predicts incident as well as prevalent thyroid dysfunction, and would resolve the question of temporality that the present design cannot address. Such a study should be powered on the effect size observed here, requiring at least 300 participants per exposure group, and should recruit from a community sampling frame such as a primary health centre or panchayat register rather than from hospital attendants. Incorporation of an oral glucose tolerance test at enrolment would permit separate analysis of isolated impaired fasting glucose, isolated impaired glucose tolerance and combined glucose intolerance.

Second, multivariable analysis must be standard in any future dataset addressing this question. At minimum, logistic regression models should adjust for age, sex and body mass index, with consideration of hypertension, lipid indices and smoking status as additional covariates; baseline characteristics should be tabulated by exposure group; and formal testing for effect modification by sex is warranted given the well-recognised female preponderance of thyroid disease. Mediation analysis incorporating a measure of insulin resistance such as HOMA-IR would allow the competing shared-heritability and insulin-resistance explanations to be distinguished rather than merely enumerated.

Third, expanded diagnostic characterisation would materially strengthen causal inference. Genotyping for the DIO2 Thr92Ala polymorphism, undertaken alongside a detailed three-generation family history, would allow the shared-heritability hypothesis to be tested directly rather than inferred, and would convert the mechanistic discussion above into a falsifiable proposition. Measurement of glutamic acid decarboxylase antibody and C-peptide in all participants would exclude latent autoimmune diabetes in adults as an alternative explanation for any observed association; anti-thyroglobulin antibody alongside anti-thyroid peroxidase antibody, and thyroid ultrasonography performed in all participants rather than only where clinically indicated, would more completely characterise the autoimmune contribution.

Fourth, and indispensably before any change in practice, a formal health-economic evaluation is required. A decision-analytic model should compare family-history-guided thyroid screening with universal screening and with no screening in the Indian prediabetic population, reporting incremental cost per case of thyroid dysfunction detected and per quality-adjusted life-year gained, and incorporating a threshold analysis to identify the minimum odds ratio at which a family-history-guided strategy becomes cost-effective at prevailing Indian willingness-to-pay thresholds. Should the true adjusted effect size prove to be of the modest magnitude observed here, such a strategy may well fail to meet conventional cost-effectiveness criteria — an outcome that would itself be of considerable value to policy, and which cannot be anticipated from prevalence data alone.

CONCLUSION

An abnormal thyroid profile was common in this cross-sectional sample of prediabetic adults from North Kerala, affecting nearly two in five, and was overwhelmingly hypothyroid in pattern with subclinical hypothyroidism predominating; in the absence of confirmatory repeat testing, this figure should be read as an upper estimate. A parental history of type 2 diabetes mellitus was associated with a higher prevalence of thyroid dysfunction, an association apparent for hypothyroidism and absent for hyperthyroidism. This association was, however, of borderline statistical significance, was not adjusted for age, sex or body mass index, and rested on a fragility index of one participant; it therefore identifies a hypothesis worth testing rather than a relationship established.

Thyroid autoimmunity, indicated by anti-thyroid peroxidase antibody positivity, was the strongest and most robust correlate of thyroid dysfunction in this cohort and was detected in a tenth of biochemically euthyroid participants, a subgroup that may warrant longitudinal follow-up in its own right.

Family history of diabetes is a costless item of clinical information and remains an attractive candidate for risk stratification within the very large Indian prediabetic population. On the present evidence, however, it cannot be recommended as a screening criterion. Prospective longitudinal studies with multivariable adjustment, confirmatory thyroid testing, exclusion of latent autoimmune diabetes, and formal cost-effectiveness modelling are required before these observations could justify any modification of clinical practice.

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