

Original citation:

Sailesh, S., Randeve, Harpal S., Callaghan, C. J. O., O'Hare, J. Paul, Philip, Sam, Saravanan, Ponnusamy and Patel, Vinod (2018) The THOR effect : thyroid hormone offsets retinopathy. Journal of Endocrinology and Thyroid Research, 3 (1). 555605.

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The THOR Effect: Thyroid Hormone Offsets Retinopathy



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Submission: July 21, 2017; Published: February 20, 2018

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Abstract

Objective: Thyroid status has been implicated in macrovascular disease both in patients with and without diabetes, however its effect on microvascular complications has not been explored. We assessed the prevalence and time to development of diabetic retinopathy in patients with type 2 diabetes with and without thyroxine treatment.

Research design and methods: The prevalence of retinopathy was determined, in a retrospective cohort study from a secondary care referral diabetes clinic patients with type 2 diabetes and coexisting treated hypothyroidism (THD; n=147) and duration matched controls without hypothyroidism (DM2; n=383). Using Kaplan-Meier survival analysis and Cox Proportional Hazards regression model we estimated the time to development of retinopathy in the two groups.

Results: Prevalence of retinopathy was 27.9% in THD group, as compared to 55.1% in the DM2 group ($p < 0.001$). THD were less than one-third as likely to have concurrent retinopathy than, DM2 patients (OR=0.32; 95% CI=0.21 to 0.48; $p < 0.001$). There was a significant difference in the median time to retinopathy between THD and DM2 patients (21.0yrs vs. 13.0yrs; Log-Rank $p < 0.001$). Risk of developing retinopathy in THD patients was two-fifths of that of DM2 patients (hazard ratio=0.418; $p < 0.001$) in a time-dependent variable analysis. The risk of developing retinopathy was concomitantly lower for patients with longer duration of hypothyroidism and thyroxine treatment prior to diagnosis of diabetes (Hazard ratio=0.957; $p = 0.004$).

Conclusion: A significant sparing effect on development of retinopathy was noted in type 2 diabetic patients with concomitant hypothyroidism (on thyroxine). The exact mechanism(s) for these observations remain to be elucidated.

Keywords: Type 2 diabetes; Hypothyroidism; Diabetic retinopathy; Thyroxine

Introduction

Diabetes related complications are a major health burden worldwide. Tight control of blood glucose and blood pressure delays the onset of complications and reduces rate of progression, including diabetic retinopathy [1,2]. Potential risk factors implicated in the onset of retinopathy include metabolic, haemodynamic and possibly hormonal aberration [3,4]. Low levels of plasma thyroid hormone has been associated with macrovascular complication [5-7]. Furthermore it has been shown that hypothyroidism is a risk factor for atherosclerosis, and thyroid hormone replacement has beneficial effects on the atherogenic process [8,9].

Patients with diabetes have a higher incidence of thyroid dysfunction, compared to that reported in the general population (10-13%) [10-12]. Indeed there exists a state of hypothyroidism in patients with diabetes and in time both hypothyroidism and diabetes can lead to harmful metabolic derangement [12,13].

The impact of thyroid status in the development of diabetic microvascular complications is unknown. There is scant information in literature on the impact of thyroid status on diabetes microvascular complications [14,15]. Based on our findings from a pilot study, [16] we therefore decided to conduct a retrospective case control study to ascertain the prevalence of retinopathy in thyroxine treated patients with diabetes.

Methods

Study design

A retrospective cohort study with data collected from case records and a clinical database was undertaken. Study subjects were selected from patients attending diabetes clinics at a single centre during the 2001 calendar year. Patients attending these diabetes clinics have regular clinical evaluation, blood pressure measurements, biochemical profiles and are monitored annually

for thyroid function and detailed eye examination included retinal photography. In a recent audit of this centre, a 100% annual eye examination and diabetes care profile was noted [17].

Patients with diabetes and primary hypothyroidism, on oral thyroxine replacement, and duration of diabetes-matched controls without biochemical evidence of hypothyroidism were selected for the study. Information with regards to retinopathy was collected from ophthalmology notes and retinal photographs. Date of diagnosis of diabetes and first entry of retinopathy were abstracted from patient records and if necessary collected from patients or from their primary care physicians, when possible, for both the groups.

We identified 152 subjects with coexisting Type 2 diabetes and hypothyroidism on thyroxine therapy. Five of these subjects were excluded from further analyses as there was no information available on their retinopathy status. From an initial attempt to match at least 3 non-hypothyroid patients per hypothyroid patient with respect to the duration of diabetes, 417 patients who had Type 2 diabetes and a thyroid function test result confirming that they were biochemically euthyroid were selected. Subsequently, non-hypothyroid patients for whom no retinopathy data (n=26) existed and who had recently received treatment for thyrotoxicosis (n =8) were excluded from further analyses. Patients were not matched on the basis of gender as an anticipated preponderance of women among hypothyroid patients was to be subsequently controlled for analysis. Data with regards to their thyroid function test, Hba1c, blood pressure, creatinine, body weight and medication were abstracted from their records for all patients.

Statistical analysis

Standard statistical methods including chi-square and Kaplan-Meier survival analyses were employed to contrast the prevalence of retinopathy, and time to development of retinopathy from diabetes diagnosis, respectively, between thyroxine-treated hypothyroid diabetics and non-hypothyroid diabetics. Tests of equality of strata in Kaplan-Meier estimates were performed using both the Log-rank test and the Wilcoxon test. For both prevalence and Kaplan-Meier estimates, separate

analyses were conducted in which hypothyroid diabetic patients who developed retinopathy prior to developing hypothyroidism were analysed as either hypothyroid (i.e. ignoring the temporal relationship between hypothyroidism and retinopathy), non-hypothyroid (acknowledging the temporal relationship) or in a separate category. In order to more explicitly account for the actual “period at risk” of hypothyroidism, univariate and multiple variable Cox Proportional Hazards Regression models were developed in which hypothyroidism was treated as a time-dependent variable in the analysis of time to development of diabetic retinopathy from diagnosis of diabetes mellitus. In addition to controlling for possible age and gender influences, the potential for any concomitant effect of duration of hypothyroidism prior to the development of diabetes on the subsequent risk of development of retinopathy was assessed through the inclusion of an additional parameter in the model accounting for the period of hypothyroidism prior to diabetes diagnosis. In all survival analyses the temporal unit of analysis was calendar year. All statistical analyses were conducted using SAS version 8.02 software (SAS Institute Inc, Cary NC, USA) and statistical significance was considered achieved for p<0.05.

Results

Baseline characteristics

Demographic details on the 147 hypothyroid and 383 non-hypothyroid type 2 diabetic patients available for analysis are presented in Table 1. Hypothyroidism was attributed to thyroidectomy (12), radio-iodine treatment (9), lithium treatment (1) or as either central (1), idiopathic (123) or unknown (1) aetiology. The mean (±SD) age of the hypothyroid group was 66.2 years (±11.2) and that of the non-hypothyroid group was 62.6 years (±10.2) (p<0.001). No differences between the hypothyroid and non-hypothyroid groups in either the duration of diabetes (12.8 years vs. 13.0 years respectively; p=0.83) or HbA1c (8.1gm% vs. 8.0gm% respectively; p=0.63) were noted, however, as anticipated men comprised a significantly lower proportion of the hypothyroid group (19.1% vs 54.8%; p<0.001). Systolic BP, along with TSH and FT4, were significantly higher in the hypothyroid group (Table 1).

Table 1: Demographics of patients with type2 diabetes and hypothyroidism on thyroxine replacement (THD) compared with patients with type2 diabetes without hypothyroidism (DM2). Cohort means for Hba1c, blood pressure, thyroid function profile and lipid profiles were calculated from the mean values for each patient, as determined from all available annual observations made over the 5-year period (1996-2001) prior to their selection.

Covariate	Cohort	N	Mean	SD	P
Age (years)	THD	147	66.2	10.28	0.001
	DM2	383	62.67	11.2	
Duration of diabetes (years)	THD	147	12.89	7.83	0.83
	DM2	382	13.04	7.35	
Systolic BP (mmHg)	THD	147	147.68	18.12	0.03
	DM2	383	144.23	15.98	

Diastolic BP (mmHg)	THD	147	79.97	8.21	0.8
	DM2	383	80.17	8.71	
Cholesterol (mmol/l)	THD	143	5.49	1.12	0.31
	DM2	383	5.38	1.11	
Triglyceride (mmol/l)	THD	130	2.16	1.38	0.13
	DM2	380	2.59	3.19	
HDL Cholesterol (mmol/l)	THD	114	1.35	0.39	0.42
	DM2	357	1.27	1.12	
LDL Cholesterol (mmol/l)	THD	43	2.9	0.92	0.9
	DM2	303	2.9	0.85	
Thyroid Stimulating Hormone (TSH in mU/l)	THD	147	4.29	4.34	<0.001
	DM2	383	1.91	0.99	
Free triiodothyronine (FT3 in pmol/l)	THD	60	3.35	1.37	0.1
	DM2	22	3.89	1.21	
FreeThyroxine (FT4 in nmol/l)	THD	136	16.81	3.87	<0.001
	DM2	146	15.17	2.56	
HbA1c (gm %)	THD	147	8.12	1.22	0.63
	DM2	382	8.02	2.29	
Weight (kg)	THD	142	82.37	18.4	0.007
	DM2	378	87.02	17	
Creatinine (nmol/l)	THD	146	103.43	41.6	0.63
	DM2	380	101.25	49	
Males	THD	28/147 = 19.1%			<0.001
	DM2	210/383 = 54.8%			

Prevalence and severity of retinopathy

The prevalence of any degree of retinopathy was 55.1% in the non-hypothyroid group, compared to only 27.9% in the hypothyroid group (Table 2 (I)A; $p < 0.001$) such that the patients who ever experienced hypothyroidism were less than one-third as likely to suffer from concurrent retinopathy than those patients who had type 2 diabetes but were never hypothyroid. (Odds Ratio=0.32; 95% CI=0.21-0.48; $p < 0.001$). There was no significant difference by gender when this was simultaneously controlled for ($p = 0.63$). However, of the 41 hypothyroid patients who had evidence of retinopathy 14 were diagnosed with hypothyroidism after developing retinopathy, with an average time between diagnoses of 4.7 years (median=3.0, SD=4.0, min=1, max=15). When the data was analysed with these 14 patients reclassified as 'non-hypothyroid' (i.e. at the time of development of retinopathy), a stronger sparing effect of hypothyroidism on the development of diabetic retinopathy was observed (Table 2- IB); Odds Ratio=0.19; 95% CI=0.12-0.31; $p < 0.001$), although once again, no difference by gender was noted when this was simultaneously controlled for ($p = 0.87$).

Of the 252 patients with retinopathy, the prevalence of more severe (classified as sight-threatening) retinopathy was greater

in the non-hypothyroid group (121/211=57.4%) than in the hypothyroid group (15/41=36.6%; $p < 0.001$, Table 2- IIA), with no gender differences ($p = 0.32$). That is to say, type 2 diabetic patients with retinopathy who ever experienced hypothyroidism were less than one-half as likely to suffer from severe, sight-threatening retinopathy than those patients who had type 2 diabetes and retinopathy but were never hypothyroid (OR=0.43; 95% CI=0.21-0.86). When the 14 patients whose diagnosis of retinopathy preceded the diagnosis of hypothyroidism were once again reclassified, the sparing effect of hypothyroidism once again became stronger (OR=0.16; 95% CI=0.06-0.44; Table 2 - IIB), while the influence of gender remained non-significant ($p = 0.55$).

Time to development of retinopathy

Two non-hypothyroid patients and one hypothyroid patient did not have dates of onset of diabetes recorded and were therefore excluded from all time to event analyses. The results of Kaplan-Meier analysis of time to retinopathy between the two groups, in which hypothyroid status was treated as a time-invariant covariate, are presented in Table 2 (III)A through C and in corresponding Figure 1 (Panel A-C).

Table 2: (I) Comparison of proportion of patients with any degree of retinopathy by hypothyroid status without (A) and with (B) reclassification of the 14 patients whose diagnosis of diabetic retinopathy preceded the diagnosis of hypothyroidism; (II) Comparison of proportion of sight threatening retinopathy (STR) among patients with any degree of retinopathy by hypothyroid status without (A) and with (B) reclassification of the 14 patients whose diagnosis of diabetic retinopathy preceded the diagnosis of hypothyroidism; (III) Time from diagnosis with diabetes to development of any degree of retinopathy in years by hypothyroid status without (A), with (B) and with separate (C) reclassification of the 14 patients whose diagnosis of diabetic retinopathy preceded the diagnosis of hypothyroidism.

(I)		Hypothyroid	Non-Hypothyroid	Odds Ratio	95% CI
Retinopathy	A	At any time		0.32 (0.33)*	0.21-0.48 (0.21-0.50)*
		41 / 147 (27.9%)	211 / 383 (55.1%)		
	B	Before Retinopathy	or Hypothyroid after Retinopathy	0.19 (0.19)**	0.12-0.31 (0.12-0.31)**
		27 / 133 (20.3%)	225 / 397 (56.7%)		
*OR and 95% CI while simultaneously controlling for effect of gender (p=0.63)					
**OR and 95% CI while simultaneously controlling for effect of gender (p=0.87)					

(I)

		Hypothyroid	Non-Hypothyroid	Odds Ratio	95% CI
STR	A	At any time		0.43(0.46)*	0.21-0.86 (0.23-0.94)*
		15 / 41 -36.6%	121 / 211 -57.4%		
	B	Before Retinopathy	or Hypothyroid after Retinopathy	0.16(0.17)**	0.06-0.44 (0.06-0.48)**
		5/27/2018 -18.5%	131 / 225 -58.2%		
*OR and 95% CI while simultaneously controlling for effect of gender (p=0.63)					
**OR and 95% CI while simultaneously controlling for effect of gender (p=0.87)					

(II)

Hypothyroid Status and Timing		Total	Retinopathy	% censored	Time to Retinopathy from Diabetes (years)		
					Median	Mean	p
A	Non-Hypothyroid	381	210	44.9	13	14.8	<0.001
	Hypothyroid at any time	146	40	72.6	21	18	
B	Non-Hypothyroid or Hypothyroid after Retinopathy	395	224	43.3	13	14.3	<0.001
	Hypothyroid before Retinopathy	132	26	80.3	20	16.7	
C	Non-Hypothyroid	381	210	44.9	13	14.8	<0.001
	Hypothyroid after Retinopathy	14	14	0	11	11.6	
	Hypothyroid before Retinopathy	132	26	80.3	20	16.7	

(III)

When all hypothyroid diabetics, regardless of when they developed hypothyroidism (before or after retinopathy) were compared to the non-hypothyroid controls, the time to development of retinopathy was significantly shorter in the patients who had never experienced hypothyroidism (Table 2- IIIA) - median = 13 vs. 21 years; p<0.001; Figure1 Panel A) with a hazard ratio (HR) of 0.425 (Table 3A), with no significant differences by gender (p=0.24). However, when the

14 patients who developed hypothyroidism after retinopathy were analysed separately (Table 2 IIC and Figure 1 Panel B) the time to development of retinopathy in this subgroup differed significantly from the other hypothyroid patients (p<0.001), but not from the non-hypothyroid group (p=0.23), and again with no overall differences noted between the genders (p=0.39). These results supported the inclusion of these 14 patients within the non-hypothyroid group in an overall contrast of patients who had

never experienced hypothyroidism or whose hypothyroidism occurred after the development of retinopathy vs. those patients whose hypothyroidism preceded the development of retinopathy (Table 2 IIIB and Figure-1 Panel C). Unsurprisingly the result was an increase in the distinction in time to development of

retinopathy between these two categories (HR=0.302; Table 3B), but again with no effect of gender (p=0.40). Risk of development of sight threatening retinopathy (STR) could not be similarly analysed owing to lack of information on dates of progression of severity of retinopathy.

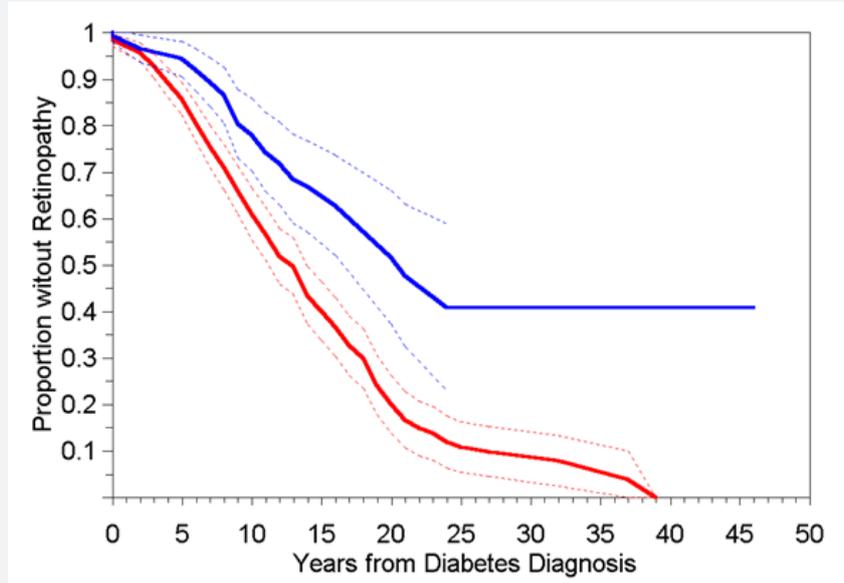


Figure 1 (panel A): Event free survival (development of retinopathy) in 146 patients with type 2 diabetes and hypothyroidism (—; 95% CI ---) compared to 381 patients with type 2 diabetes but no hypothyroidism (—; 95% CI ---), where no significant differences by gender were observed (p=0.24).

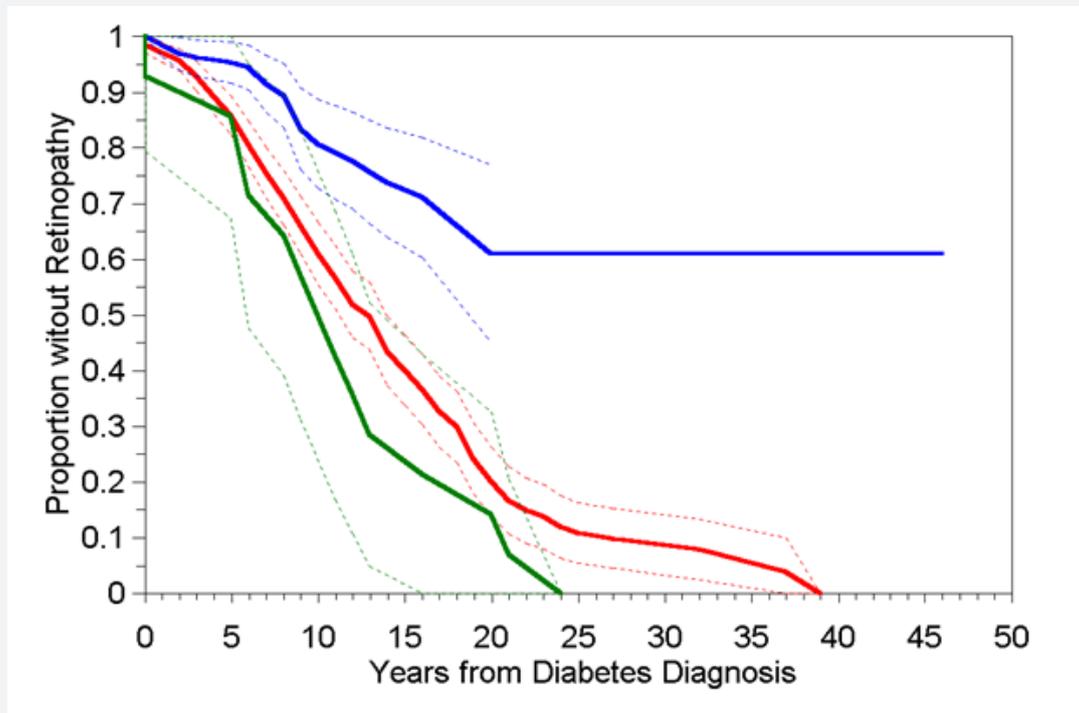


Figure 1 (Panel B): Event free survival (development of retinopathy) in 132 patients with type 2 diabetes and hypothyroidism, where the diagnosis of hypothyroidism preceded the development of retinopathy (—; 95% CI ---) compared to 381 patients with type 2 diabetes but no hypothyroidism (—; 95% CI ---) and 14 patients with type 2 diabetes and hypothyroidism, where the development of retinopathy preceded the diagnosis of hypothyroidism (—; 95% CI ---), where no significant differences by gender were observed (p=0.40).

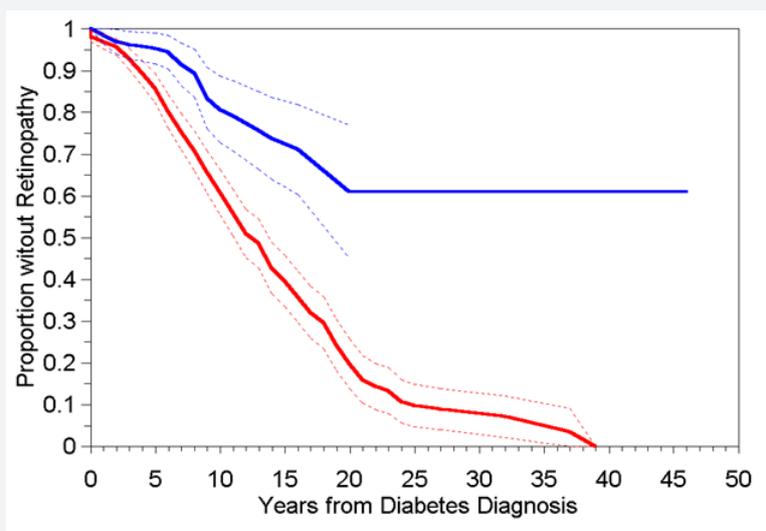


Figure 1 (Panel C): Event free survival (development of retinopathy) in 132 patients with type 2 diabetes and hypothyroidism, where the diagnosis of hypothyroidism preceded the development of retinopathy (—; 95% CI ---) compared to 395 patients with type 2 diabetes but no hypothyroidism or where the development of retinopathy preceded the diagnosis of hypothyroidism (—; 95% CI ---), where no significant differences by gender were observed ($p=0.39$).

Table 3: Results of Cox Proportional Hazards Regressions of time from diagnosis with type 2 diabetes to development of any degree of retinopathy in years.

	Covariates in Model	Hazard Ratio	P
A	Hypothyroid at any time - time-invariant	0.425	<0.001
B	Hypothyroid prior to development of retinopathy - time-invariant	0.302	<0.001
C	Hypothyroid - as time-dependent variable	0.418	<0.001
D	Age at diabetes diagnosis	1.022	<0.001
	Gender (Male)	1.246	0.1
	Ethnic Group (Caucasian)	0.82	0.28
	Hypothyroid - as time-dependent variable	0.395	<0.001
E	Age at diabetes diagnosis	1.019	0.003
	Gender (Male)	1.22	0.14
	Ethnic Group (Caucasian)	0.845	0.36
	Hypothyroid - as time-dependent variable	0.464	<0.001
	Years hypothyroid diagnosis preceded diabetes diagnosis	0.957	0.004
F	Age at diabetes diagnosis	1.021	0.002
	Gender (Male)	1.222	0.13
	Ethnic Group (Caucasian)	0.798	0.24
	Hypothyroid - as time-dependent variable	0.49	0.003
	Years hypothyroid diagnosis preceded diabetes diagnosis	0.956	0.004
	Receiving insulin - at final 2002 observation, time-invariant	1.167	0.3
G	Age at diabetes diagnosis	1.018	0.027
	Gender (Male)	1.25	0.18
	Ethnic Group (Caucasian)	0.873	0.55

	Hypothyroid – as time-dependent variable	0.458	0.002
	Years hypothyroid diagnosis preceded diabetes diagnosis	0.96	0.011
	Receiving insulin – as time-dependent variable*	1.747	0.002
*Information on the commencement of insulin therapy was available for only 147 of the 307 patients reported to be receiving insulin in 2002 such that 160 patients receiving insulin, but without date of initiation are censored at time=0.			

Hypothyroidism as time-dependent variable

In Cox Proportional Hazard Regression models in which hypothyroidism was treated as a time-dependent variable in assessing the risk of developing diabetic retinopathy (Table 3C) an unadjusted hazard ratio of 0.418 ($p < 0.001$) was observed, again denoting a significantly reduced risk of developing retinopathy for those patients who suffer from hypothyroidism. Further adjusting for the effects of age at diabetes diagnosis, gender and ethnic group marginally reduced the hazard ratio further to 0.395 ($p < 0.001$; Table 3D). Of the 147 patients with hypothyroidism and diabetes 102 patients had hypothyroidism diagnosed at least 1 year prior to, 38 after and 7 at the same time of diagnosis of diabetes. Thus, in a model also incorporating a covariate corresponding to the years of hypothyroidism experienced by a patient prior to their diagnosis of diabetes, not only did hypothyroidism maintain its apparently protective effect ($HR = 0.464$; $p < 0.001$), but there was an additional reduction in risk of developing retinopathy in 102 hypothyroid patients for each year their hypothyroidism preceded their diabetes ($HR = 0.957$; $p = 0.004$; Table 3E).

Discussion

In the present study we demonstrate for the first time that patients with type 2 diabetes and coexisting hypothyroidism (on thyroxine replacement) have a decreased risk of developing diabetic retinopathy. In thyroxine-treated hypothyroid patients with diabetes (THD) and controls, beside thyroid function, recent biochemical profiles did not differ appreciably between the two groups (Table 1). The sparing effect of retinopathy in THD was significant despite patients being older and having higher systolic blood pressure than controls. The mean TSH and free thyroxine values were significantly higher in the THD group as compared to controls; the higher TSH value in the context of high free thyroxine value in THD group may be explained by certain non-compliant individuals, as seen in clinical practice. Importantly, patients who developed hypothyroidism after retinopathy were no different from controls, however we could not analyse the effect of progression of this group to sight threatening retinopathy (STR) because of insufficient information with regards to time of onset of STR.

Effect of thyroid extracts on diabetic retinopathy has been previously studied in 19 insulin dependent diabetics over a period of 2 years by Schneider et al. Twelve of the 19 cases showed improvement while on thyroid extract with reduction in haemorrhages and exudates, and this improvement was maintained whilst the patients were on thyroid extract [18].

Although there have been a few case reports highlighting the absence of complications in patients with coexisting diabetes and hypothyroidism who were on thyroxine replacement, these have not been confirmed in a larger population [14].

Our data shows a larger sparing effect, proportional to the interval of diagnosis, was observed in patients who developed hypothyroidism before the diagnosis of diabetes mellitus, and persisted after controlling for age and gender. The possibility that being diagnosed to have hypothyroidism may have resulted in an increased surveillance for diabetes in these patients, and therefore be a plausible explanation of our observations, is unlikely as it is not standard practice to screen hypothyroid patients for Type 2 diabetes. Potential explanations include that the two groups may be genetically different and hence have a different predisposition rate to retinopathy, or possibly the thyroxine replacement in THD subjects had in some way altered their hypothalamic-pituitary axis, which contributed to the sparing effect from development of retinopathy.

In patients with diabetes there exists a dysfunctional state of thyroid homeostasis, [12,19] which is dependent on the degree of metabolic control [20,21]. Improving diabetes control per se does not seem to influence free thyroid hormone level or its effect on the pituitary axis which could possibly explain why certain patients develop retinopathy in spite of good control and vice versa [22]. It is evident from animal and human studies plasma free T3 and free T4 are decreased and rT3 is increased, in addition there also exists a defect in hypothalamic regulation of the thyroid –pituitary feedback system suggesting a state sick euthyroid in patients with diabetes [23,24]. In diabetes the conversion of FT4 to FT3 is also decreased in several tissues and regulation of TSH secretion is altered in poorly controlled diabetes [25,26]. The dysfunctional state of thyroid homeostasis may have contributed to the higher prevalence of retinopathy in the non-hypothyroid group by virtue of not being on thyroxine supplement.

Studies have shown regression of retinopathy after complete ablation of the pituitary gland [27]. The regression of retinopathy is believed to be as a result of loss of anterior pituitary hormones, including growth hormone. Interaction of other hormones including thyroid hormone (deficiency or adequate replacement) has not been clearly elucidated. Grant et al. [28], have shown a beneficial effect in diabetic patients with severe non-proliferative retinopathy treated with high dose octreotide, although following octreotide treatment patients required thyroxine replacement to maintain a euthyroid state [28]. Given

the recent evidence of thyroid homeostasis and macrovascular disease the role of pituitary-thyroid axis in the aetiopathogenesis of diabetic microvascular disease is interesting.

This altered state of thyroid homeostasis in diabetes may play a role in the increased atherosclerotic process, a major risk factor for both micro- and macro-vascular complication [12,19]. Studies in diabetic rats with retinal microangiopathy, as evidenced by capillary basement membrane thickening, plasma thyroxine was found to be reduced after 8 months, and triiodothyronine at 8 and 12 months as compared to controls [29]. In addition, thyroxine deficiency in diabetic rats results in altered vascular reactivity which is reversible on thyroxine supplement [30].

The limitations of our present observational study include data over time with regards to all the covariates could not be analysed in a time varying analysis. In addition progression of retinopathy to STR in patients with concurrent hypothyroidism could not be analysed. Questions with regards to dosage of thyroxine and other possible aetiopathogenic factors including the dynamics of hypothalamic pituitary axis over time were not recorded with sufficient intensity to be analysed in the current study and would undoubtedly require a large prospective study. These studies could possibly increase the understanding with regards to pathogenesis of diabetic retinopathy and possible therapeutic implications in future warranting further research.

In conclusion, our present study shows that concurrent hypothyroidism, treated with thyroxine, appears to have a sparing effect on the risk of developing retinopathy among patients with type 2 diabetes. The exact mechanism(s) of this sparing effect are unclear. Further prospective studies are warranted in order to elucidate the precise nature of this phenomenon.

Acknowledgement

This study was supported in part by a grant from the Diabetes and Medical Research Fund.

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DOI: [10.19080/JETR.2018.03.555605](https://doi.org/10.19080/JETR.2018.03.555605)

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