

Original Article

Impact of achieving euthyroidism on pulmonary artery systolic pressures in hyperthyroidism-associated pulmonary hypertension - a systematic review

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Abstract: In this systematic review, we seek to clarify the impact of treatment of hyperthyroidism on pulmonary hypertension in patients with both these conditions. We included 39 of 709 articles retrieved, that studied patients with hyperthyroidism and pulmonary hypertension (PH). From these, those with a documented pre-treatment Pulmonary Artery Systolic Pressure (PASP) > 35 mmHg and complete follow up were analyzed, yielding 3 case series and 22 case reports with a total of 81 cases. A significant improvement in PASP was noted with achieving euthyroidism in the 3 case series. The case reports showed a significant reduction in mean PASP from 60.5 ± 13.2 mmHg to 37.5 ± 10.1 mmHg ($p < 0.001$) in patients with Grave's disease with achieving euthyroidism. No deaths were reported during the follow up period. Achievement of a euthyroid state in patients with hyperthyroidism is associated with statistically significant reductions in PASP.

Keywords: Hyperthyroidism, pulmonary hypertension

Introduction

Pulmonary hypertension (PH) and hyperthyroidism are complex diseases with numerous etiologies, various pathogenetic mechanisms, natural histories and clinical features, consequently requiring specific treatment. PH is a pulmonary vascular disease, defined as pulmonary artery systolic pressure (PASP) > 35 mmHg, that is associated with high mortality, particularly when it progresses to right heart failure [1, 2]. Overt primary hyperthyroidism, defined as a subnormal thyroid stimulating hormone (TSH) level with elevated serum free T4 and/or T3, is known to lead to a hyperdynamic circulatory state [3, 4]. While the association between thyroid disease and pulmonary hypertension (PH) has been known for almost three decades, the exact prevalence of PH in patients

with thyroid disease depends on which population of patients are studied [5]. Data from a large pulmonary arterial hypertension (PAH) registry seems to indicate that 21.6% of patients with PAH had associated thyroid disease, including hyperthyroidism and hypothyroidism [6]. The prevalence of thyroid dysfunction among patients with PH seems to be higher in prospective studies with reports of 49-52% of patients with PH having concomitant autoimmune thyroid disease [7, 8]. Several studies investigating patients with thyroid disease have determined that the prevalence of pulmonary hypertension in these cases ranged from 34-65% [9-17]. The mechanism of the association between hyperthyroidism and PH may be related to the effect of thyroid hormone on the cardiovascular system, with increases in heart rate, left ventricular contractility and cardiac

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output, resulting in high-output cardiac failure in thyrotoxicosis [18, 19]. Thyroid hormone may also have direct effects on the pulmonary vasculature [20-25]. In addition, autoimmunity is a common link between the two diseases that has been explored in various studies [7, 15].

Improvement in pulmonary artery pressures (PAP) with treatment of hyperthyroidism supports possible overlapping pathogenetic mechanisms between these two diseases as concluded by the prior systematic review on this subject [26]. It is unclear whether this improvement in PAP with achievement of a euthyroid state has a mortality benefit. As the last systematic review was in 2011, the purpose of the present study was to clarify the association between PH and hyperthyroidism with contemporary evidence and to determine whether treatment of hyperthyroidism confers a mortality benefit in these patients [26].

Methodology

Search strategy and eligibility criteria

Online searches were performed using PubMed and Lilacs. We used the MeSH terms “Hypertension, Pulmonary”, “Thyroid disease”, “Hyperthyroidism”, “Thyrotoxicosis” and “Thyroiditis, Autoimmune”. The Boolean term “AND” was used to join “Hypertension, Pulmonary” with the other search terms. Two reviewers (SRC and TF) independently evaluated the titles and abstracts. We included case reports or case series in the English language that reported on the association of PH and hyperthyroidism. Articles pertaining to pediatric patients < 18 years of age and those lacking information regarding treatment of hyperthyroidism and pre- and post-treatment PAPs were excluded. Some studies pooled pre- and post-treatment PAPs in patients who did not have both diagnoses of hyperthyroidism and PH and these were excluded from the quantitative analysis but were qualitatively described. A decision on whether to include the article was made by consensus and a third reviewer (PR) was consulted in cases of disagreement or uncertainty. Articles were stored in ENDNOTE and duplicates were removed using the feature available in the ENDNOTE software.

Data extraction and assessing quality of data

The full texts of the references selected were retrieved and reviewed by two reviewers (SRC

and TF). Relevant information, including the year of publication, study design, aims and objectives, number of patients in the study with PH and hyperthyroidism with complete follow up, patient age, patient gender, method of measurement of PAP, severity of PH, type of thyroid disease, treatment administered, time at which PAP was re-measured, total duration of follow up, pre-treatment PAP, post-treatment PAP and number of deaths were filled into data extraction forms. When entering the data, an effort was made to only include those patients from each study with hyperthyroidism that also had pre-treatment PH (PASP > 35 mmHg) along with complete follow up [1]. Strengths and limitations of each study were noted and articles were graded for quality of evidence as “Good”, “Fair” or “Poor”, utilizing the “Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports” (<https://wiki.joannabriggs.org/display/MANUAL/Appendix+7.4+Critical+appraisal+checklist+for+case+reports>) for case reports and the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tools (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>) for the remaining articles. All articles fell into the “Good” or “Fair” categories. No randomized controlled trials have been performed on this subject, therefore extracted data from case reports and observational studies provided Level IV or V evidence at best.

Statistical analysis

All the individual case reports were pooled together and analyzed as one large series of 29 patients. Data from the other available large case series were also extracted and computed if not readily available.

The age and gender of each patient in the case reports were extracted and presented using mean \pm standard deviation and frequencies or percentages respectively. The mean age and standard deviation were computed for each study (only if not available) and cumulatively for the combined studies altogether. Data on pre- and post-treatment PASP were extracted from each individual study and case report. In studies where there was no pooled means and standard deviations, these were manually calculated. The differences in pre- and post-treatment PASP were analyzed using a paired-T-test. A *p* value of < 0.05 two-tailed was considered statistically significant. SPSS (version 23; IBM) was used for all the analyses.

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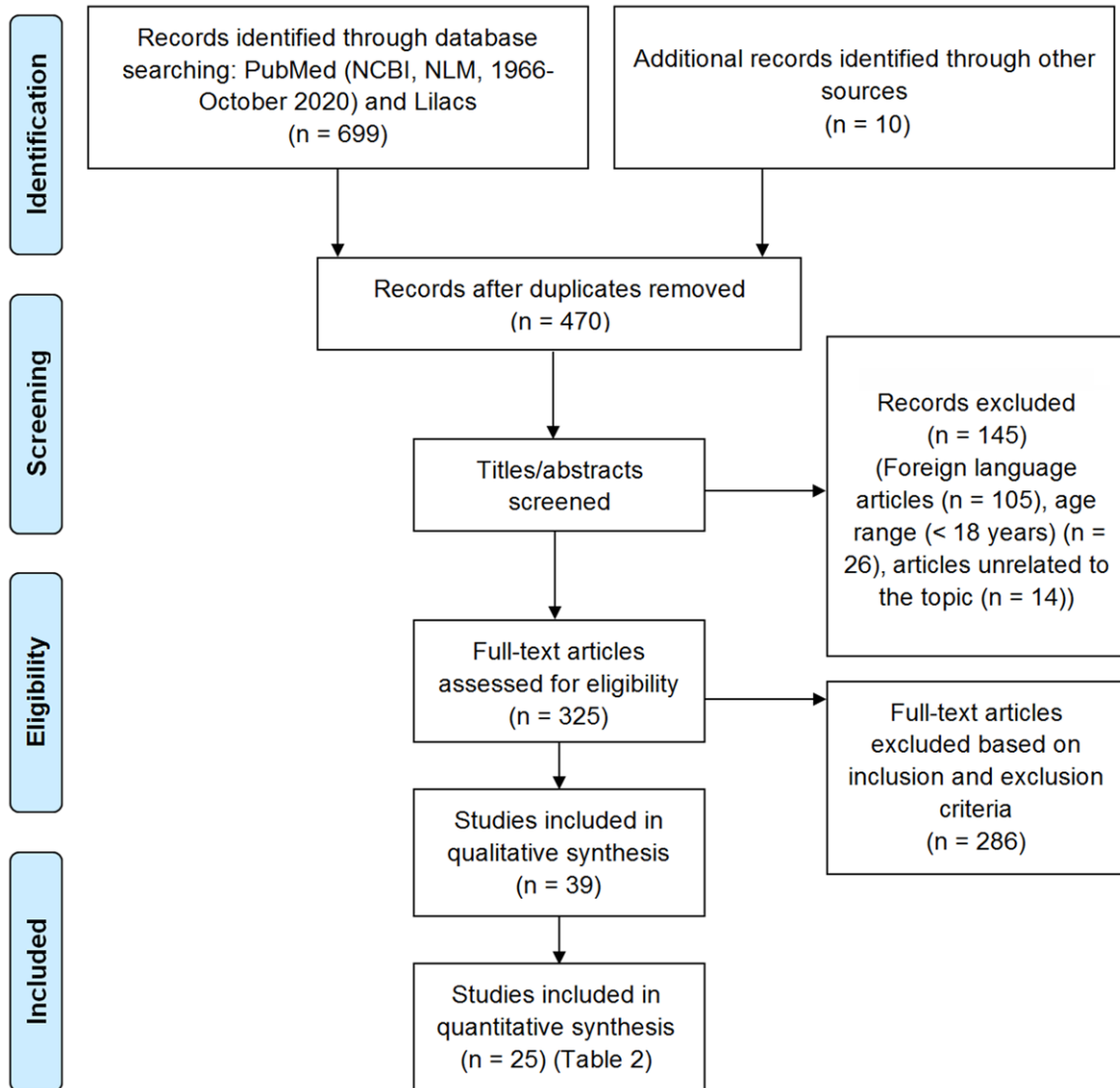


Figure 1. PRISMA flow diagram illustrating the selection process. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097.

Results

Search results

A PRISMA flow diagram illustrating the selection process is shown in **Figure 1**. The main search strategy yielded 699 articles. Ten additional articles were identified by reviewing the reference list of other articles, resulting in a total of 709 articles. After duplicates, pediatric cases, foreign language and unrelated articles were removed, the remaining 325 full texts were screened for eligibility based on our inclusion and exclusion criteria. Finally, 39 articles

were included in the analysis [9-14, 16, 27-58]. Twenty eight [14, 27-31, 33-42, 44-48, 50, 52-54, 56-58] were case reports or small case series and 11 [9-13, 16, 32, 43, 49, 51, 55] were larger case series, case-control or cohort studies. The 28 case reports/small case series had a total of 37 patients. Two cases from Singarayar et al. [50], were excluded as they did not have post-treatment PA pressures measured, leaving a total of 35 patients (**Table 1**). Of the 11 larger case series, case-control or cohort studies, eight [10-12, 16, 32, 43, 49, 55] did not report pre-treatment and/or post-treatment PAP separately for those with hyper-

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Table 1. Summary of results of 28 case reports/small case series with a total of 35 patients

Author, Year of publication	Age (in years)/ Sex	Diagnosis	Treatment	Pre-treatment PASP (mmHg)	Post-treatment PASP (mmHg) ^a	Time at which post-treatment PASP was measured (months)	Total duration of follow up (months)
Thurnheer, 1997 [54]	26, F	GD	Thiamazole, propranolol, I ¹³¹	35	21	6	6
	79, F	MNG	I ¹³¹	34	26	2	2
	54, F	GD	PTU	56	35	1	1
	24, M	GD	Thiamazole, beta-blocker	33	21	12	12
Nakchabandi, 1999 [44]	46, F	GD	PTU, furosemide, warfarin, metoprolol, I ¹³¹	78 ^b	32 ^b	7	12
Virani, 2003 [56]	40, F	GD	PTU, RAI	73 ^c	38 ^c	6	13
	38, F	GD	PTU, RAI	78 ^c	41 ^c	5	10
Lozano, 2004 [41]	29, F	GD	PTU, KI	51	26	3	6 (subtotal thyroidectomy was performed at 6 months)
Ma, 2005 [42]	48, F	GD	Carbimazole, RAI	65	Normal	8	34
Soroush-Yari, 2005 [14]	41, M	GD	PTU, RAI	57	36	9	24
	68, M	GD	Methimazole, RAI	52	32	24	24
	59, M	GD	PTU, RAI	51	34	24	60
Paran, 2006 [46]	38, F	GD	PTU, propranolol, dexamethasone	70	48	0.5	"several weeks"
Park, 2006 [47]	71, F	Hyperthyroidism	Furosemide, spironolactone, digoxin, atenolol, and methimazole	65 ^c	Normal ^c	1	1
Waseem, 2006 [57]	61, F	GD	Propranolol, PTU	> 60	Normal	1.6	12
Ismail, 2007 [36]	56, F	GD	Methimazole	75	45	Few weeks	Few weeks
Hegazi, 2008 [33]	43, F	GD	Carbimazole, diuretics and captopril	70	55	4	14
Syriou, 2008 [52]	48, F	MNG	Carbimazole, furosemide, spironolactone, warfarin, digoxin, diltiazem, quinapril, propranolol	40	Normal	4	16
Tam, 2008 [53]	45, M	Hyperthyroidism	Carbimazole, propranolol	26	21.6	5	42
	34, F	Hyperthyroidism	Furosemide, ACE-inhibitor, digoxin, PTU	> 69 ^c	59 ^c	1.5	36
Kang, 2008 [39]	54, F	GD	Bosentan, amlodipine, and methimazole	80	38	1	9
Huang, 2009 [34]	53, F	GD	Furosemide, PTU, propranolol	69 ^c	39 ^c	4	18
Hwang, 2010 [35]	48, F	GD	Methimazole, Furosemide	> 57	> 57	4	4
Ivanović, 2011 [37]	36, F	GD	Furosemide, propranolol, propylthiouracil and warfarin	55 ^c	Normal ^c	3	3
Wong, 2012 [58]	75, F	Type II amiodarone-induced hyperthyroidism	Propranolol, furosemide	60	28	3	3
Bonou, 2012 [28]	34, F	Hyperthyroidism	Unimazole, propranolol, furosemide, spironolactone	45	Normal	5	10
Ganeshpure 2012 [31]	30, F	GD	Furosemide, carbimazole, beta-blockers, RAI	70	45	2	2
Kamalanathan, 2012 [38]	38, M	GD	Furosemide, carbimazole, low-dose propranolol	54 ^c	26 ^c	4	4
Frogoudaki, 2016 [30]	54, F	GD	Methimazole, propranolol, furosemide; thyroidectomy	55	30	Not mentioned	Not mentioned

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Khan, 2016 [40]	45, M	GD	Carbimazole	78	45	Few weeks	Few weeks
Baagar, 2017 [27]	35, F	GD	Dexamethasone, cholestyramine, Lugols iodine, propranolol, methimazole	60.16 ^c	52.64 ^c	3	3
Rashidi, 2017 [48]	35, F	GD	Methimazole, RAI	60 ^c	35 ^c	2.3	2.3
Faccia, 2018 [29]	44, F	GD	Methimazole, methyl-prednisolone, low-dose diuretics, betablockers and low molecular weight heparin	45-50	35	0.3	1
Singarayar, 2018 ^d [50]	25, F	GD	Carbimazole, beta blocker	47	24	5	9
Nigussie, 2020 [45]	31, F	GD	Propranolol, methimazole, furosemide, dexamethasone, and iodine	58.18 ^c	47 ^c	Unclear	2.3

^aEarliest pulmonary artery pressure measured after achieving a euthyroid state. ^bPulmonary artery systolic pressure measured on pulmonary artery catheterization. ^cRight ventricular systolic pressure measured on ECHO. ^dTwo cases from Singarayar et al. were excluded from the table as no post-treatment pulmonary artery pressures were measured in them: one was lost to follow up and the other died within 9 days of admission due to hemorrhagic stroke and multi-organ failure. GD: Grave's disease, MNG: Multinodular goiter, PTU: Propylthiouracil, RAI: Radioactive iodine = ¹³¹I.

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thyroidism and PH (PASP > 35 mmHg) and these are described qualitatively below. The remaining 3 larger case series or cohort studies [9, 13, 51] had a total of 162 patients with hyperthyroidism, only 52 of which also had PH with complete follow up. **Table 2** summarizes the information of these 52 patients and 29 of the 35 patients from the case reports/small case series, yielding a total of 81 cases. Six patients from the case reports/small case series were not included in **Table 2** as their post-treatment PAP's were reported as "Normal" and an accurate mean could not be calculated [28, 37, 42, 47, 52, 57].

Mean age and gender distribution

It is to be noted that the 6 patients from Siu et al. [13], and the 8 patients from Suk et al. [51], who were subsequently lost to follow up and therefore not part of the 81 patients, were included in the mean age and gender distribution calculation. Therefore, the total number of patients included in the mean age and gender distribution calculation was 95.

Demographics and treatment of hyperthyroidism (Table 2)

The mean age of the patients in **Table 2** was 46.0 ± 12.3 years and 67.4% were female. In **Table 2**, 69 patients had Graves' disease, 15 had multinodular goiter, 1 had type 2 amiodarone-induced hyperthyroidism and 2 had hyperthyroidism, the etiology of which was not specified ($n = 87$). This includes the six additional patients from Siu et al. [13], who were lost to follow up. The patients were treated with different permutations and combinations of anti-thyroid medications, radioactive iodine (RAI) ablation and surgery. Among the anti-thyroid medications, the most commonly used ones were propylthiouracil and methimazole. While the article by Siu et al. [13], does not mention the proportion of patients who were treated with anti-thyroid drugs and/or radioactive iodine, when the data from the other 70 patients in **Table 2** are combined, 65 patients received anti-thyroid medications, 4 underwent surgery and 11 underwent RAI ablation ($n = 70$). This includes 8 additional patients from Suk et al. [51], who were subsequently lost to follow up.

Pulmonary artery pressures

PAP's among the 81 cases were documented on echocardiogram as the PASP or mean pul-

monary artery pressure (mPAP) in 52 and 20 patients respectively. 8 patients had their pulmonary artery pressures estimated on echocardiogram as the right ventricular systolic pressure (RVSP) while 1 patient underwent pulmonary artery catheterization for direct pressure measurement.

The time to post-treatment pulmonary artery pressure measurement ranged from 10 days to 2 years, and the total duration of follow up ranged from a few weeks to 5 years. The three large case series [9, 13, 51] in **Table 2** all report statistically significant improvements in pulmonary artery pressures with treatment of underlying hyperthyroidism. The mean pulmonary artery systolic pressures from the collated data of the case reports in the patients with Grave's disease improved from 60.5 ± 13.2 mmHg to 37.5 ± 10.1 mmHg ($p < 0.001$). In the patient with MNG and 3 patients with hyperthyroidism from amiodarone or unspecified etiology, the PASP improved from 34 mmHg to 26 mmHg and 51.7 ± 22.7 mmHg to 36.2 ± 20.0 mmHg ($p = 0.207$) respectively. Six cases [28, 37, 42, 47, 52, 57] were excluded from the table since their post-treatment pulmonary artery pressures were merely reported as "normal" after achievement of a euthyroid state.

Articles that did not mention post-treatment pulmonary artery pressures separately in those with pulmonary hypertension

While the remaining 8 articles [10-12, 16, 32, 43, 49, 55] did not report pre-treatment and/or post-treatment PAP's separately for those with PH and hyperthyroidism, they all reported improvement in PAP's with treatment of hyperthyroidism.

Marvisi et al. [11], studied 47 patients with Grave's disease and 67 patients with nodular goiter and found that 50 (43%) of them had mild PH. Of those with PH, 33 were treated with methimazole and 17 were treated with partial thyroidectomy [11]. While they did not comment on the statistical significance of the improvement in PAP with achievement of a euthyroid state, they did show that the PAP's improved more rapidly with treatment with methimazole than with partial thyroidectomy [11]. When Yazar et al. [16], studied 25 consecutive patients with hyperthyroidism and compared them to 25 healthy controls, they found that not only were the PASP's significantly higher in those with hyperthyroidism, these pres-

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Table 2. Summary of results from three larger case series/cohort studies and from the case reports/smaller case series

Author, Year of publication	Number of patients (n) ^a	Age (in years)/ Sex	Diagnosis	Treatment	Pre-treatment PASP (mmHg)	Post-treatment PASP (mmHg) ^a	p-value	Time at which post-treatment PASP was measured (months)	Total duration of follow up (months)	Death during study period (Y/N)
Armigliato, 2006 [9]	13 ^c	49 ± 15.02, 54% F	GD (12) MNG (1)	Methimazole (10), Surgery (2), Iodine (1)	41.6 ± 5.1 ^d [36-45 mmHg (10), 46-50 mmHg (1), > 50 mmHg (2)]	29.8 ± 4.1 ^d	< 0.001 ^d	9	9	N
Siu, 2007 [13]	19	43 ± 3, 60% F (n = 25) ^f	GD (12), MNG (13) ^f	Antithyroid medications (Carbimazole or PTU) or RAI	47 ± 2	34 ± 2	< 0.01	6	6	N
Suk, 2011 [51]	20	49 ± 14, 71% F (n = 28) ^f	GD	Methimazole (28), total thyroidectomy (1)	41.1 ± 3.8 (mPAP)	26.5 ± 6.3 (mPAP)	< 0.01	7 ± 2	7 ± 2; 24 months noted for one patient	N
Summary of case reports and small case series (22) ^{*,&,&} [14, 27, 29-31, 33-36, 38-41, 44-46, 48, 50, 53, 54, 56, 58]	29 ^{*,&,&}	44.4 ± 13.9, 75.9% F	GD (25) [*]	Anti-thyroid drug (25), RAI (9), thyroidectomy (1), Others ^g (16)	60.5 ± 13.2 ^h	37.5 ± 10.1 ⁱ	< 0.001	10 days to 2 years	Few weeks to 5 years	N
			MNG (1) ^{&}	RAI	34	26	NA			
			Hyperthyroidism (3) ^{&}	Anti-thyroid drug (2), Others ^j (3)	51.7 ± 22.7 ^k	36.2 ± 20.0	0.207			

^aNumber of patients in the study who had both pulmonary hypertension and hyperthyroidism and had pre- and post-treatment pulmonary artery pressures mentioned. ^bEarliest pulmonary artery pressure measured after achieving a euthyroid state. ^cThe 13 patients in this study with PASP > 35 mmHg were included in this table. ^dThese values were calculated manually using the raw data provided in the paper. The pre-treatment PASP values for the 2 patients with pre-treatment PASP of > 50 mmHg were taken as 50.1 mmHg. The post-treatment PASP values of the 2 patients with post-treatment PASP of < 30 mmHg were taken as 29.9 mmHg. ^eIncludes patients with pulmonary hypertension and hyperthyroidism who were lost to follow up. ^fThree articles, namely, Ma, Waseem and Ivanovic, were excluded from this table as the post-treatment PA pressure was mentioned as "Normal" without an exact value and therefore an accurate mean PA pressure could not be calculated. All three articles reported normalization of PA pressures after treatment of Grave's disease. ^gOne article, Syriou et al., was excluded from the table as the post-treatment PA pressure was mentioned as "Normal" without an exact value and therefore an accurate mean PA pressure could not be calculated. The article reported normalization of PA pressures after treatment of MNG. ^hTwo articles, Bonou et al., and Park et al., were excluded from the table as the post-treatment PA pressures were mentioned as "Normal" without an exact value and therefore an accurate mean PA pressure could not be calculated. The articles reported normalization of PA pressures after treatment of hyperthyroidism. This included one case of type II amiodarone-induced hyperthyroidism (Wong et al.), that was treated by discontinuation of amiodarone, propranolol and furosemide. ⁱBeta-blockers, diuretics, anticoagulants, steroid, iodine (potassium iodide, Lugol's iodine, iodine), bosentan, cholestyramine, amlodipine, captopril. ^jIn order to calculate this, the pulmonary artery pressure from Hwang et al., of > 57 was taken as 57.1 and from Faccia et al., of 45-50 was taken as 45. ^kIn order to calculate this, the pulmonary artery pressure from Hwang et al., of > 57 was taken as 57.1. ^lBeta blockers, diuretics, angiotensin-converting enzyme inhibitor, digoxin; the patient with type 2 amiodarone-induced hyperthyroidism was treated by stopping amiodarone and with furosemide and propranolol. ^mIn order to calculate this, the pulmonary artery pressure from Tam et al., of > 69 was taken as 69.1.

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tures also improved significantly with achievement of a euthyroid state. The articles by Marvisi et al. [11], and Yazar et al. [16], could not be included in **Table 2** as the mean and standard deviation of the pre-treatment PAP's did not entirely fall within the pulmonary hypertension range (PASP > 35 mmHg). Multiple other supporting reports have also suggested improvement in PH following treatment of hyperthyroid state [10, 12, 33, 43, 49].

Tudoran et al. [55], studied 142 women with newly-diagnosed overt hyperthyroidism, recurrent hyperthyroidism and subclinical hyperthyroidism and concluded that in patients with recurrent hyperthyroidism, while the cardiac output normalizes, the elevated pulmonary vascular resistance did not reduce sufficiently contributing to the lack of normalization of PASP in this group [55].

Impact of achieving euthyroidism on mortality in patients with PH and hyperthyroidism

Among the 35 patients from the 28 case reports summarized in **Table 1**, 13 patients had a total duration of follow up of ≥ 12 months, the mean duration of follow up among them being 24.4 months, during which there were no deaths [14, 33, 34, 42, 44, 52-54, 56, 57]. It should be mentioned however that one of the two cases from Singarayar et al., that were excluded from **Table 1**, due to reasons mentioned above, died 9 days after hospitalization due to haemorrhagic stroke and multi-organ failure [50]. In **Table 2**, among the 52 patients from larger case series with PH, there were no deaths on follow up that ranged from 6 to 9 months with one patient from Suk et al., who had 24 months of follow up [9, 13, 51]. Among the 8 larger case series that did not mention pre- and/or post-treatment PAP's separately for those with PH and hyperthyroidism, no deaths were reported at a follow up ranging from 2 to 34 months [10-12, 16, 32, 43, 49, 55].

Discussion

In our systematic review of current literature, we found a total of 39 articles [9-14, 16, 27-58] related to the association between hyperthyroidism and elevated PAP's. Multiple studies [9-13, 16, 32, 43, 49, 51, 55] reported an association between hyperthyroidism and elevated PAP's, with another [32] suggesting that those

with PH had higher free T4 concentrations than those without PH.

While the exact mechanism of this association remains unclear, it is known that thyroid hormone exerts a specific impact on the cardiovascular system, with increased heart rate, increased left ventricular contractility, reduced systemic vascular resistance and increased cardiac output [19]. In thyrotoxicosis, elevated thyroid hormone levels can lead to high-output cardiac failure [18] and the hyperdynamic circulation might cause endothelial shear stress in the pulmonary vasculature, with downstream effects of endothelial dysfunction, intimal proliferation, vascular remodeling and vasoconstriction with resultant increased pulmonary vascular pressures [22-25]. There are also some studies which show that thyroid hormones may have a direct effect on pulmonary vasculature in terms of increasing endothelial cell growth and proliferation in the pulmonary circulation [20, 21]. Additionally, autoimmunity is a common link between the two diseases that has been explored in various studies [7, 15]. Sugiura and colleagues showed a linear correlation between pulmonary artery systolic pressures and TSH receptor antibody levels [15]. It is possible that these TSH receptor antibodies, in addition to stimulating thyroid hormone production, may also lead to immune mediated damage of the endothelium with consequent endothelial cell dysfunction and possible pulmonary hypertension [15]. Whether this association is merely an epiphenomenon, or whether this is a true etiologic relationship remains to be determined [59].

The large case series by Armigliato et al. [9], Suk et al. [51], and Siu et al. [13], all reported statistically significant improvements in PAP's with treatment of underlying hyperthyroidism. The mean PASP's from the collated data of the case reports reported a statistically significant improvement in PAP's in the patients with Grave's disease. The modality of treatment seems to influence the rapidity of improvement in PAP's as seen in the study by Marvisi et al. [11], that showed that the PAP's improved more rapidly with treatment with methimazole than with partial thyroidectomy. Similarly, as seen in the article by Tudoran et al. [55], the rapidity in improvement in PAP's may also be influenced by whether the hyperthyroidism was newly diag-

nosed or recurrent as this likely influenced the degree of alteration of pulmonary hemodynamics. In our own experience, we have seen a significant overlap of patients with elevated PAP's and thyroid disease, treatment of hyperthyroid state does seem to result in improved PAPs, albeit not always confirmed with invasive hemodynamics. While anecdotally, improved hemodynamics have translated to better clinical outcomes, making a mortality association would be inappropriate.

Our review is not without limitations. While no deaths were reported during the period of follow up, a mortality benefit cannot be commented on without performance of a randomized control trial comparing PH-associated mortality between those treated for hyperthyroidism and those not treated for hyperthyroidism. This would clearly be unethical to perform. According to the 2015 ESC/ERS Guidelines, clinical improvement and outcomes in PH are largely driven by and associated with right ventricular function which is not reliant solely on improved pulmonary pressures [60]. Progression of clinical symptoms, WHO functional class, exercise capacity, B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP), features on echocardiography, and hemodynamic measurements on right heart catheterization (specifically right atrial pressure and cardiac index) are other parameters that are of prognostic significance in PAH [60]. The majority of studies included in our review documented an improvement in resting PASP on echocardiogram, but did not comment on improvements in the parameters mentioned above, which would have more of an association with mortality. Furthermore, the gold standard for diagnosis of pulmonary hypertension is a right heart catheterization with mean pulmonary artery pressure > 25 mmHg with additional measurement of pulmonary vascular resistance; unfortunately, a majority of our cases were diagnosed on the basis of echocardiography [61]. Whether the improvement in pulmonary artery pressures in some cases was merely due to reduction in cardiac output as a result of treatment of hyperthyroidism is unclear without right heart catheterization data in those cases. Thus, this is an area that needs further study with longer periods of follow up as well as documentation of the above-mentioned parameters in order to perform a more accu-

rate determination of the mortality benefit of treating underlying hyperthyroidism in patients with PH.

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Disclosure of conflict of interest

None.

Abbreviations

BNP, B-type natriuretic peptide; mPAP, Mean pulmonary artery pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; PH, Pulmonary hypertension; PASP, Pulmonary Artery Systolic Pressure; PAP, Pulmonary artery pressure; RVSP, Right Ventricular Systolic Pressure; TSH, Thyroid Stimulating Hormone.

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