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Research Article

The Association of Donor Thyroid Hormone Supplementation on Heart Transplant Recipient Survival

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Introduction. The use of thyroid hormone supplementation (THS) for donor optimization has not been standardized and remains an area of academic investigation and clinical interest. The purpose of this study is to investigate the impact of THS supplementation on heart transplant recipient outcomes. *Methods*. Adult heart transplant recipients in the UNOS database recorded from January 1, 2000 to June 30, 2022 formed the study cohort. Simple comparisons were made with *t*-tests or chi-squared tests. Logistic regression models were used to predict 30 day and 1 year survival. Accelerated failure time models were employed to analyze time to death and time to rejection. *Results*. The cohort consisted of 46,542 heart transplants, of which 28,911 (62%) received THS prior to organ procurement. In adjusted models, donor THS was associated with a reduction of 11% in the odds of death within 30 days (OR = 0.89; $p = 0.048$); however, this relationship did not extend to one year post-transplant survival (OR = 1.00; $p = 0.968$). After a sex-based analysis, 30-day survival benefit was seen only in male-to-male donor-recipient pairings (OR for death = 0.82; $p = 0.007$). Overall survival and post-transplant rejection was also improved in the male-to-male group (HR = 0.94; $p = 0.002$ and HR = 0.96; $p = 0.048$) and the female-to-female group (HR = 0.87; $p = 0.003$ and HR = 0.90; $p = 0.013$). There was no associated survival benefit with THS in sex mismatched groups. *Conclusion*. THS in donors is associated with improved 30-day post-transplant survival and overall survival after OHT in sex-matched donor-recipient pairs. Further study is warranted.

1. Introduction

The majority of organs for transplantation are procured from brain dead donors and it is well documented that brain death is accompanied by hormonal alterations including marked drops in thyroid hormone blood levels, which have been shown to be responsive to supplementation [1]. Hormonal supplementation with triiodothyronine (T3) or thyroxine (T4) has been promoted as a means to improve donor cardiac function and thus increase the yield of donor hearts available for transplantation [2–4]. Despite these findings, the use of thyroid hormone supplementation (THS) for donor optimization has not been standardized and remains an area of academic investigation and clinical interest [5, 6]. The purpose of this study is to investigate the impact of THS in donors on post-transplant outcomes for heart recipients.

2. Methods

2.1. Design. This was a retrospective study of a large database. Since all information is deidentified, the Cleveland Clinic Weston Florida IRB did not require patient consent to perform this study.

2.2. Setting Population. The United Network of Organ Sharing (UNOS) database was analyzed using adult donors (age greater than 15 years) and recipients (age ≥18 years) with inclusion dates beginning January 1, 2000 and ending June 30, 2022.

2.3. Data Collection. Of those donors that received THS ($N = 28{,}911$), the vast majority (98%) were given T4 alone. One percent was given T3 alone and 1% was given both T3 and T4. For the present analysis, these three were combined into one binary variable, T3 or T4 (T3/T4). Explicitly stated, our primary comparison was between donors who received T3 and/or T4 prior to transplant procurement vs. those that received neither.

2.4. Data Analysis. Summary statistics were compiled where appropriate and simple comparisons were made with *t*-tests or chi-squared tests. Logistic regression models were used to predict 30 day and 1 year survival, while accelerated failure time models with Weibull distributions were employed to analyze time-to-death and time-to-transplant rejection. These models were adjusted for donor age, sex, ethnicity, BMI, ischemic time, and steroid support as well as recipient age, sex, ethnicity, BMI, length of stay, UNOS region, ventricular assist devices (VAD), creatinine, and days on the waiting list. Donor and recipient sex was constructed as a four-category variable and this was interacted with THS usage to ascertain whether differential effects between the donor/recipient sex pairs of the THS-survival relationships were observed. Appropriate linear combinations were constructed to examine comparisons of interest. THS usage across time was estimated tabulated and plotted with unadjusted percentages. All statistical analyses were done with Stata v17.0.

3. Results

There were 47,660 hearts transplanted during this inclusion time period. Of these, 1110 were excluded due to missing THS information and another 8 were excluded for being labeled as an inactive recipient status leaving 46,542 as the final cohort sample size. Mean donor age was 32.29 ± 11.31 years for the cohort (32.28 ± 11.30 no TSH vs 32.30 ± 11.32 years TSH; $p = 0.877$). Nonwhite donors comprised 35% of the overall cohort, 35% of the no TSH group, and 34% of the TSH group (0.055). Mean donor left ventricular ejection fraction was 61.59 ± 7.11 for the entire cohort (61.92 ± 7.17 no TSH vs. 61.39 ± 7.07% TSH; $p < 0.001$).

Of the 46,543 donors included, 28,911 (62%) received THS and 17,631 (38%) did not. There were small but statistically significant differences between these two groups regarding recipient age, diabetes status, creatinine, and use of ventricular assist devices (VAD) (Table 1). Donors differed on ischemic time, diabetes status, left ventricular ejection fraction (LVEF), and steroid administration. Most absolute differences in these variables between the two groups of interest were inconsequential (Table 2). Sex specific donor-to-recipient percentages were consistent across groups, despite the low p value, with male-to-male transplants making up the vast majority of the cohort.

In adjusted models including all patients, donor THS showed a reduction of 12% in the odds of death within 30 days (OR = 0.88; $p = 0.032$); however, this relationship did not extend to one year mortality (OR = 1.00; $p = 0.969$). THS had a positive impact in both overall survival and post-transplant rejection, reducing the hazard of death and rejection by 6% and 4%, respectively (HR = 0.94; $p < 0.001$ and HR = 0.96; $p = 0.013$) (Table 3) (Figure 1).

We further evaluated if these effects were differential across donor-recipient sex pairings. These results are also shown in Table 3/Figure 2. The 30-day survival benefit was strongest in the male-to-male pairing (OR for death = 0.81; $p = 0.006$), but was not observed in other groups (all $p > 0.310$). Similarly, the overall survival and post-transplant rejection benefits were similar in the male-to-male group (HR = 0.93; $p = 0.001$ and HR = 0.96; $p = 0.038$) and were enhanced in the female-to-female group (HR = 0.88; $p = 0.003$ and HR = 0.90; $p = 0.016$). We did not observe any associated survival benefit with donor THS in the sex mismatched groups (all $p > 0.319$).

It was hypothesized that donor steroid administration would provide further survival benefits, but this was not observed in neither main effects of steroid administration (all $p > 0.115$) nor when steroid support was interacted with THS (all $p > 0.431$).

Rates of THS across the study period are shown in Figure 3. The early 2000s saw a steady increase in usage, with a large increase beginning in 2005. THS usage peaked in 2009 with nearly 80% of heart donors having the therapy. Since the 2009 peak, usage has seen a steady decline with more recent years falling below 50%.

4. Discussion

Our results demonstrate that THS for brain dead heart donors offers a modest survival benefit for heart transplant recipients, particularly within the first 30 days. This relationship was strongest in the case of male donor hearts transplanted into male recipients. Overall survival benefits were observed for sex matched transplants but were not observed for sex mismatched transplant recipients. A conference abstract for this paper has previously been published [7].

The role of hormone supplementation in general has been borne out through clinical studies which have demonstrated the impact of brain death on circulating hormone levels and the benefits of THS for donor heart optimization [1, 3, 8]. While hormone supplementation protocols are not standardized, these prior findings are reflected in the relatively high rate of usage demonstrated in our results, even with the recent decrease in utilization. Novitzky et al. performed a similar analysis of the UNOS registry which included 63,593 donors from 2000 to 2009 for whom THS data were available [5]. While this study was not specifically looking at heart donors, they demonstrated that THS resulted in significantly increased heart procurement and

Table 1: Participant characteristics.

	Overall ($N = 46542$)	No THS ($N = 17631$)	THS ($N = 28911$)	p value
Recipient LOS	21.41 (25.06)	21.18 (24.75)	21.55 (25.25)	0.124
Ischemic time	3.25 (1.07)	3.30 (1.08)	3.22 (1.06)	<0.001
Distance	188.16 (217.90)	192.52 (219.61)	185.50 (216.80)	0.001
Age	52.75 (12.71)	52.59 (12.77)	52.86 (12.67)	0.027
Nonwhite recipient	15076 (32%)	5692 (32%)	9384 (32%)	0.697
BMI	27.24 (4.91)	27.16 (4.89)	27.29 (4.92)	0.003
Region				
Region 1	1989 (4%)	998 (6%)	991 (3%)	
Region 2	5576 (12%)	1479 (8%)	4097 (14%)	
Region 3	5573 (12%)	2400 (14%)	3173 (11%)	
Region 4	4805 (10%)	1727 (10%)	3078 (11%)	
Region 5	7474 (16%)	3388 (19%)	4086 (14%)	
Region 6	1447 (3%)	406 (2%)	1041 (4%)	<0.001
Region 7	4093 (9%)	2100 (12%)	1993 (7%)	
Region 8	2799 (6%)	968 (5%)	1831 (6%)	
Region 9	3131 (7%)	1040 (6%)	2091 (7%)	
Region 10	3886 (8%)	1259 (7%)	2627 (9%)	
Region 11	5769 (12%)	1866 (11%)	3903 (14%)	
VAD				
No VAD	26369 (57%)	9471 (54%)	16898 (58%)	
LVAD	13773 (30%)	4667 (26%)	9106 (31%)	
RVAD	108 (0%)	44 (0%)	64 (0%)	
TAH	339 (1%)	86 (0%)	253 (1%)	<0.001
LVAD + RVAD	971 (2%)	329 (2%)	642 (2%)	
Unspecified	1374 (3%)	815 (5%)	559 (2%)	
Unknown	3608 (8%)	2219 (13%)	1389 (5%)	
ECMO	904 (2%)	336 (2%)	568 (2%)	0.655
IABP	5006 (11%)	1983 (11%)	3023 (10%)	0.008
Creatinine	1.27 (0.64)	1.28 (0.71)	1.26 (0.60)	0.003
Total bilirubin	1.09 (1.89)	1.12 (2.03)	1.06 (1.79)	0.001
PRA	4.18 (14.69)	4.59 (15.75)	3.58 (12.95)	0.007
Diabetic recipient	12080 (26%)	4389 (25%)	7691 (27%)	<0.001
Days on waiting list	216.85 (378.88)	219.70 (379.27)	215.11 (378.64)	0.205
Gender matching				
Male donor to male recipient	28054 (60%)	10445 (59%)	17609 (61%)	0.001
Female donor to female recipient	7039 (15%)	2728 (15%)	4311 (15%)	
Female donor to male recipient	6556 (14%)	2601 (15%)	3955 (14%)	
Male donor to female recipient	4893 (11%)	1857 (11%)	3036 (11%)	

Means (standard deviations) are presented for continuous variables. Counts (%) are presented for categorical variables. LOS: length of stay; BMI: body mass index; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; PRA: panel reactive antibodies; THS: thyroid hormone supplementation.

a statistically significant improvement in survival at 30 days and 1 year. More recently, Peled et al. performed an analysis of the impact of THS using the registry of the International Society for Heart and Lung Transplantation (ISHLT) for a period from 2006 to 2016 [6]. This analysis included 23,002 adult heart transplants of which 15,821 received THS and revealed THS to be associated with an increased risk of early graft loss and similar long-term survival with or without THS. Our study of a large, more contemporary, registry than these two studies support the evidence of a benefit from THS but one that is more pertinent to select heart transplant recipients. The difference between the study by Peled et al. may be attributed to their use of early graft loss, which is defined as death or retransplant within 48 hours, as a primary end point. While this was associated with THS, our more long term based analysis is actually in accord with their findings of decreased incidence of transplant vasculopathy and similar long term survival between groups.

In particular, the sex-based analysis of our study demonstrated an association with benefit and THS only in sex matched donor-recipient pairings, with no difference in survival observed with THS in sex mismatched groups. While the underlying etiology for such a relationship remains controversial, several previous studies have demonstrated a similar relationship for sex mismatched heart transplants [9, 10]. Khush et al. performed an analysis of the ISHLT thoracic transplant registry including 60,584 heart transplants from 1990 to 2008 to examine outcomes based on donor and recipient sex [11]. The demonstrated significantly worse outcomes for sex mismatched pairings compared to sex matched pairs. Similarly, Meiser et al. performed an analysis of the ISHLT registry from 1990 to

Table 2: Donor characteristics.

	Overall ($N = 46542$)	No donor THS ($N = 17631$)	Donor THS ($N = 28911$)	p value
Donor age	32.29 (11.31)	32.28 (11.30)	32.30 (11.32)	0.877
Nonwhite donor	16085 (35%)	6188 (35%)	9897 (34%)	0.055
Donor BMI	27.23 (5.85)	27.24 (5.89)	27.23 (5.82)	0.756
Donor on inotropic support	21754 (49%)	8119 (49%)	13635 (48%)	0.091
Diabetic donor	1546 (3%)	519 (3%)	1027 (4%)	<0.001
Cause of death				
Anoxia	11963 (26%)	4887 (28%)	7076 (24%)	
CVD/stroke	9334 (20%)	3780 (21%)	5554 (19%)	
Trauma	23959 (51%)	8432 (48%)	15527 (54%)	<0.001
CNS tumor	317 (1%)	132 (1%)	185 (1%)	
Other	969 (2%)	400 (2%)	569 (2%)	
Donor history of MI	396 (1%)	173 (1%)	223 (1%)	0.017
Donor history of drug use (any)	15823 (34%)	6032 (34%)	9791 (34%)	0.444
Donor LVEF	61.59 (7.11)	61.92 (7.17)	61.39 (7.07)	<0.001
Donor on steroid support	34399 (74%)	12607 (72%)	21792 (75%)	<0.001

BMI: body mass index; CVD: cardiovascular disease; CNS: central nervous system; MI: myocardial infarction; LVEF: left ventricular ejection fraction. Means (standard deviations) are presented for continuous variables. Counts (%) are presented for categorical variables.

Table 3: Survival associations for various predictors across four models are adjusted for donor age, BMI, ethnicity, ischemic time, and steriod use, as well as recipient age, BMI, ethnicity, LOS, region, VAD, creatinine, and days on waiting list.

	Death within 30 d (OR)	Death within 1 yr (OR)	Overall survival (HR)	Post-tx rejection (HR)
THS vs. none (pooled over sex)	**0.88 p = 0.032 (0.79, 0.99)**	1.00 $p = 0.969$ (0.93, 1.07)	**0.94 p < 0.001 (0.91, 0.97)**	**0.96 p = 0.013 (0.93, 0.99)**
THS vs. none (male donor ->male recipient)	**0.81 p = 0.006 (0.70, 0.94)**	1.00 $p = 0.976$ (0.91, 1.09)	**0.93 p = 0.001 (0.90, 0.97)**	**0.96 p = 0.038 (0.92, 1.00)**
THS vs. none (female donor ->female recipient)	0.90 $p = 0.457$ (0.68, 1.19)	0.99 $p = 0.935$ (0.84, 1.18)	**0.88 p = 0.003 (0.80, 0.96)**	**0.90 p = 0.016 (0.82, 0.98)**
THS vs. none (female donor ->male recipient)	1.14 $p = 0.319$ (0.88, 1.49)	0.97 $p = 0.718$ (0.82, 1.14)	0.99 $p = 0.744$ (0.91, 1.07)	0.99 $p = 0.803$ (0.91, 1.07)
THS vs. none (male donor ->female recipient)	0.94 $p = 0.718$ (0.66, 1.33)	1.08 $p = 0.475$ (0.87, 1.34)	1.01 $p = 0.863$ (0.91, 1.12)	1.02 $p = 0.749$ (0.92, 1.12)

OR = odds ratio; HR = hazard ratio; THS: thyroid hormone supplementation. Bold values are where significance was demonstrated.

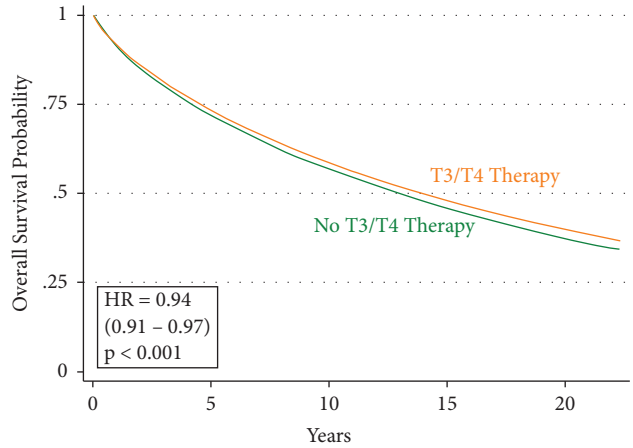

Figure 1: Overall survival probability for donors receiving thyrsoid hormone supplementation vs. those not receiving thyroid hormone supplementation.

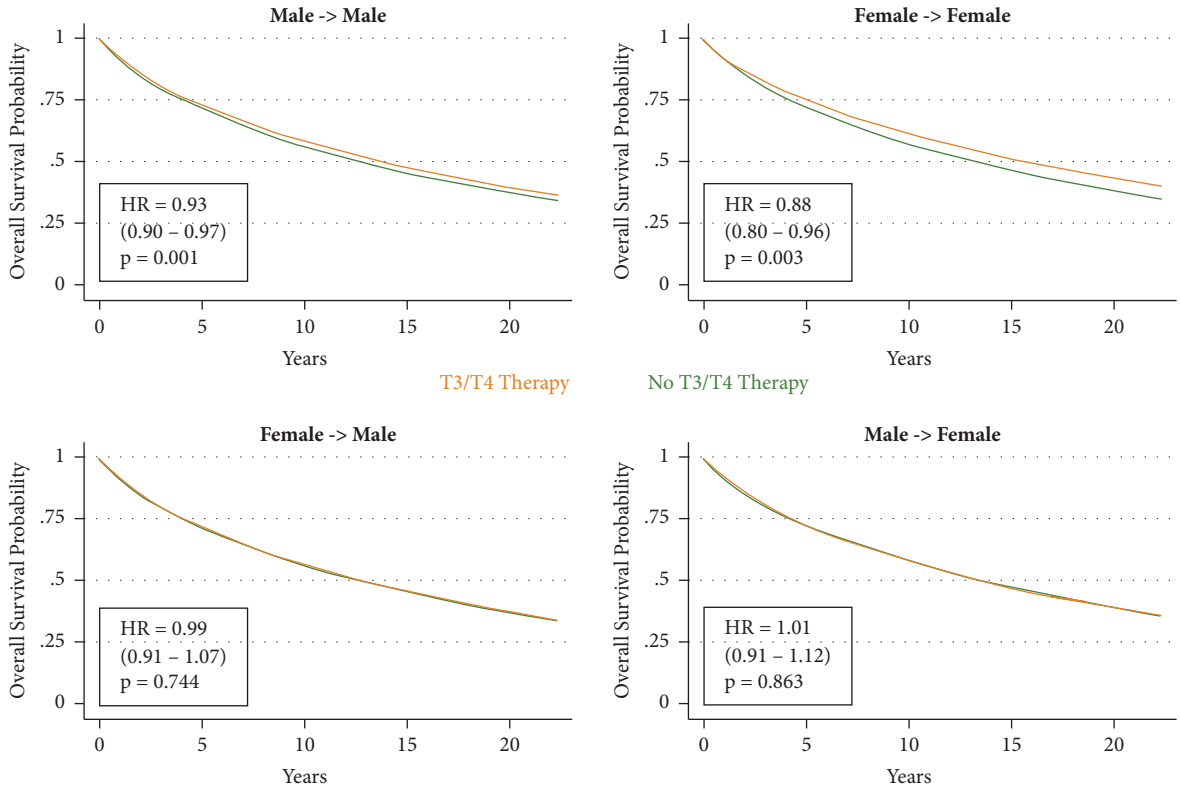

Figure 2: Overall survival probability based on donor-recipient sex pairing.

2009 which included 67,855 heart transplants and demonstrated decreased 1 year survival for female-to-male pairings and concluded that sex matched pairings would optimize clinical outcomes if feasible [12]. It is possible that hormone supplementation further contributes to these differences by maintaining a physiologic hormonal status and that hormone matching is a contributor to the benefit seen with sex matching; however, this would require further analysis.

Our analysis did not demonstrate clinical benefit from steroid administration in addition to, or in the absence of, THS. The study by Novitzky et al. included an analysis for corticosteroid administration which revealed a benefit but only in the cohort that did not receive THS [5]. Other studies have been inconclusive or contradictory with some demonstrating increased rates of procurement after corticosteroid supplementation but that such supplementation exacerbates hyperglycemia which in turn worsens post-transplant outcomes [13, 14]. Some centers advocate a protocol of low dose corticosteroid administration to improve rates of organ procurement with improved

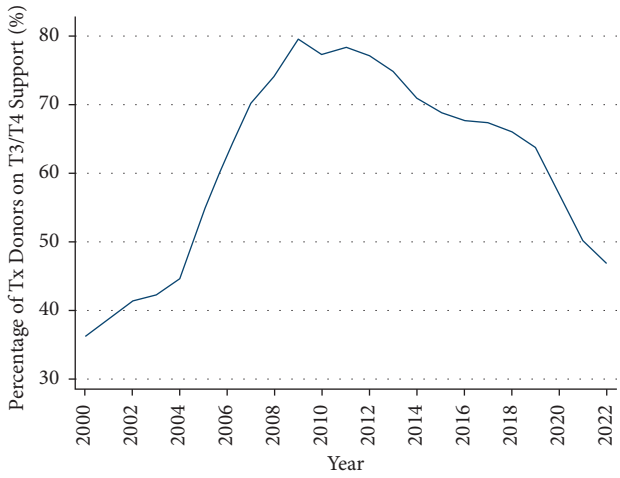

Figure 3: Thyroid hormone support usage across the study period.

glycemic control [15]. This is clearly an issue that warrants further investigation.

4.1. Limitations. Limitations of this study include its retrospective nature and the inability to distinguish between T3 and T4 supplementation. In addition, the lack of standardized protocols for the administration of THS limits the ability to make broader generalization or recommendations about its use based on this analysis.

5. Conclusions

Donor THS is associated with improved 30-day post-transplant survival as well as overall survival after OHT in sex-matched donor-recipient pairs. Further study, particularly with a standardized protocol for THS supplementation in heart donors is warranted.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

This abstract of this manuscript was previously presented at the 2022 Annual conference of the American College of Surgeons.

Conflicts of Interest

Hannah Copeland has been a speaker for Paragonix and Abbott. David Baran has received consulting fees from Getinge, Livanova, Abbott, and Abiomed. He is on the Steering Committee for Procyrion, Natera, and Care Dx. He has been a speaker for Pfizer. All other authors declare that they have no conflicts of interest.

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