Research article

Reducing disparities in the treatment of hyperparathyroidism

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A B S T R A C T

Background: Hyperparathyroidism is common with African American patients historically experiencing disparate outcomes. With a comprehensive outreach program and systematic treatment plans, we sought to evaluate our institution's ability to reduce disparities in hyperparathyroidism.
Methods: We performed a retrospective review of prospectively collected data at a single medical center for all patients undergoing parathyroidectomy by endocrine surgeons from 2015 to 2021 for primary (PHPT) and tertiary (THPT) hyperparathyroidism. Patient demographics, pre- and post-operative clinical and biochemical data were collected and analyzed by race.
Results: Of the 757 patients included, 675 patients had PHPT with 135 (20 %) African-American (AA) and 528(78 %) female. Of 82 patients with THPT, 44 (53 %) were AA and 34 (32 %) were female. AA patients were younger than Caucasian (CA) patients with a mean age ($\pm$SD) of 56 $\pm$ 15 vs 60 $\pm$ 14 years in PHPT (p < 0.01) and 50 $\pm$ 10 vs 55 $\pm$ 10 years in THPT (p = 0.02).
Median (IQR) preoperative PTH was higher in AA with PHPT 134 (97–190) vs 102 (75–144) pg/mL (p < 0.01) and in AA with THPT 285 (189–544) vs 218 (145–293) (p = 0.01) pg/mL. AA PHPT patients had significantly higher preoperative mean ($\pm$SD) calcium levels 10.9 $\pm$ 0.8 vs 10.6 $\pm$ 0.8 mg/dL(p < 0.001). Biochemical cure rates at 6 months and complication rates were not different between races.
Conclusions: AA patients with PHPT and THPT disease experienced similar cure rates to their CA counterparts despite having a more severe biochemical disease. Health care disparities may be ameliorated with treatment by high volume surgeons embedded in a comprehensive health care system.

1. Introduction

Healthcare disparities are prevalent in many medical and surgical disciplines throughout the country and the world [1–3]. Racial disparities have been studied for diseases of the thyroid, parathyroid, and adrenal glands of particular interest to the field of endocrine surgery [4–10]. Hyperparathyroidism consists of a spectrum of diseases characterized by inappropriately elevated parathyroid and/or calcium levels, potentially causing numerous multi-organ disease sequelae [11–15]. Surgical treatment is the standard of care for cure [16–18]. Hyperparathyroidism is common in African Americans, with disparities in access to care, treatment, and outcomes previously described [9,19]. Beyond describing the disparities that plague our health care system, there is much need for interventions and studying those interventions that improve health care outcomes.

Our institution is a quaternary health care system situated in Alabama, USA. Alabama's unique history and location in the southeast of the United States generates a patient population that over represents African Americans compared to the greater United States [20]. Alabama is also described as belonging to the "deep south", characterized by mostly rural locales with limited health care access [21], and contains the so-called "Black Belt" of America. The Black Belt is a region of the American South with a complex history of racism, segregation, and economic divestment over the past century that is accompanied by disproportionally high rates of medical problems

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and complications [22–24]. Healthcare and other professionals in this region answer a call to reduce these endemic healthcare disparities. Given this unique geographic and sociopolitical environment, our group is uniquely situated to address the reduction of healthcare disparities within endocrine surgical diseases [25].

We have previously published on the racial disparities in primary hyperparathyroidism presentation and treatment [26]. African Americans, especially males, were found to be less likely to be referred to endocrine surgeons and less likely to undergo parathyroidectomy than their peers. Given this, we enacted a comprehensive outreach program and systematic treatment plans for patients with hyperparathyroidism. There are few data specifically examining racially based outcomes for primary hyperparathyroidism patients. Additionally, very little research has been performed specifically evaluating disparities in the care of tertiary hyperparathyroidism, which we define in a specific subset of patients after renal transplantation [27]. The purpose of this study was to evaluate our institution's surgical outcomes in managing hyperparathyroidism and our ability to reduce disparities in this patient population when compared to historical controls and the overall outcomes reported in endocrine surgical literature.

2. Materials/methods

2.1. Patients

With IRB approval (IRB-300004448), we performed a retrospective review of prospectively collected data at a southern quaternary referral center for all patients undergoing parathyroidectomy by high-volume endocrine surgeons from 2015 to 2021. We included adult (age>18years) patients with primary (PHPT) and tertiary (THPT) hyperparathyroidism as these patients maintain normal creatinine, limiting confounders to diagnosis, cure, and recurrence. There were no discrete referral requirements for patients and we permit self-referrals. Since 2015, through educational outreach, our group instructs referring providers to send all patients with a biochemical diagnosis of hyperparathyroidism prior to any imaging and permit the endocrine surgeon to decide who needed further evaluation and treatment. This is based on prior data showing that parathyroid imaging delays referral to surgery [28]. We excluded those who had previously undergone parathyroidectomy elsewhere.

Patient demographics, pre-and post-operative clinical data were obtained. Only self-reported Black/African American (AA) and Caucasian (CA) patients were included and compared, as other racial/ethnic groups were too small to analyze independently. Clinical data included subjective symptoms and objective findings and imaging. Biochemical data included adjusted serum calcium (our laboratory normal range: 8.4–10.4 mg/dL), parathyroid hormone levels (upper limit of normal: 88 pg/mL), activated vitamin D levels, and serum creatine levels (normal 0.4–1.2 mg/dL). Low vitamin D is treated prior to surgery per our institutional protocol, but surgery is not delayed for these patients [29–31].

Table 1
Preoperative characteristics primary and tertiary hyperparathyroidism (n = 757).

PHPT (n=675)	AA (179, 24 %)	CA (578, 76 %)	p-value
	n = 135	n = 540	
Female	113 (84 %)	415 (77 %)	0.08
Age years (mean ± SD)	56 ± 15	60 ± 14	**<0.01**
BMI (mean ± SD)	32.4 ± 7.9	30.3 ± 7.4	**<0.01**
Fatigue symptom	99 (73 %)	406 (75 %)	0.66
Bone/Joint Pain symptom	66 (49 %)	305 (53 %)	0.11
Baseline Creatinine mg/dL (median [IQR])*	0.9 [0.7–1.1]	0.9 [0.7–1.1]	0.86
Baseline Ca mg/dL (mean ± SD)	10.9 ± 0.8	10.6 ± 0.8	**<0.001**
Baseline PTH pg/mL (median [IQR])	134 [97–190]	102 [75–144]	**<0.01**
Baseline vitamin D ng/L (mean ± SD)*	29.4 ± 18.1	33.9 ± 15.0	**<0.01**
Bone Disease^	33 (25 %)	213 (40 %)	**<0.01**
Kidney stones	30 (22 %)	215 (40 %)	**<0.001**
THPT (n=82)	n = 44	n = 38	
Female	14 (32 %)	20 (53 %)	0.06
Age (mean ± SD), years	50 ± 10	55 ± 10	**0.02**
BMI (mean ± SD)	29.8 ± 6.4	31.1 ± 6.9	0.37
Fatigue symptom	33 (75 %)	30 (79 %)	0.67
Bone/Joint Pain symptom	14 (32 %)	14 (37 %)	0.63
Baseline Creatinine mg/dL (median [IQR])	1.6 [1.3–1.8]	1.4 [1.1–1.8]	0.13
Baseline Ca mg/dL (mean ± SD)	10.5 ± 0.9	10.8 ± 0.5	0.16
Baseline PTH pg/mL (median [IQR])	285 [189–544]	218 [145−293]	**<0.01**
Baseline vitamin D ng/L (mean ± SD)	22.1 ± 10.5	28.7 ± 13.5	**0.02**
Bone disease^	6 (14 %)	9 (24 %)	0.24
Kidney stones	4 (9 %)	7 (18 %)	0.22

p-values in **bold** indicate statistical significance (<0.05).
* indicates missing values for PHPT: n = 44 (Black n = 6, White, n = 38); missing baseline vitamin D, n = 29 (AA n = 6, CA n = 23). Those missing creatinine. BMI, kidney stones, and bone disease all missing 2 % or less of data.
** indicates missing values for THPT: n = 4 (AA n = 2, CA n = 2).
^ "Decreased Bone Density" indicates the patient carries a diagnosis of osteopenia, osteoporosis, or atraumatic fracture.

Complication rates were collected and defined as neck hematoma, readmission or Emergency Department visit, temporary or permanent hypoparathyroidism, and temporary or permanent hoarseness. Cure was defined as lack of persistent or recurrent disease for at least 6 months after parathyroidectomy. Recurrence was defined per guidelines as rising calcium and/or parathyroid hormone levels after operative cure [16,32,33].

2.2. Surgical approach

All hyperparathyroidism patients undergo a radio-guided approach for all parathyroid surgery, except where contraindicated, as described previously [34,35]. We do not routinely obtain focused parathyroid or thyroid imaging unless in cases of a re-operative field (4D CT is obtained) or suspicion of concomitant thyroid disease. We begin surgical exploration on the localized side of disease if preoperative imaging was obtained. We utilize intraoperative PTH monitoring and the procedure is halted upon achieving at least a 50 % drop from preoperative, day of surgery values.

For patients with tertiary hyperparathyroidism and normal graft function, we prefer a subtotal parathyroidectomy approach, resecting 3.5 glands routinely. Radio-guidance and intraoperative PTH monitoring is similarly employed as supported by the literature [35,36]. We employ a dedicated nurse practitioner to ensure that patients are prepared preoperatively (i.e.: holding anticoagulants and other medications appropriately) and followed closely post-operatively with a phone call on post-operative day 1. This enables routine discharge on post-operative day 0 and early identification and treatment of any concerns, such as symptomatic hypocalcemia. We utilize standardized treatment pathways, including post-operative calcium and vitamin D supplementation for all subtypes of hyperparathyroidism.

Statistical analysis including T-tests, chi-squared analysis, and ANOVA, as appropriate, were performed with R software [37]. Significance was defined as p < 0.05.

3. Results

There were 757 patients treated over the 7 year period at our institution for PHPT or THPT. Of these, 179 (24 %) self-identified as Black or African American (AA) and 578 (76 %) self-identified as White or Caucasian American (CA). A total of 675 patients had PHPT with 135 (20 %) African Americans and 528 (78 %) females (see Table 1). There were 82 patients with THPT, of these 44 (53 %) were AA, and 48 (58 %) were male. AA patients were younger than their CA counterparts with a mean (±SD) age of 56 ± 14 vs 60 ± 14 years in PHPT (p = 0.007) and 49 ± 9.5 vs 55 ± 10 years in THPT (p = 0.017).

Preoperative subjective symptomatology was not significantly different between races, with similar fatigue and bone/joint pain rates in all groups (p > 0.05). More CA patients with PHPT carried a diagnosis of bone disease (self-reported or documented without T or Z scores) (213 (40 %) versus 33 (25 %) (p < 0.01)) and nephrolithiasis (215 (40 %) versus 30 (22 %) (p < 0.001)) than their AA counterparts. There were no differences in these diagnoses for THPT. DEXA scans were only documented 28 % of our patients, so T and Z scores could not be calculated.

The median (IQR) of preoperative PTH was higher in AA with PHPT 134 (97–190) vs 102 (75–144) pg/mL (p < 0.01) and in AA with THPT 285 (189–544) vs 218 (145–293) (p = 0.01) pg/mL. The AA PHPT patients had significantly higher preoperative mean (±SD) calcium levels 10.9 ± 0.8 vs 10.6 ± 0.8 mg/dL(p < 0.001). Mean vitamin D levels in both groups were lower for AA patients at 29.4 ± 18.0 vs. 33.9 ± 15 ng/L in PHPT (p < 0.01) and at 22.1 ± 10.5 vs 28.6 ± 13.5 ng/L in THPT (p < 0.02).

Upon surgical treatment, the final etiology of the disease was not different by race (Table 2). Biochemical cure rates at 6 months and complication rates including hematoma (n = 1), readmission (n = 0), Emergency Department visit (PHPT: n = 4, THPT: n = 1), hoarseness (PHPT: temporary n = 4, permanent n = 1; THPT: temporary n = 1, permanent n = 0), and hypoparathyroidism requiring supplementation longer than 2 weeks (PHPT: temporary n = 41, persistent n = 1; THPT: temporary n = 12, persistent n = 3), were

Table 2
Postoperative outcomes (n = 757).

PHPT (n=675)	AA (179, 24 %)	CA (578, 76 %)	p-value
	n = 135	n = 540	
Adenoma	83 (62 %)	308 (57.4 %)	0.12
Multigland disease	50 (37 %)	229 (42 %)	
Postoperative Complication[+]	1 (0.7 %)	24 (4.4 %)	0.31
Cure[#]	112/117 (96 %)	496/506 (98 %)	0.14
THPT (n=82)	n = 44	n = 38	
Adenoma	3 (6.8 %)	3 (7.9 %)	0.95
Multigland disease	41 (93 %)	35 (97 %)	
Postop Complication[+]	4 (14 %)	6 (24 %)	0.64
Cure[#]	32/36 (89 %)	36/37 (97 %)	0.16

p-values in **bold** indicate statistical significance (<0.05).
+post-operative complication includes neck hematoma, readmission/ED visit, temporary or permanent hypoparathyroidism, and temporary or permanent hoarseness.
#Cure is only calculated for those with ≥6 months follow-up.

similar between races for PHPT and THPT patients (p > 0.05). There were no differences between races in persistence, recurrence, or reoperation. Reoperation was completed in 8 patients with PHPT, 6 were cured after reoperation. Reoperation was completed in 3 patients with THPT, 2 were cured.

4. Discussion

In our diverse patient population with hyperparathyroidism (primary and tertiary), AA patients presented with a more severe biochemical disease at a younger age, but achieved equivalent levels of cure and complication rates. These data are important for reporting on and assessing outcomes and the effects of interventions for minority patients, especially when focusing on reducing disparities.

The biological reason for the difference in biochemical presentation among African Americans is unclear. One hypothesis is that a higher prevalence of vitamin D deficiency may artificially drive up parathyroid hormone levels, causing an earlier presentation to medical attention. Vitamin D deficiency is more common in AAs in general, which may mimic a secondary hyperparathyroidism picture [38].

This may be a contributing factor, but would not explain the concomitant higher levels of serum calcium among AAs in the PHPT cohort [39–41]. More research needs to be done to elucidate this.

Our cure rates are similar to the previously published data among high-volume surgeons of all-comers with a cure rate of >97 % in PHPT and >90 % in THPT.[40][41] However, we found with no differences in cure or complications between races. Subjective symptoms of fatigue appeared similar for all groups and were the most frequently reported symptom among patients, as supported by prior work [14].

When assessing bone disease and kidney stones, the preoperative diagnosis rates varied by race for PHPT but not THPT. This racial difference has been demonstrated in other nationwide studies of PHPT and may stem from a physiologic difference or a difference in access to imaging [42]. It is not surprising that our patients were unlikely to have had screening DEXA scans since our mean age across all groups was under the recommended at which point bone density screening is recommended (65 years) [43]. Therefore, those who had obtained screening most likely had sufficient access to medical care and saw a provider who was compelled to order this outside of the guidelines. This favors those patients with more access to medical providers, which historically disadvantages African-American patients [27,44]. Similarly, the diagnosis of kidney stones requires compelling subjective symptoms and imaging so a diagnosis may be limited by both access and implicit bias [45]. We hypothesize that this may be linked to the underdiagnoses of clinical problems such as nephrolithiasis, even in the face of more severe biochemical presentation in AA patients.

Previous work has similarly shown that racial minorities experience delayed access and increased complications after parathyroid surgery, possibly related to limited access to high volume surgeons and increased comorbidities [5,42,46]. Most published research on disparities in patients with hyperparathyroidism are completed by evaluating national inpatient databases, which is complicated by inherent limitations. When examining single or multi-institutional data with the benefit of granular detail, the sources of these disparities may be more carefully explored [9].

Our study adds to the currently limited literature on racial disparities, specifically for tertiary hyperparathyroidism. Often secondary and tertiary hyperparathyroidism surgical patients 'outcomes are co-reported, but a dedicated racial analysis in the post-transplantation state could not be found in the literature. Therefore, this likely represents an understudied group [47,48]. In this study, patients with THPT did not demonstrate differences in evaluation or symptoms by race. We believe this may be related to the frequent encounters with medical providers that co-occur with the post-transplantation state.

Due to historical systemic bias, geography, and other social determinants of health, many minority patients may not have access or insurance coverage to see high-volume endocrine surgeons at specialty medical centers expeditiously. Our group posits that highly motivated outreach and support programs as well as a willingness to see and operate on patients without extensive, often unnecessary, additional evaluation, can increase the ability to streamline minority and underserved patients to high volume centers, which we believe may reduce healthcare disparities in parathyroid disease [49,50]. Taken together, our approach may explain why we do not see similar disparities in outcomes in our AA patients as seen in other nationwide studies. There are some limitations in this study. This is a single-center study whose results may not be applicable generally. We do not routinely order preoperative kidney ultrasounds or DEXA scans due to the required delay in surgical management, therefore there are limits in our ability to comment on the biologic basis of racial differences in incidence of osteoporosis or nephrolithiasis. Additionally, the population of tertiary hyperparathyroidism patients is small, which introduces selection bias. However, given the rarity of the diagnosis leading to surgical intervention, this selection bias is difficult to overcome. A multi-institutional collaboration may reduce this bias.

In conclusion, with protocolized care in the hands of high-volume surgeons embedded in comprehensive health care system, AA patients with PHPT and THPT disease experience similar cure rates to their CA counterparts despite a more severe biochemical disease. These results differ from nationally published data on disparities. Providers who care for these patients in both the medical and surgical fields should be aware of these racial/ethnic differences in presentation and how it may influence the treatment of patients with hyperparathyroidism.

Declarations

Ethics statement: This study was approved by University of Alabama Institutional Review Board: #300004448. This study complies with all stated regulations. Consent was waived given the exempt nature of data collection. IRB ethics committee certificate has been made available.

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Conflict of Interest/Disclosures

The authors have no related conflicts of interest to declare.

CRediT authorship contribution statement

Andrea Gillis: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rongzhi Wang:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Polina V. Zmijewski:** Writing – review & editing, Data curation, Conceptualization. **Chandler McLeod:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Kimberly Ramonell:** Writing – review & editing, Data curation, Conceptualization. **Jessica Fazendin:** Writing – review & editing, Conceptualization. **Herbert Chen:** Writing – review & editing. **Brenessa Lindeman:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Andrea Gillis reports financial support was provided by National Cancer Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32244.

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