Original Article

Abnormal Laboratory Values for Metabolic and Hormonal Syndromes Are Prevalent Among Patients Undergoing Rotator Cuff Repair

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Purpose: To determine the prevalence of systemic laboratory abnormalities among patients undergoing rotator cuff repair (RCR). **Methods:** Patients who underwent RCR at the authors' institution for 1 year between October 2021 to September 2022 were retrospectively identified. Preoperative laboratory values, including serum sex hormones, vitamin D, hemoglobin A1C, and a lipid panel, were obtained as part of our routine practice during the study period. Demographics and tear characteristics were compared in patients with laboratory data and those without. For included patients with laboratory data, mean laboratory values and percentage of patients with abnormal laboratory values were recorded. **Results:** During a 1-year period of time, 135 RCRs were performed, of which preoperative labs were obtained on 105. Of these, 67% were sex hormone deficient, 36% were vitamin D deficient, 45% had an abnormal hemoglobin A1C, and 64% had an abnormal lipid panel. In total 4% had "normal" labs. **Conclusions:** In this retrospective study, sex hormone deficiency is highly prevalent among patients undergoing RCR. Nearly all patients undergoing RCR have systemic laboratory abnormalities involving either sex hormone deficiency, vitamin D deficiency, dyslipidemia, and/or prediabetes. **Level of Evidence:** Level IV, prognostic case series.

Introduction

Rotator cuff pathology is among the most common musculoskeletal disorders.[1,2] Rotator cuff tears (RCTs) account for ~4.5 million visits to physicians each year and have a lifetime incidence between 25% and 40% in the United States.[3,4] Although RCTs have classically been associated with etiologies such as traumatic injury and progressive degeneration, there are data suggesting that rotator cuff tendinopathy is due, in part, to systemic causes.[5-13] For example, hypertension, diabetes, smoking, osteoporosis, dyslipidemia, hyperuricemia, depression, and genetic predisposition have all been demonstrated to be risk factors associated with the development of RCTs.[5-13] Additionally, a recent analysis of a large insurance claims database demonstrated that sex hormone deficiency (SHD; i.e., hypogonadism) positively associated with the incidence of RCR.[14]

This most recent study from Smith and colleagues suggests that SHD, or a testosterone-deficient state in males and an estrogen-deficient state in females, may also contribute to the biologic milieu in the development of RCTs. SHD is a clinical syndrome associated with impaired functional activity of the gonads, which

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can be classified as primary, secondary, or mixed.[15] Primary SHD is due to dysfunction at the level of the gonads, where testosterone production in the testes and estrogen production in the ovaries is insufficient in males and females, respectively. Secondary SHD is due to dysfunction at the level of the hypothalamus or pituitary, where gonadotropin-releasing hormone and/or gonadotropin release (i.e., follicle-stimulating hormone, luteinizing hormone) is insufficient. Mixed SHD is due to dual defects of the gonads and pituitary-hypothalamic axis. SHD is often due to congenital (e.g., Klinefelter syndrome in males, Turner syndrome in females) or acquired (e.g., secondary to irradiation, infection, trauma, kidney disease, liver disease, etc.) causes.[16] Sex hormone physiology is complex and involves numerous organ systems; however, this article will focus on SHD and its relationship to the musculoskeletal system, specifically that of the rotator cuff. For example, in the in vitro and animal literature, androgens have been shown to prevent supraspinatus muscle atrophy and fatty infiltration and, thus, may improve outcomes after rotator cuff repair (RCR).[17-19] In a murine study, the effect of an estrogen-deficient state on tendon-to-bone healing after RCR found that estrogen deficiency (ED) was associated with less development of chondroid tissue, decreased bone mineral density at the enthesis, and poorer repair biomechanics.[20] In human studies, polymorphisms in the estrogen-related receptor β gene have been shown to be significantly associated with rotator cuff disease and rotator cuff repair failure.[10,21,22] However, while SHD has been shown to be associated with RCR, the prevalence of systemic laboratory abnormalities among individuals currently undergoing RCR is unknown. Understanding how common SHD is in a typical shoulder and elbow clinical practice, and how SHD manifests via various endocrine markers will further help providers characterize this comorbidity and will provide guidance for future systemic and locally targeted intervention strategies.

The purpose of this study was to determine the prevalence of systemic laboratory abnormalities among patients undergoing RCR. We hypothesized that most patients would have laboratory evidence of either hypogonadism, vitamin D deficiency, dyslipidemia, or prediabetes.

Methods

Protocol Approval

Each institution approved the human protocol for this investigation, and all investigations were conducted in conformity with ethical principles of research. Informed consent for participation in the study was not required by our Institutional Review Board (IRB). This study was performed under the University of Utah IRB as approved protocol #144900.

Patients who underwent RCR at the authors' institution for 1 year between October 2021 and September 2022 were retrospectively identified. Exclusion criteria were patients under the age of 18 years, those not undergoing RCR, and patients with incomplete laboratory data. In all patients undergoing RCR at the University of Utah Hospital, we obtained the following serologic laboratories preoperatively: 25-OH Vitamin D, Hgb A1C, and a lipid panel that includes cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol. In women, we obtained estradiol levels. In men, we obtained testosterone levels, free-testosterone levels, sex hormone-binding globulin levels, and bioavailable testosterone levels. Additionally, calculations from these data allowed us to measure the percentage of free testosterone. We retrospectively reviewed these patients to determine the prevalence of abnormalities within these laboratory examinations. Sex hormone levels were recorded as the primary outcome measure, while the Vitamin D, Hgb A1C, and lipid panel were recorded as the secondary outcome measures. Ranges provided by our laboratory were used to define "normal" (Table 1). Our laboratory limits for total testosterone, free testosterone, estradiol, and luteinizing hormone were comparable to existing definitions for sex hormone deficiency.[23]

Within these patients, we also reviewed their charts to collect the following preoperative demographic data: age, gender, shoulder laterality, hand dominance, American Society of Anesthesiologist (ASA) score, body mass index, work status, medical comorbidities sufficient for calculation of the Charlson Comorbidity Index, smoking status, and indication for surgery. On preoperative magnetic resonance imaging (MRI), we measured tear width, tear retraction, supraspinatus Goutallier[24] classification, infraspinatus Goutallier classification, subscapularis Goutallier classification, and teres minor Goutallier classification. Moreover, within this cohort, we collected preoperative values for an American Shoulder and Elbow Surgeons (ASES) Score,[25] Simple Shoulder Test (SST) scores, the visual analogue scores (VAS) for pain and function, and range of motion. On the basis of the intraoperative records, we collected the number of anchors, the repair construct, the biceps treatment, and whether a concomitant subscapularis repair was performed.

Statistical Analysis

All analyses were conducted in Excel 16 (Microsoft, Redmond, WA) and SPSS 28 (IBM, Armonk, NY). Continuous data were evaluated for normality using the Komolgorov-Smirnov test. Data with a Gaussian

Table 1. Normal Ranges (Low and High Limits) for Laboratory Values

Laboratory Test	Low	High	Means ± SD	% (*N*) Abnormal
Thyroid stimulating hormone (mU/L)	0.34	4.94	1.9 ± 1.3 (0.1 to 6.2)	5% (2/40)
Luteinizing hormone (IU/L)	1.7	8.6	12 ± 11 (0 to 35)	44% (11/25)
Estradiol (pg/mL)	27	433	59 ± 65 (0 to 280)	25% (13/25)
Testosterone (ng/dL)				
By LC-MS/MS	300	1080	348 ± 260 (8 to 1158)	46% (16/35)
By ELISA	300	890	467 ± 330 (0 to 1500)	33% (23/69)
Bioavailable testosterone (ng/dL)				
By LC-MS/MS	130	680	166 ± 151 (1 to 657)	71% (24/34)
By ELISA	131	682	201 ± 186 (0 to 1325)	64% (42/66)
Free testosterone (pg/mL)				
By LC-MS/MS	47	244	58 ± 51 (0 to 221)	49% (17/25)
Calculated	47	244	77 ± 74 (0 to 446)	29% (20/70)
Sex hormone binding globulin (nmol/L)	11	80	49 ± 28 (10 to 182)	7% (5/72)
Percent of free testosterone (%)	1.6	2.9	1.6 ± 0.5 (0.6 to 3)	63% (43/68)
Vitamin D, 25-Hydroxy (ng/mL)	30	80	37 ± 18 (12 to 109)	36% (34/96)
Alkaline phosphatase (U/L)	40	120	79 ± 23 (22 to 145)	2% (1/47)
Bone alkaline phosphatase (U/L)	0	55	35 ± 14 (16 to 67)	13% (3/24)
Calcium (mg/dL)	8.4	10.5	9.4 ± 0.4 (8.4 to 10.3)	0% (0/56)
Hemoglobin A1C (%)			5.6 ± 0.6 (4.6 to 8.6)	44% (46/103)
Normal	0	5.6		
Prediabetes	5.7	6.4		
Diabetes	6.5	100		
Cholesterol (mg/dL)	0	239	187 ± 37 (93 to 258)	5% (5/102)
Low-density lipoprotein (mg/dL)	0	129	108 ± 31 (11 to 163)	28% (28/101)
Very-low-density lipoprotein (mg/dL)	0	30	27 ± 14 (8 to 79)	34% (63/98)
High-density lipoprotein (mg/dL)	40	59	50 ± 14 (28 to 92)	21% (22/102)

Normal ranges (low and high limits) for laboratory values provided by our institution's laboratory compared to laboratory values of the included patients, as well as the percent and number that were abnormal for each of those values. ELISA, enzyme-linked immunosorbent assay; LC-MS/MS, liquid chromatography/mass spectrometry.

distribution were compared between groups using Student's *t*-tests. Data with a non-Gaussian distribution were compared using Mann-Whitney *U*-tests. Categorical data will be compared between groups using Chi-square tests or Fischer's Exact tests, as appropriate depending upon cell populations.

Results

Study Cohort

During the study period, 135 rotator cuff tears were performed. When the 105 included patients were compared to the 30 excluded patients, there were no differences in age, gender, whether the surgery was on the dominant side, smoking status, body mass index, ASA scores, Charlson comorbidity index, ASES score, range of motion, MRI characteristics, or intraoperative variables. The preoperative VAS pain scores were statistically, but not clinically, significantly higher in the excluded group (5.9 ± 2.5 vs 4.8 ± 2.4; $P = .038$), and the included group had more anchors used (2 ± 1 vs 3 ± 1; $P = .011$). The characteristics of the included patients are shown in Table 2. Patients were included if they had any of the preoperative labs available; only 85/105 (81%) of the included patients had a complete set of preoperative laboratory values. Of these 85 patients, 80 (94%) had either abnormal sex hormone levels, were already on sex hormone supplementation, had low vitamin D levels, had an abnormal hemoglobin A1C, or had an abnormal lipid panel. Among these 85, 5 patients (6%) had completely normal laboratory values, 24% (20) had at least one of the above categories abnormal, 17% (14) had two, 28% (24) had three, 18% (15) had four, and 8% (7) had five or more. Thus, most patients undergoing rotator cuff repair have systemic preoperative laboratory abnormalities (Fig 1).

Sex Hormone Deficiency (Hypogonadism)

Within the 105 included patients, 69 (66%) were male, of whom 11 (16%) were taking hormone replacement therapy. Of the 69 males, 41 (59%) had either a low testosterone or a low bioavailable testosterone level (hypogonadal; Table 1). Of these 41, 11 had concomitant luteinizing hormone levels drawn, of which 2 (18%) were high, suggesting primary gonadal failure as the etiology of hypogonadism. The other 9 (82%) had normal or low luteinizing hormone levels, suggesting hypothalamic-pituitary disorders, or secondary hypogonadism. In combination, 71% (49/69) either had a low testosterone (i.e., were hypogonadal) or were already being supplemented. Within the 105 included patients, 36 (34%) were female, of whom

Table 2. Comparison of Included and Excluded Patients

Variable	Excluded ($n = 30$)	Included ($n = 105$)	P Value
Age (years)	58 ± 11	60 ± 10	.463
Female sex	40% (12/30)	34% (36/105)	.564
Dominant side	96% (25/26)	95% (69/73)	1.000
Current smokers	10% (3/30)	5% (5/103)	.178
Body mass index	30 ± 5	29 ± 6	.706
ASA score	2 ± 1	2 ± 1	.467
Charlson comorbidity index	2 ± 1	2 ± 2	.444
VAS pain	5.9 ± 2.5	4.8 ± 2.4	.038
ASES	41 ± 18	48 ± 19	.124
Active forward elevation (°)	148 ± 35	135 ± 45	.180
Adducted external rotation (°)	61 ± 18	53 ± 20	.088
Preop tear width (mm)	15 ± 9	19 ± 11	.092
Preop tear retraction (mm)	21 ± 10	18 ± 12	.424
Supraspinatus atrophy >1	20% (4/20)	28% (25/88)	.881
Infraspinatus atrophy >1	20% (2/20)	9.1% (8/88)	.260
Subscapularis atrophy >1	10% (2/20)	15.9% (14/88)	.373
Teres minor atrophy >1	0% (0/20)	1% (1/88)	.661
Revision rotator cuff repair	10% (3/30)	9% (9/105)	.729
Adducted internal rotation			
Lateral thigh	4% (1/23)	5% (5/95)	
Buttock	9% (2/23)	14% (13/95)	
Lumbosacral junction	13% (3/23)	15% (14/95)	
L3	17% (4/23)	29% (28/95)	
T12	30% (7/23)	25% (24/95)	
T7	26% (6/23)	12% (11/95)	.605
Number of anchors	2 ± 1	3 ± 1	.011
Repair construct			
Single row	53% (16/30)	38% (40/105)	
Double row	47% (14/30)	62% (65/105)	.135
Concomitant biceps tenodesis	83% (25/30)	85% (89/105)	.633
Subscapularis repair	33% (10/30)	31% (32/105)	.766

Continuous data are displayed as means ± SD, and discrete data are displayed as % (N). Muscular atrophy data reference Goutallier stage >1. ASA, American Society of Anesthesiologists; ASES, American Shoulder and Elbow Surgeons Score; VAS, visual analog scale for pain.

1 (3%) was taking hormone replacement therapy. Of the 25 females with a preoperative estradiol level, 13 (52%) were low (i.e., hypogonadal). In combination, 56% (14/25) of females either had a low estradiol level or were already being supplemented. Within the overall cohort with preoperative labs, 67% (63/94) of included patients were either hypogonadal or already taking hormone replacement therapy.

Vitamin D Deficiency and Thyroid

Of the 95 patients with preoperative vitamin D levels, 34 (36%) were abnormally low, with 3 having severe deficiency (<12 ng/mL), 6 having deficiency (12-19 ng/mL), and 25 having insufficiency (20-29 ng/mL). Only a single patient had a high alkaline phosphatase level, and this patient had a normal vitamin D level. There were no patients with abnormal calcium levels. Only 2 patients had abnormally high thyroid-stimulating hormone levels.

Diabetes and Prediabetes

Within our cohort, 103 patients had preoperative hemoglobin A1C levels. Of these, 57 (55%) were normal, 38 (37%) showed prediabetes, and 8 (8%) showed diabetes. Of those with hemoglobin A1C levels considered normal, 4% had a known diagnosis or diabetes or prediabetes. Of those with hemoglobin A1C levels considered prediabetic, 34% had a known diagnosis of diabetes or prediabetes. Of those with hemoglobin A1C levels consistent with diabetes, 75% had a known diagnosis of diabetes or prediabetes. Overall, these preoperative labs uncovered a previously unknown diagnosis of diabetes or prediabetes in 26% (27/103) of patients.

Dyslipidemia

Examining lipid panels, 5% (5/102) had high cholesterol, 28% (28/101) had high low-density lipoprotein, 34% (36/98) had high very-low-density lipoprotein, and 21% (22/102) had low high-density lipoprotein. In combination, 64% (63/98) of patients had an abnormality in at least 1 of the above lipid levels. When considering patients with a complete lipid panel and hemoglobin A1C, only 21/97 (20%) were normal, with 80% having at least one metabolic abnormality.

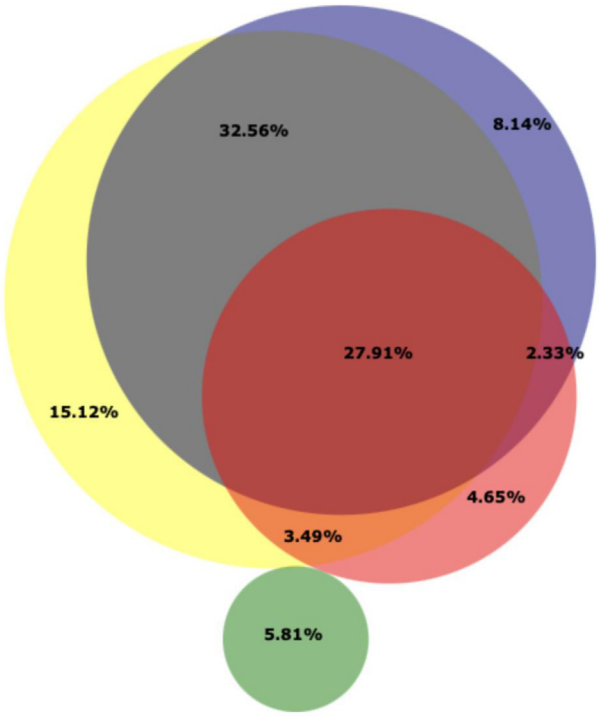

Fig 1. This Venn diagram shows percent of patients undergoing rotator cuff repair that had normal or abnormal systemic lab abnormalities. Green, normal; Red, vitamin D deficient; Yellow, abnormal lipids and/or abnormal hemoglobin A1C; Blue, hypogonadal or taking hormone supplementation. Created using DeepVenn.[35]

Discussion

In this retrospective case series, nearly all (94%) patients undergoing rotator cuff repair were either hypogonadal, vitamin D deficient, diabetic/prediabetic, or had dyslipidemia. Among males, 71% either were hypogonadal or were already being supplemented, among females 56% either were hypogonadal or were already being supplemented, and among the combined cohort, 67% either were hypogonadal or already taking hormone replacement therapy. Thirty-six percent had abnormally low vitamin D levels. Metabolic syndromes were common—37% had prediabetes, 8% had diabetes, and 26% of patients received a new diagnosis of either prediabetes or diabetes. In combination, 64% (63/98) of patients had an abnormality in at least one of their lipid levels. These results demonstrate that systemic laboratory abnormalities are common among patients undergoing rotator cuff repair.

Within our study, the prevalence of sex hormone deficiency, as defined based upon a low testosterone/bioavailable testosterone level or based upon the patient already receiving hormone replacement therapy, was 67%. Multiple prior studies have been conducted to determine the prevalence of testosterone deficiency using similar criteria in normal populations. Fink et al. conducted a cross-sectional study of men over the age of 65, and only 17% of men had testosterone levels <300 nL/dL, which was the same level used within our laboratory to define deficiency.[26] In another cross-sectional study, Harman et al. found hypogonadism in 12% of men under 50, 19% of men aged 50-60, and 28% of men aged 60-70, again using similar laboratory cutoffs.[27] These are historical controls and comparison to historical controls has limitations in that the populations are different, and the criteria used to define hypogonadism may be different. However, these rates are numerically much lower than the prevalence observed in our study population, confirming the findings of another recent study suggesting that hypogonadism associated with cuff tears.[14] Certainly, this definition alone does not account for whether these patients were symptomatic from the hormone deficiency, and future studies are planned in this regard. Additionally, given the findings of this study, in addition to other in vitro and animal studies, suggesting sex hormone deficiency is associated with poorer tendon-to-bone healing following RCR,[20] as well as androgen supplementation preventing rotator cuff atrophy and fatty infiltration,[17-19] future research should determine whether normalizing preoperative sex hormone levels (i.e., estrogen in females and testosterone in males) would improve postoperative outcomes in patients undergoing RCR.

Within our study, the prevalence of vitamin D deficiency was 36%. A prior Korean study demonstrated that 44% of patients undergoing rotator cuff repair are vitamin D deficient, especially younger patients.[28] Prior literature suggests that up to 75% of adults in the United States are vitamin D deficient.[29] Given the known connection between vitamin D deficiency and bone quality,[29] the known connection between osteoporosis and failure after rotator cuff repair,[30] and the favorable side effect profile with vitamin D supplementation,[31] future studies should determine whether vitamin D supplementation may improve outcomes in patients undergoing rotator cuff repair with vitamin D deficiency.

Within our study, the prevalence of dyslipidemia was 64%, and prediabetes was 37%. Multiple prior studies have demonstrated a connection between dyslipidemia and rotator cuff disease.[32-34] In combination with our own findings, these studies provide further support for the theory that rotator cuff disease is, in part, due to systemic abnormalities. Twenty-seven percent of patients within our study received a new diagnosis of either prediabetes or diabetes as part of preoperative testing. These results are strongly suggestive that these metabolic syndromes are common among patients undergoing rotator cuff repair and that this patient population may be underdiagnosed with these disorders. Given the importance of these disorders for overall

health, the high prevalence in this setting suggests that routine screening could be considered.

Finally, further research will be necessary to determine whether these systemic biologic abnormalities are modifiable risk factors—i.e., whether supplementation with vitamin D for those patients with vitamin D deficiency improves outcomes.

Limitations

This study has several limitations. The sample size is limited. This dataset reflects the practices of the two senior authors at the University of Utah Hospital and may not be generalizable to other settings. Within this study, sex hormone deficiency was defined by laboratory analysis alone, and these findings do not consider clinical symptomatology. We did not measure sex hormone levels in those taking hormone replacement therapy. Additionally, it is common for laboratory values to be outside the upper or lower limits of normal reference ranges, but the clinical relevance of this is unknown. We included those patients with some, but not all, of the included laboratory values to increase study power, which could create selection bias. However, given that most patients (78%) were included and that there were no clinically significant differences between the included and the excluded groups (Table 2), there are no signs of selection bias. Postoperative functional scores or imaging was not performed on these patients; therefore, the impact of sex hormone deficiency on rotator cuff healing was not investigated. The findings of this study alone cannot be used to demonstrate that these abnormalities should be treated.

Conclusion

In this retrospective study, sex hormone deficiency is highly prevalent among patients undergoing RCR. Nearly all patients undergoing RCR have systemic laboratory abnormalities involving either sex hormone deficiency, vitamin D deficiency, dyslipidemia, and/or prediabetes.

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