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Original Article

Glucocorticoid-Induced Osteoporosis: Increased Awareness as a Management Strategy for Prevention of this Complication in Patients with Systemic Autoimmune Rheumatic Disease

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Abstract

Background: It has been estimated that about 1% of the US population is treated with long-term glucocorticoids. High doses of glucocorticoids particularly those used by rheumatologists and others for systemic autoimmune rheumatic disease result in bone loss, causing glucocorticoid-induced osteoporosis and an increase in the risk of fractures. The increased risk is related to both the daily dose and the cumulative dose of the glucocorticoids. Despite the availability of effective preventative and treatment options, glucocorticoid-induced osteoporosis is often not mitigated with the use of these preventive therapies. The risk of glucocorticoid-induced osteoporosis often also goes underrecognized, because it occurs in a different group of patients compared to age-related osteoporosis. As a result, glucocorticoid-induced osteoporosis is not always treated until after fractures may have occurred. Our objective is to determine if a structured health-care provider's educational intervention with intermittent educational updates would lead to improvement in the identification, evaluation, and prevention of glucocorticoid-induced osteoporosisin those patients at the highest risk of glucocorticoid-induced osteoporosis.

Methods: In this single-center, prospective study, patients over 40 years of age, receiving a total cumulative dose of glucocorticoids of >5 g or a single dose of >30 mg of prednisone or its equivalent was enrolled. All providers attended an academic Journal Club, where the current American College of Rheumatology guidelines regarding glucocorticoid-induced osteoporosiswas reviewed. All providers received monthly reminders during academic meetings within the department.

Results: There was a statistically significant improvement between pre- and post-educational data, with increasing use of glucocorticoid-induced osteoporosis preventive measures, which was sustained over the 12-month duration of the study.

Conclusion: This research shows the importance of provider education as a means of disseminating information and improving the quality of patient care.

Keywords: Osteoporosis, preventive health, glucocorticoid, educational activities, osteoporotic fractures

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Introduction

Osteoporosis (OP) is a common condition that can be associated with high morbidity and mortality. Osteoporosis is either age related (primary) or commonly medication related (secondary), both of which have significant impacts on patients. The effects of a fragility fracture extend beyond the individual patient and have implications for the health system as a whole. The National Osteoporosis Foundation (NOF) demonstrated over 1 year that 2.3 million new osteoporotic fractures occurred in a study population of 2 million. Within 30 days of these osteoporotic fractures, approximately half of these individuals required at least 1 inpatient hospital stay. Approximately 1 in 5 of the individuals died within 12 months of the fracture. The cost associated with these fractures was in excess of $20,000 per patient.[1]

Due to both their anti-inflammatory and immunosuppressive properties, glucocorticoids (GC) are among the most common medications used in rheumatology. Glucocorticoids are used frequently in high doses and for prolonged periods in patients with systemic autoimmune rheumatic disease (SARD). A classic example of this is in patients with systemic lupus erythematosus (SLE), especially in lupus nephritis where

large doses of steroids are commonly used.[2] Glucocorticoids use has been attributed to several complications including being a common cause of secondary OP.[3] Glucocorticoid-related OP is also known as glucocorticoid-induced osteoporosis (GIO). Approximately, 1% of the general population is on long-term GC, many of whom are not being treated for GIO.[4] Some studies have suggested that between 11% and 50% of patients on GC will have a fracture,[5] and this increased incidence of fracture can be seen as soon as 3-6 months following the initiation of GC.[6] Both OP and GIO are particularly important to rheumatologists as SARD like rheumatoid arthritis (RA)[7] and SLE[8] are associated with an increased risk of secondary OP via changes in inflammatory cytokines that affect bone metabolism including receptor activator of nuclear factor kappa-B ligand, osteoprotegerin, tumor necrosis factor, and oxidized low-density lipoprotein. , RA[9] and SLE[10] patients also have the traditional risk factors including a higher incidence of vitamin D deficiency, the interplay between which, further increases the risk of GIO.[11] Given the extent of bone-related side effects, most rheumatologists now consider the use of steroid-sparing medications and GIO prevention a vital part of GC therapy.[12] The American College of Rheumatology (ACR) guidelines on GIO help to address risk stratification noting that doses of ≥30 mg/day or a cumulative dose of ≥5 g significantly increase the risk for hip and vertebral fractures.[13] As a result of GIO occurring in a different patient group compared to age-related osteoporosis, it is not always addressed. In addition, there has been a significant increase in our understanding of the increased risk of both osteoporosis and GIO in patients with SARD, and this is sometimes overlooked. This study aimed to investigate the use of the journal club format in improving the prevention of GIO. We did not look at individual providers testing and prescribing habits, as the goal was not to identify providers that needed to improve but to improve the group as a whole.

We aimed to see if improving provider awareness of GIO and the related fractures would lead to a sustained increase in surveillance, relevant testing, and the utilization of GIO mitigation measures as outlined in the ACR guideline document.

Main Points

- Glucocorticoid (GC)-induced osteoporosis (GIO) is a common and well-understood complication of GC use that is often overlooked and results in increased morbidity and mortality of our patients.
- The American College of Rheumatology (ACR) has developed and published guidelines that can be used to strategize the basis of our clinical intervention.
- Our study confirms that providing a structured health-care provider's education session based on the ACR guidelines increases the identification, risk stratification, and appropriate use of GIO mitigation measures.
- Given the high doses, and duration of GC therapy used in rheumatology, increasing the awareness of GIO and its intervention should be something all rheumatologists should be more aware of in all clinical encounters.

Material and Methods

This was a single-center, longitudinal study that was conducted at Virginia Tech Carilion School of Medicine, a university/academic-based tertiary referral center that provides care to the community of Southwest Virginia. The Institutional Review Board (IRB) reviewed and confirmed that access to protected health information (PHI) was minimal. The PHI used in this study involved minimal risk to the participants and in addition, the research could not practically be done without access to and the use of PHI. This study was therefore issued a full waiver of the health insurance Portability and Accountability Act approved by the Ethics Committee and granted approval by Carilion Clinic IRB (Approval No: IRB- 20-804, Date: June 2020), meaning that informed consent was not required from the participants. The records of all patients within the division of rheumatology receiving a total cumulative dose of steroids of 5 g or greater or a single dose of 30 mg or greater of prednisone or its equivalent were identified quarterly by the organization's Health Analytics Research Team (HART). This list once generated was housed in RedCap. RedCap is a secure application used to house data and is on the organization's intranet. The HART created our data collection tool that was linked to the patient's electronic medical records. This allowed discreet data (such as laboratory test results and prescriptions) to be imported directly to RedCap. This imported data did need to be verified by the research team. Data that was free text within the Electronic Medical Records (EMR) needed to be reviewed and collected by the research team as well.

Our patient study population included any patient followed by the Rheumatology Department at our center regardless of diagnosis who were aged 18 and older and prescribed prednisone of a dose greater than 30 mg or a cumulative dose of > 5 g in the preceding 3 months. We collected patient demographic data related to GIO risk including age, sex, ethnicity, body mass index, vitamin D and calcium levels, current and past medical history of both rheumatic and non-rheumatic diseases, steroid dose and duration, prior bone mineral density (BMD) results, and the use of or lack of use of GIO preventive measures. We collected data related to steroid prescriptions every quarter for a total of 4 quarters (12 months). The quarters were as follows: Quarter 1 (Q1) was the preceding 3 months to study initiation (to establish a baseline); Q2 was the first quarter after initiation; Q3 was the middle quarter; and Q4 was the last quarter. At the initiation of this study, all the rheumatology providers attended a Grand Round where the ACR Guideline for the prevention and treatment of GIO was presented, reviewed, and discussed. This educational session was supplemented with monthly reminders at other educational meetings within the division.

Our health-care team is composed of 5 physicians and a nurse practitioner, all of whom provide care only at the center. Every member of the team attended the journal club and filled out the pre-/post-meeting evaluation about the effectiveness of the program.

No patient from Q1, Q2, Q3, and Q4 who met our inclusion criteria and was enrolled was excluded from the statistical analysis. Continuous variables were analyzed using the *t*-test. Categorical variables were analyzed using chi-square tests. Mental health variables were analyzed using McNemar's tests. Statistical analysis was performed using SAS9.4, and a *P*-value <.05 was considered statistically significant. There were no missing data items, and all patients in Q1, Q2, and Q3 in the cohort were included in the statistical analysis.

Results

Following the Continuing Medical Education (CME) educational activity where the ACR guideline on prevention and treatment of GIO[12] was discussed, the feedback and comments noted an increased awareness of GIO and an intention to increase surveillance for those patients at risk of GIO. Although the total number of unique patients in each quarter dropped, we noted no statistically significant change in the patient demographics over

Table 1. Demographics

	Q1 (N = 72)	Q2 (N = 54)	Q3 (N = 49)
Demographics			
Age (years) at initiation of steroid	55.3 ± 19.8	53.4 ± 16.7	50.4 ± 17.1
Body mass index (M^2) at initiation of steroid	29.0 ± 6.7	29.4 ± 8.4	28.7 ± 8
Gender (female %)	73.6	74.1	71.4
Race			
White (%)	83.3	77.8	79.6
Hispanic (%)	1.4	5.6	2.0
Insurance			
ANTHEM BCBS (%)	16.9	26.9	25
Commercial (%)	11.3	11.5	6.3
Medicaid(%)	12.7	9.6	10.4
Medicare (%)	59.2	51.9	58.3

the 12-month duration of this study (Table 1). The majority of the patients were White, and this reflects the ethnic makeup of Southwest Virginia. In our patients, those at the highest risk of GIO include those with systemic vasculitis (made up over 20% of the cohort), systemic lupus erythematosus, inflammatory muscle disease, and RA where long courses of prednisone are more commonly used. As the patients were followed in the rheumatology clinic when prednisone was prescribed it was for 2-3 months. No patient on "prednisone bust" met the criteria as the duration and dose of prednisone were not high enough. In addition, these patients were younger than those traditionally considered at risk for age-related osteoporosis.

Comparing Q1 (3 months before the educational intervention) to the remaining quarters, there was no significant increase in vitamin D testing. We noted a meaningful change in the ordering health-care provider behavior that resulted in a change in the ordering of both tests and treatments. There was a statistically significant increase in vitamin D replacement ($P < .01$). The lower the vitamin D levels, the more likely it was for replacement theory to be imitated, with over 75% of those with <10 ng/mL being treated but only less than 50% of those between 30 and 20 ng/mL being treated. There was also a significant increase in the use of oral bisphosphonates ($P < .015$) in patients at risk of GIO. These increases were independent of the patients underlying rheumatic diagnosis and were sustained over the last 2 quarters of this study (Table 2). Although not statistically significant, there was also a sustained increase in the use of RANKL inhibitors across both quarters following the intervention. There was a drop in the total number of bone mineral testing requested, though this was not statistically significant. Other laboratory tests including renal function and calcium levels did not change and this relates to the fact that these tests are incorporated into the comprehensive metabolic panel. In the last quarter (Q4), we had only 11 patients. Nonetheless, the results followed the same trends. About 89% of the patients were on long duration of GC resulting in cumulative doses of >5 g. Their demographics, GIO tests, and treatment were similar to Q3.

Discussion

As GC are highly effective in the treatment of SARD including severe disease, their side effects are often underestimated by patients.[14] It is often difficult for patients to taper and discontinue GC. This is especially true in situations lacking therapeutic options such as SLE and vasculitis. This underestimation is not limited to diseases with limited options. In RA where we have a considerable number of therapeutic agents in multiple classes, a substantial number of patients remain on GC for several years. Some of the difficulty in discontinuing GC may result from patients' perception, as they may perceive GC as necessary hormone required to control their disease.[15] In addition to GIO, the long-term use of GC often results in other significant and varied complications,[16] some of these complications may be mitigated with strategies ranging from education to therapeutic intervention.[17] Several studies have shown that patient awareness and education about osteoporosis improves the rate of osteoporosis detection and treatment outcomes.[18, 19]

The rates of adverse outcomes noted in patients on long-term GC have been used by our colleagues in the primary care field as an indicator of the quality of care patients receive.[20] However, our study focused on improving the quality of care by increasing the awareness of GIO in health-care providers via education intervention. In our study, we demonstrated that an educational intervention targeted at increasing the awareness of GIO in rheumatologists led to a positive impact on both the surveillance and subsequent identification and treatment of patients at risk of GIO. This benefit was sustained over the 12 months duration of the study. As BMD is not required to evaluate for GIO, we anticipated a reduction in the use of BMD testing. However, this use of BMD stayed consistent across the duration of the study. We did however noted a significant reduction in the number of normal BMD results (Table 2), and we attributed

Table 2. Glucocorticoid-Induced Osteoporosis

	Q1 (N = 72)	Q2 (N = 54)	Q3 (N = 49)
Entry into cohort			
Single dose ≥ 30 mg	73.2%	55.6%	51.0%
Cumulative dose ≥ 5000 mg	82.1%	96.2%	85.7%
Test results			
Serum vitamin D (normal)	41.3% (19/46)	52.8% (19/36)	51.6% (16/31)
Bone mineral density (requested)	31.9% (23/72)	36.5% (19/52)	40.4% (19/47)
Bone mineral density (normal)	43.5% (10/23)	10.5% (2/19)	21.1% (4/19)
GIO prevention measures			
Vitamin D supplementation	18.1%	61.1%	67.3%
Bisphosphonates	9.7%	35.2%	34.7%
RANKL inhibitors	4.2%	11.1%	14.3%

GIO, Glucocorticoid-Induced Osteoporosis; Q1, Quarter 1; Q2, Quarter 2; Q3, Quarter 3; Q4, Quarter 4; RANKL, receptor activator of nuclear factor-κB ligand.

this to the reduction in the use of BMD testing for GIO screening at induction of GC when the BMD is likely to be normal. The increased diagnosis of osteoporosis on BMD indicated that the educational intervention may have increased the inappropriate use of the BMD test in confirming age-related osteoporosis. Continued education serves to refresh the provider's knowledge base and acts as a prompt for health-care providers to initiate GIO preventive steps. This leads to an improvement in the quality of care our patients receive.

Health information technology (HIT) has been used successfully to improve patient safety and increase the quality of care.[13] The combination of provider education and HIT may therefore serve as an option for increasing the appropriate use of GIO preventive measures. For example, the addition of a HIT alert triggered when health-care providers prescribe GC at doses or durations which put patients at risk for GIO. We should remember that HIT is not universally loved by providers. In addition to the potential benefits of HIT, it comes with the risk of increased provider burnout and staff turnover. Overall, HIT is less effective in maintaining a desired outcome as a result of alarm fatigue, which leads to providers not responding tothe presence of multiple, repeated, nusacnce alarm.[21]

Further studies are needed, particularly those focusing on sustaining GIO surveillance and the use of preventive measures. Barriers to GIO screening, prevention, and treatment are also areas for further research. Our study did not look at the frequency of educational updates required to sustain the improved response in the screening and treatment of GIO. Studies looking at longer-term follow-up would also be impactful, as a number of our patients with vasculitis and SLE may be on GC for over 2 years. Other limitations of this study include it being a single-center study with a modest number of patients, especially in Q4. We also did not look at the impact of patient-related factors and the impact on GIO. Overall, our patients only stand to benefit from further research into increasing the awareness and treatment of GIO.

Ethics Committee Approval: This study was approved by Ethics Committee of Carilion Clinic University (Approval No: IRB-20-804 , Date: June, 2020).

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