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Glucocorticoid Use and its Association with Skeletal Health among U.S. Adults with Diabetes

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Abstract

Aims—Determine the prevalence of glucocorticoid use in U.S. adults with diabetes and whether prevalence is associated with reduced skeletal health, as measured by fracture history and bisphosphonate use.

Methods—Participants were age ≥20 years from the cross-sectional National Health and Nutrition Examination Survey (1999–2010; N=15,661). Diabetes was determined by self-report, fasting plasma glucose ≥126 mg/dL (≥6.99 mmol/L), or A1c ≥6.5% (≥47.5 mmol/mol) (n=4,539). Prevalences of fractures and bisphosphonate use were determined by diabetes status and glucocorticoid use. Logistic regression was stratified by sex and assessed the effect of glucocorticoid use and diabetes associated with fractures and bisphosphonates.

Results—The age-standardized prevalence of glucocorticoid use was higher among persons with diabetes (3.2% vs. 2.0% without diabetes, $p=0.001$). Among adults with diabetes, the prevalence of fractures was significantly higher among those taking glucocorticoids vs those not (38.3% vs. 26.1%, $p=0.048$). The prevalences of fractures and bisphosphonate use were generally similar in those with and without diabetes when stratified by glucocorticoid use. In logistic regression analysis among men, the combination of diabetes and glucocorticoid use (compared to those with neither) was highly associated with bisphosphonate use, while adjusting for demographic factors. Among women, having diabetes and glucocorticoid use increased the odds of fractures, while adjusting for demographic factors and menopause.

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Conclusions—The prevalence of fractures was greater for those with diabetes taking glucocorticoids versus those not taking glucocorticoids. This study provides a national framework for further research on elucidating these associations.

Keywords

diabetes; glucocorticoids; bisphosphonates; fractures

1. Introduction

The prevalence of diabetes has significantly increased over the past several decades with 29 million people in the United States having diabetes in 2014 [1]. It is well known that diabetes increases the risk of macrovascular disease and microvascular disease [2]. Persons with diabetes, regardless of sex or whether diabetes is type 1 or type 2, are also at higher risk of fractures, despite having higher bone mineral density (BMD) compared to those without diabetes [3–6]. A recent review underscores that skeletal fragility is associated with diabetes, but notes that the underlying mechanisms have not been fully elucidated [7].

Asthma, autoimmune, and inflammatory disorders, are also prevalent both in the general population as well as in those with diabetes [8, 9]. Glucocorticoids are one of the most widely used classes of medications to treat these and other inflammatory conditions [10]. However, it is unclear whether individuals with diabetes use glucocorticoids to the same extent as those without diabetes. Depending on the dose, length of administration, product potency and other factors, glucocorticoids can have profound metabolic effects unmasking or worsening existing diabetes; their negative effects on the skeleton are well known [11–13]. Moreover, glucocorticoid administration is the primary cause of secondary osteoporosis and fractures [14–16]. Nevertheless, it is not known whether glucocorticoid administration may further increase the risk of fractures in persons with diabetes. Finally, most bisphosphonates, a medication class used for the treatment of osteoporosis, have specific indications for persons receiving glucocorticoids [17]. However, it is unknown whether bisphosphonate use differs by diabetes status and use of glucocorticoids.

Data from the 1999–2010 National Health and Nutrition Examination Survey (NHANES), a nationally representative survey, were used to explore the prevalence of use of glucocorticoids among adults with and without diabetes and whether occurrence of fractures and bisphosphonate use differed by glucocorticoid use and diabetes status. Our aim was to document the magnitude of concomitant use of glucocorticoids in adults with diabetes in the United States, as well to assess their impact on bone health directly by self-report of fractures and indirectly by use of bisphosphonates.

2. Methods

2.1 Survey

The National Health and Nutrition Examination Survey (NHANES) is a stratified multistage probability survey conducted in the U.S. non-institutionalized population and has been described elsewhere [18]. The cross-sectional survey includes an in-home interview where

demographic and basic health information are obtained, and a physical examination which includes obtaining biosamples at a mobile examination center (MEC).

2.2 Subjects

Participants were adults age ≥ 20 years who completed the 1999–2010 interview and MEC visit ($n=15,661$). Diagnosed diabetes was determined if participants answered “yes” when asked whether a physician or other health care professional ever told them that they had diabetes. Undiagnosed diabetes was determined if participants had a fasting plasma glucose ≥ 126 mg/dL (6.99 mmol/L) or an A1c $\geq 6.5\%$ (≥ 47.5 mmol/mol). We combined those with diagnosed and undiagnosed diabetes ($n=4,539$) and compared them to those without diabetes ($n=11,122$). Age, sex, race/ethnicity, education, and household income were self-reported. Race/ethnicity was reported as non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic other. Education was categorized as less than high school, high school graduate or General Educational Development (GED) certificate, and greater than a high school education. Household income was categorized as $<\$25,000$, $\$25,000$ – $\$54,999$, $\$55,000$ – $\$74,999$, $>\$75,000$; since household income was only used as a covariate in supplementary regression analysis, a missing category (5.3% of the total sample) was also included to retain sample size. Participants reported whether they had any type of health insurance coverage. Among women, menopause was defined as current age >50 years and self-report of not having a regular period in the past 12 months.

2.3 Outcomes

Glucocorticoid and bisphosphonate use were determined by asking participants to report any prescription medications they were currently taking. Participants were asked to show the interviewer the medication bottles during the in-home interview but failure to provide medication bottles did not discount self-report of medications. Any over-the-counter topical glucocorticoid treatments were not included in this analysis. In NHANES 1999–2004, fractures included those located at the hip, wrist or spine; in NHANES 2005–2010 participants, could additionally report any other type of fractures that occurred after age 20 years.

2.4 Statistical Analysis

Descriptive statistics [percent (%), standard error (SE)] were used to assess the prevalence of glucocorticoid use by diabetes status for the total survey period (1999–2010) and by 4-year survey cycles (1999–2002, 2003–2006, and 2007–2010). Descriptive statistics were also used to determine the prevalence of fractures and bisphosphonate use by glucocorticoid use and diabetes status. Estimates were standardized to the NHANES 2007–2010 population with diabetes using the age categories of 20–59 years and ≥ 60 years. Logistic regression (odds ratios, 95% confidence intervals) was stratified by sex and used to determine the association between diabetes and glucocorticoid use with fractures or bisphosphonate use, adjusting for age, race/ethnicity, income, education, and menopause (among women). The estimates presented show the odds ratio of fractures and bisphosphonate use for adults with diabetes who use glucocorticoids compared to those without diabetes who do not use glucocorticoids. Statistical analyses used sample weights and accounted for the cluster design (SUDAAN User’s Manual, Release 9.2, 2008; Research Triangle Institute).

3. Results

3.1 Participants

Compared to those without diabetes, participants with diabetes were older and a lower proportion were women; a higher proportion of participants with diabetes were non-Hispanic black or Hispanic, were of lower socioeconomic status based on education and income, and were more likely to have health insurance (Table 1). A higher proportion of women with diabetes were post-menopausal.

3.2 Prevalence of Glucocorticoid Use

The prevalence of glucocorticoid use was lower in 2007–2010 vs 1999–2002 among adults with diabetes but was stable for those without diabetes (Table 2). The overall crude prevalence of glucocorticoid use in persons with diabetes was 3.2% which was significantly higher compared to persons without diabetes (1.6%, $p<0.001$). Results remained significant when estimates were age-standardized to the 2007–2010 population with diabetes (3.2% with diabetes vs. 2.0% without diabetes, $p=0.001$). This relationship generally persisted for both crude and age-standardized estimates when results were analyzed by four year study periods.

3.3 Prevalence of Fractures and Bisphosphonate Use by Glucocorticoid Use

3.3.1 Among Persons with Diabetes—The age-adjusted prevalence of fractures and bisphosphonate use was significantly higher among persons with diabetes taking glucocorticoids compared to those not taking glucocorticoids (38.8% vs. 26.2% and 8.6% vs. 2.2%, respectively, $p<0.05$ for both) (Table 3).

3.3.2 Among Persons without Diabetes—The age-adjusted prevalence of fractures was higher, but not significantly, among persons without diabetes taking glucocorticoids compared to those not taking glucocorticoids (32.0% vs. 25.0%) (Table 3). The age-adjusted prevalence of bisphosphonate use was significantly higher for persons without diabetes taking glucocorticoids compared to those not taking glucocorticoids (10.2% vs. 3.6%, $p=0.010$).

3.4 Prevalence of Fractures and Bisphosphonate Use by Diabetes Status

Among persons using glucocorticoids, the age-standardized prevalence of fractures in persons with diabetes compared to those without diabetes (38.8% vs. 32.0%), was not significantly different (Table 3). The prevalence of fractures was similar by diabetes status for those not taking glucocorticoids. The age-standardized prevalence of bisphosphonate use was lower for those with diabetes compared to those without, while stratifying by glucocorticoid use.

3.5 Association of Glucocorticoid Use and Diabetes with Fractures and Bisphosphonate Use by Logistic Regression

Among men, there was no significant association between the combination of having diabetes and using glucocorticoids with fractures (OR=1.70, 0.76–3.79) (Table 4). However,

men with diabetes who used glucocorticoids (vs. those with neither) were significantly more likely to use bisphosphonates while adjusting for demographic characteristics (OR=18.2, 4.55–72.7). Among women, the combination of having diabetes and using glucocorticoids (vs. those with neither) significantly increased the odds of fractures (OR=2.34, 1.43–3.82), while adjusting for demographic factors and menopause. However, among women, the presence of both diabetes and glucocorticoid use did not significantly increase the odds of bisphosphonate use compared to those with neither (OR=1.92, 0.64–5.76), while adjusting for these demographic factors.

4. Discussion

The prevalence of use of glucocorticoids was explored in a nationally representative sample of persons with and without diabetes which also assessed their effect on skeletal integrity based on self-reported history of fractures and current use of bisphosphonates. We hypothesized that both fractures and bisphosphonate use would be increased as a result of glucocorticoid administration. In addition, we hypothesized that the joint combination of both glucocorticoid use and diabetes would increase the likelihood of fractures and bisphosphonate use. Glucocorticoids produce numerous metabolic derangements including bone fragility [10–14]. Although there are many glucocorticoid formulations available that have distinct potencies, drugs in this class, as a group, negatively affect the bone mineral density by decreasing bone formation and subsequent increments in bone resorption negatively affecting skeletal strength [15, 16].

Based on NHANES data during 1999–2010, glucocorticoid use was lower in 2007–2010 vs 1999–2002 among adults with diabetes but did not change significantly in adults without diabetes. These results are similar to other studies using data from NHANES [10,18,19]. In the current study, the use of glucocorticoids was higher at each time point between 1999 and 2010 for persons with diabetes compared to those without diabetes.

There is increasing evidence that individuals with both type 1 diabetes and type 2 diabetes are at higher risk of fractures, and bone and mineral abnormalities have been extensively described in patients with diabetes mellitus [3–7]. These derangements may be caused by direct effects of insulin deficiency or resistance and hyperglycemia on the bone and bone marrow microenvironment, thereby affecting bone formation [20]. Moreover, the presence of advanced glycation end products of bone matrix proteins is thought to affect bone strength [21]. It is not clear, however, if this propensity for fractures in persons with diabetes is secondary to mechanical factors alone or in combination with other factors that have not yet been clarified. In the current study, we found that, among women, the joint combination of having diabetes and use of glucocorticoids was associated with a significantly greater likelihood of having fractures, while adjusting for demographic characteristics and menopause. However, this association was not found to be significant in men, in contrast to the greatly elevated odds of bisphosphonate use.

A recent published report in nondiabetic postmenopausal women indicated that a three month glucocorticoid administration did not result in abnormal BMD as assessed by dual-energy X-ray absorptiometry (DEXA) but it had deleterious effects in cortical and trabecular

bone microarchitecture in vertebrae and long bones. These abnormalities included altered trabecular network, connectivity and thinner anatomy [22]. Whole bone stiffness was also negatively affected by glucocorticoids, despite normal BMD by DEXA. A three month observation, however, is clearly not enough time to properly assess BMD.

The negative effects of glucocorticoid use on the skeleton are well established. Multiple mechanisms may explain these deleterious effects including increases in bone resorption and reduction of bone formation, reduction in calcium absorption, impairments in vitamin D action and metabolism, and calcium urinary excretion [14]. In this cohort we found that fractures in areas well known to be affected by idiopathic osteoporosis were more common overall in persons taking glucocorticoids compared to those not taking glucocorticoids. In those with diabetes, the prevalence was augmented in those on glucocorticoids.

The use of bisphosphonates was markedly increased in persons using glucocorticoids compared to those not receiving these drugs, regardless of diabetes status. However, in logistic regression analysis, we found that among men, the joint combination of having diabetes and use of glucocorticoids was highly significantly related to use of bisphosphonates, as compared to those with neither; this strong association however was not found among women. This may underscore that women, who have an increased risk of fractures compared to men, are not receiving these medications to the same degree. The lack of an association with bisphosphonates among women cannot be due to differences in race/ethnicity or socioeconomic status because we adjusted for these factors in our analysis [23–26]. Nevertheless, evidence elsewhere shows that individuals with diabetes are more prone to fractures [27]. This is very concerning because it highlights the lack of treatment in the context of increased risk but it is not surprising because the underuse of bisphosphonates in those with the diagnosis of osteoporosis has been well established [28–29].

There are no long-term, clinical studies on the use of bisphosphonates among adults with diabetes or on the added impact of use of glucocorticoids. However, two small retrospective studies showing the use of bisphosphonates in postmenopausal women with or without diabetes indicated favorable changes in BMD but there was no information on fracture prevention [30–31]. In diabetic women, three years of alendronate treatment was associated with increased BMD at all sites studied, whereas women in the placebo group experienced a decrease in BMD at all sites except the lumbar spine [32]. The effects of glucocorticoids, however, were not addressed in any of these studies.

A strength of this study is the use of a nationally representative survey, thus, results can be generalized to the U.S. non-institutionalized population which clinical studies cannot provide. In addition, we were able to utilize laboratory measures to comprehensively define adults with diabetes. However, this study has some limitations. The small sample size and the binary nature of some information did not allow for more granular analyses. Because fractures were self-reported, subclinical fractures commonly involving the spine may have been missed; we do not, however, expect that underreporting occurred differentially in any group. We were unable to analyze BMD and vitamin D status which could have potentially provided additional information for the interpretation of the results; in addition, we did not have information on chronic obstructive pulmonary disease across all survey years, an

important condition for use of inhaled glucocorticoids. We could not define the type of glucocorticoid or bisphosphonate used or the dosing and the length of treatment. Furthermore, the underlying conditions that triggered their use and the temporal relationship between glucocorticoid or bisphosphonate use and diabetes diagnosis could not be determined in this cross-sectional study. However, the temporal relationship was not the goal of this analysis which focused simply on whether prevalence of fractures/bisphosphonate use was higher in those with diabetes who also used glucocorticoids, to guide the clinical decision of whether such therapy should be initiated or continued. Type 1 and type 2 diabetes could not be definitively distinguished which are two conditions that may have different risks for the complications explored as well as unique underlying mechanisms. However, given the nationally representative sample, the majority of the sample population with diabetes would have type 2 diabetes.

4.1 Conclusions

These analyses indicate that glucocorticoid use is greater in persons with diabetes compared to those without diabetes. Persons with diabetes taking glucocorticoids have a higher prevalence of fractures compared to those with diabetes but not taking glucocorticoids. In contrast to men, women who had diabetes and were taking glucocorticoids had increased odds of fractures but there was no association with bisphosphonate use. This suggests that fracture risk is not well recognized by practitioners and that fractures may not trigger the prescription of bisphosphonates. The intersection of diabetes, glucocorticoid use, skeletal integrity and effect of fracture preventing medications has been poorly understood and unexplored. Although this analysis provides a national overview of these relationships, further research is needed to fully elucidate these associations and underlying mechanisms.

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Table 1

Characteristics of adults age ≥ 20 years by diabetes status, NHANES 1999–2010

	All (N=15,661)	Diabetes (N=4539)	No Diabetes (N=11,122)
	% (SE)	% (SE)	% (SE)
Age (mean)	46.5 (0.28)	59.3 (0.35)	44.9 (0.29)
Sex , % women	52.0 (0.40)	48.1 (0.98)	52.4 (0.43)
Race/ethnicity			
Non-Hispanic White	70.9 (1.28)	64.0 (1.92)	71.7 (1.26)
Non-Hispanic Black	11.0 (0.71)	16.0 (1.11)	10.4 (0.69)
Hispanic	12.7 (1.02)	13.7 (1.43)	12.6 (0.99)
Non-Hispanic Other	5.4 (0.39)	6.3 (0.70)	5.3 (0.40)
Education			
<High school	19.6 (0.57)	31.2 (0.94)	18.2 (0.58)
High school/GED ^I	25.0 (0.62)	26.4 (1.19)	24.8 (0.67)
>High school	55.4 (0.91)	42.4 (1.29)	57.0 (0.94)
Income			
<25,000	27.5 (0.75)	36.0 (1.12)	26.4 (0.76)
25,000–54,999	29.0 (0.68)	30.8 (1.14)	28.8 (0.73)
55,000–74,999	12.8 (0.55)	9.1 (0.75)	13.2 (0.59)
≥75,000	25.4 (25.4)	16.9 (0.96)	26.5 (0.91)
Missing	5.3 (0.35)	7.2 (0.70)	5.1 (0.34)
Health Insurance , % yes	81.4 (0.63)	87.7 (0.70)	80.2 (0.67)
Menopause , % yes among women	38.1 (0.81)	73.1 (1.24)	34.2 (0.87)

^I General Educational Development certificate

Table 2
Prevalence of glucocorticoid use among adults age 20 years with and without diabetes, NHANES 1999–2010

	Glucocorticoid Use					
	All		Diabetes		No Diabetes	
	N	% (SE)	N	% (SE)	N	% (SE)
Crude Estimates						
1999–2010	15,661	1.7 (0.13)	4539	3.2 (0.29)	11,122	1.6 (0.14) ^b
1999–2002	4874	2.0 (0.21)	1278	3.9 (0.64)	3596	1.8 (0.22) ^b
2003–2006	4724	1.9 (0.28)	1316	3.3 (0.52)	3408	1.7 (0.31) ^b
2007–2010	6063	1.4 (0.18)	1945	2.5 (0.38)	4118	1.2 (0.19) ^b
Age-Standardized Estimates^a						
1999–2010	15,661	2.1 (0.16)	4539	3.2 (0.29)	11,122	2.0 (0.19) ^b
1999–2002	4874	2.3 (0.25)	1278	3.9 (0.63)	3596	2.1 (0.31) ^b
2003–2006	4724	2.5 (0.35)	1316	3.3 (0.51)	3408	2.4 (0.43)
2007–2010	6063	1.7 (0.22)	1945	2.5 (0.38)	4118	1.5 (0.23) ^b

^aStandard population is NHANES 2007–2010 population with diabetes; age groups include 20–59 years and 60 years

^bp<0.05, Significance testing: diabetes vs. no diabetes

Table 3

Prevalence of fractures and bisphosphonate use by glucocorticoid use among persons with and without diabetes, NHANES 1999–2010

	Total				Diabetes				No Diabetes			
	Glucocorticoids Use		Glucocorticoids Use		Glucocorticoid Use		Glucocorticoid Use		Glucocorticoid Use		Glucocorticoid Use	
	All (n=15,565) % (SE)	Yes (n=313) % (SE)	No (n=15,252) % (SE)	All (n=4489) % (SE)	Yes (n=138) % (SE)	No (n=4351) % (SE)	All (n=11,076) % (SE)	Yes (n=175) % (SE)	No (n=10,901) % (SE)	All (n=11,076) % (SE)	Yes (n=175) % (SE)	No (n=10,901) % (SE)
Crude Estimates												
Fractures, any ^a	23.0 (0.63)	29.7 (3.50) ^c	22.9 (0.62) ^c	26.5 (1.01) ^d	38.3 (5.98) ^c	26.1 (1.04) ^c	22.6 (0.68) ^d	27.6 (4.09)	22.5 (0.68)	22.6 (0.68) ^d	27.6 (4.09)	22.5 (0.68)
Bisphosphonates	1.8 (0.12)	8.4 (1.97) ^c	1.7 (0.12) ^c	2.3 (0.28)	8.5 (2.94) ^c	2.1 (0.28) ^c	1.7 (0.13)	8.4 (2.34) ^c	1.6 (0.12) ^c	1.7 (0.13)	8.4 (2.34) ^c	1.6 (0.12) ^c
Age-Standardized Estimates^b												
Fractures, any	25.3 (0.71)	33.3 (3.27) ^c	25.1 (0.71) ^c	26.6 (1.00)	38.8 (5.82) ^c	26.2 (1.02) ^c	25.1 (0.83)	32.0 (3.98)	25.0 (0.83)	25.1 (0.83)	32.0 (3.98)	25.0 (0.83)
Bisphosphonates	3.3 (0.19)	9.7 (1.99) ^c	3.2 (0.19) ^c	2.4 (0.28) ^d	8.6 (2.89) ^c	2.2 (0.29) ^{c,d}	3.7 (0.24) ^d	10.2 (2.51) ^c	3.6 (0.24) ^{c,d}	3.7 (0.24) ^d	10.2 (2.51) ^c	3.6 (0.24) ^{c,d}

^aIn NHANES 1999–2004 fractures included those located at the hip, wrist or spine; in NHANES 2005–2010 participants could additionally report any other type of bone fracture.^bStandard population is NHANES 2007–2010 population with diabetes; age groups include 20–59 years and 60 years^cp<0.05 comparing glucocorticoid use within diabetes status groups^dp<0.05 comparing estimates between diabetes status groups

Table 4

Logistic regression [OR (95% confidence interval)]^a analysis for fractures and bisphosphonate use by sex

	Fractures	Bisphosphonate Use
	OR (95% CI)	OR (95% CI)
Men		
Glucocorticoid use and diabetes (vs. no use and no diabetes)	1.70 (0.76–3.79)	18.2 (4.55–72.7)
Women		
Glucocorticoid use and diabetes (vs. no use and no diabetes)	2.34 (1.43–3.82)	1.92 (0.64–5.76)

^a Adjusted for age, race, education, income, health insurance, and menopause (women only)