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Glucocorticoid use and its association with skeletal health among U.S. adults with diabetes☆

Sarah Stark Casagrande [a,*], Catherine C. Cowie [b], Saul Malozowski [b]

[a] Social & Scientific Systems, Inc., 8757 Georgia Avenue, Silver Spring, MD, USA 20910
[b] National Institute of Diabetes and Digestive and Kidney Diseases, 6707 Democracy Blvd., Bethesda, MD, USA 20892

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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 = 4539). 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.
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.

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 (National Diabetes Statistics Report, 2014). It is well known that diabetes increases the risk of macrovascular disease and microvascular disease (National Diabetes Statistics Report, 2014). 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 (de Liefde et al., 2005; Hofbaour et al., 2007; Nicodemus & Folsom, 2001; Schwartz & Sellmeyer, 2007). A recent review underscores that skeletal fragility is associated with diabetes, but notes that the underlying mechanisms have not been fully elucidated (Shanbhogue et al., 2016).

Asthma, autoimmune, and inflammatory disorders are also prevalent both in the general population as well as in those with diabetes (http://www.cdc.gov/asthma/asthmadata.html; http://www.cdc.gov/arthritis/data_statitics/national-statistics.html). Glucocorticoids are one of the most widely used classes of medications to treat these and other inflammatory conditions (Overman et al., 2013). 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 (Reid, 2000; Seibel, et al., 2013; Weinstein, 2011). Moreover, glucocorticoid administration is the primary cause of secondary osteoporosis and fractures (Canalis et al., 2007; Manolagas & Weinstein, 1999; Mazziotti et al., 2006). 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

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* Corresponding author.
E-mail addresses: scasagrande@s-3.com (S.S. Casagrande), cowie@nih.gov (C.C. Cowie), malozowskis@extra.niddk.nih.gov (S. Malozowski).

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treatment of osteoporosis, have specific indications for persons receiving glucocorticoids (Lespessailles, 2013). 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 NHANES is a stratified multistage probability survey conducted in the U.S. non-institutionalized population and has been described elsewhere (Centers for Disease Control and Prevention (CDC), 1999–2010). The cross-sectional survey includes an in-home interview where demographic and basic health information is 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 ≥6.5% (≥47.5 mmol/mol). We combined those with diagnosed and undiagnosed diabetes (n = 4539) 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. 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

Table 1
Characteristics of adults age ≥ 20 years by diabetes status, NHANES 1999–2010.

	All (N = 15,661)	Diabetes (N = 4,539)	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[a]	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)

[a] General Educational Development certificate.

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