Assessment of Fracture Risk in Patients with Type 2 Diabetes Treated with Thiazolidinediones (TZDs)

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Background and Introduction:

Thiazolidinediones (TZDs) are a commonly used medication in the treatment of Type II Diabetes Mellitus (T2DM), and, as of 2005, accounted for more than 20% of oral hypoglycemic medicine use in the United States [4, 10]. The mechanism of action involves ligand (TZD)/receptor binding with the Peroxisome Proliferator-Activated Receptor γ (PPAR γ) whereby nuclear products increase the insulin sensitivity in select tissues [1]. The gene products TNF-α and Leptin have been shown to have effects that induce insulin resistance in peripheral tissues [15, 16]. Through activation of the PPAR γ receptor on adipocytes, the expression of both TNF-α and Leptin is reduced, a proposed mechanism for the insulin sensitizing effects of TZDs [17].

There are several known side effects of TZD usage, including edema, weight gain, and heart failure [2]. Several recent studies have indicated an increase in fracture risk in patients treated with TZDs [4, 9]. Although the exact cause of this increase in fracture risk has not been definitively described, it has been observed that patients on TZD therapy have decreased bone mineral density at several sites including lumbar spine and hip [12]. Gray et al. (2007) conducted a randomized, placebo-controlled trial that showed a decreased bone mineral density (BMD) in humans treated with rosiglitazone. The study included healthy, non-diabetic, post-menopausal women with no signs of osteoporosis. After 14 weeks of rosiglitazone treatment, there was a significant decrease in bone mineral density (-1.9% rosiglitzaone vs. -0.2% placebo) at the hip [14]. In 2008, Loke et al. performed a meta-analysis of the effects of TZDs on fracture risk for patients with T2DM. The study, which analyzed 10 randomized controlled trials lasting greater than one year and involving roughly 13,000 patients, found that long term TZD use doubles the risk of fracture among women with T2DM [9]. Furthermore, the 2006 Health, Aging, and Body Composition (Health ABC) observational study reported increased bone loss in women, but not men, who were taking any drug from the TZD category (pioglitazone, rosiglitazone, or troglitazone) [12]. A possible mechanism for the observed loss of BMD in humans may be secondary to a shift in differentiation of mesenchymal stem cells (MSCs). Ali AA et al. (2005) showed that PPAR γ activation influenced the differentiation of MSCs from osteoblasts towards adipocytes, a possible implication for the TZD related decrease in bone health [11].

The Vermont Diabetes Information System (VDIS) database is a registry-based support system targeted to primary care physicians and their patients. As of 2004, the VDIS includes 7348 patients from 10 hospitals, 55 practices, and 121 primary care providers in Vermont and northern New York [8]. The database uses automated data collection to upload multiple lab test reports, including A1c values, for all participating patients. Current medication lists for all subjects is also included in the VDIS.

In 2004, a follow up questionnaire was formulated and results were obtained from approximately 1,000 patients from the VDIS. The questionnaire comprised of over 200 questions, including those pertaining to lifestyle, history of any present/chronic illnesses, medications, and the impact on quality of life from living with diabetes. This survey and subsequent results provide a real world assessment of the impact of diabetes in a cohort of patients representative of the Northeast US. Analysis of which can provide the clinician with region specific information on potential treatments and their efficacies. Our goal of assessing fracture risk could aid the physician in the decision of whether or not to initiate TZD usage when
taking into account other risk factors, such as documented osteoporosis or increased chance for falls.

**Methods and Results:**

To assess the proposed correlation between fracture risk and TZD therapy, our group devised a plan centered on utilizing the VDIS database. From a 2 year follow-up survey/questionnaire on approximately 1000 of the patients enrolled in the VDIS, there were over 400 total variables of information, including TZD usage, available for us to analyze. We defined an outcome—fracture—and a predictor—TZD usage—and modeled a simple equation: P(fracture) = f (TZD usage). In order to control for potential confounding variables, we carefully assessed the nature of each of the 400 data points, and decided whether or not the particular variable was a potential confounder; in other words, whether or not the specific variable (creatinine clearance, for example) would correlate with both the dependent (TZD therapy) and independent (fracture history) factors. This process was done in order to avoid a Type I error, or a “false positive” conclusion that our dependent variable—TZD therapy—was in fact correlated with our independent variable—fracture risk—when in reality it was NOT. Out of this initial analysis, we came up with approximately 20 variables (see Figure 1) that we subjected to a chi-square test to determine if, in fact, the variable was a confounding factor.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>A1c value of baseline test</th>
<th>Body Mass Index (BMI)</th>
<th>Age at diagnosis</th>
<th>Exercise</th>
<th>How often test blood sugar</th>
<th>Hypoglycemic episodes in last month</th>
<th>Had foot ulcer that took &gt;4wk to heal</th>
<th>Foot/Leg pain related to DM</th>
<th>Kidney problems</th>
<th>Alzheimers or other dementia</th>
<th>Difficulty with movement after stroke</th>
<th>Eye, nerve, kidney damage related to DM</th>
<th>Race</th>
<th>Marital status</th>
<th>Education level</th>
<th>Household income</th>
<th>Eye, nerve, kidney damage related to DM</th>
<th>Duration of DM in years</th>
</tr>
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</table>

Figure 1: Potential confounding variables from the 2004 follow-up VDIS Questionnaire

Fracture history was, unfortunately, not one of the 400 variables from the questionnaire. Our group, therefore, used the 2009 International Classification of Diseases, Clinical Modification (ICD-9-CM) to obtain insurance billing codes used for fracture diagnoses and treatments. Our next step will be to cross-match these fracture codes with discharge summaries for inpatient and ER visits for our cohort of patients. This cross-match will produce a reliable fracture history.

**Updates and Final Goals:**

1) At the present time, we have our dependent variable (TZD usage) and have begun to acquire our independent variable (fracture history). As stated above, we need to now cross-match the codes used for fracture diagnosis and treatment with discharge summaries. Once we have this data, we will be ready to defend against confounding variables. The final step will be
to calculate a relative risk of fracture in our cohort. To do so, we will divide the number of fracture incidences by total number of patients to get a fracture percentage of our cohort. We will then compare this percentage to the national average to get our final relative risk and assessment of fracture risk in patients with diabetes treated with TZDs.

2) Upon completion, we plan on submitting our paper for the Vermont ACP medical student poster competition and/or the American Diabetes Association (ADA)/American Association of Clinical Endocrinologists (AACE) medical student research abstract competitions. The project will also be submitted to a peer reviewed journal for publication.

3) This project provided a great avenue for me to enhance and learn a wide variety of new skills in medical research. I gained experience in shaping a clinical question, devising a hypothesis, working on biostatistics, interpreting data, collaborating with other colleagues, and writing a medical paper. These skills will serve me very well in further research endeavors.
References:


