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ORIGINAL ARTICLE

The Effects of Thiazolidinedione Therapy on NT-proBNP Levels in Patients with Type 2 Diabetes

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We sought to determine whether thiazolidinedione (TZD) therapy affects levels of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with type 2 diabetes.

Materials and Methods: This study population consisted of 76 patients with type 2 diabetes and no history of heart failure. Subjects had NT-proBNP levels determined prior to initiating TZD therapy, and after 3 months of treatment. We compared within-person changes in NT-proBNP over the 3 month duration. We determined if the magnitude of change in NT-proBNP over the treatment period was correlated with baseline parameters or nature/dose of TZD medication.

Results: The subjects were 42% female and 58% male, and the mean age and duration was 59.8±11.8 years old and 11.4±8.3 years respectively. The baseline mean A1C and BMI was 8.7±1.1% and 30.9±8.7 kg/m^2 respectively. We found that NT-proBNP levels did not vary significantly between baseline (mean±SD: 143.8±203.9 pg/mL) and 3 month follow-up (150.6±186.2 pg/mL). Conversely, A1C levels declined significantly ($p<0.0001$) and BMI increased significantly ($p< 0.05$).

Conclusion: Adding TZD therapy to patients with type 2 diabetes and no history of heart failure does not have a significant effect on NT-proBNP levels.

Key Words: Thiazolidinedione, NT-proBNP, Type 2 diabetes, Congestive heart failure

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Introduction

Thiazolidinediones (TZDs) are a unique class of oral anti-hyperglycemic agents used in the treatment of type 2 diabetes. The efficacy of the two second-generation TZDs, pioglitazone and rosiglitazone, has been well established.[1-4] However, side effects of TZD therapy include weight gain, fluid retention (6% to 7% of patients) and edema (2% to 5% of patients).[2-7] These are particularly concerning for patients with a history of cardiac dysfunction, as fluid retention and edema can serve to exacerbate heart failure.[6,7]

Given the highly significant epidemiological relationship between diabetes and heart failure,[8,9] several studies have explored the association between TZD therapy and cardiovascular endpoints.[10-12] Despite Delea et al's suggestion that TZD therapy might increase the risk of heart failure,[10] a review and consensus statement released by the American Diabetes Association in 2004 concluded that the cardiovascular risk associated with TZD therapy is, in fact, quite low.[13] As well, in 2004, results of a year-long randomized controlled trial suggested that there is no difference in cardiovascular outcomes for

patients taking pioglitazone and patients on a non-TZD therapy.[12]

More recently, the PROactive Study demonstrated an increased incidence of serious heart failure with pioglitazone (5.7% absolute risk) versus placebo (4.1% absolute risk) in patients with type 2 diabetes and preexisting cardiovascular disease. However, increased mortality or morbidity in treatment versus placebo patients with serious heart failure was not found.[14]

Nissen and Wolski's meta analysis of 42 clinical trials determined that rosiglitazone was associated with approximately 43% greater risk for myocardial infarction (MI) and approximately 64% greater risk for cardiovascular death than placebo or other anti-diabetic therapies.[15] However this data should be considered carefully: the MI and cardiovascular death absolute risk differences between treatment and control groups are 0% and 0.1% respectively. As well, the methodology that was used required the exclusion of trials with zero events in the treatment and placebo groups and alternative meta-analysis approaches that use continuity corrections show statistically nonsignificant low odds ratios;[16] thus it can be concluded that it is uncertain whether risk for MI or cardiovascular death is increased or decreased for patients undergoing rosiglitazone therapy.

Interestingly, it has been suggested that TZDs actually have macrovascular benefits for patients both with and without pre-existing cardiovascular disease. Specifically, these medications have been found to reduce blood pressure, improve endothelial function -possibly by exerting protective effects on the vessel wall, decrease the prevalence of inflammatory markers, and reduce the prevalence of non-fatal myocardial infarction and stroke.[2,12,17-19] In summary, it is thought that the cardiovascular and glycemic benefits of TZD therapy often outweigh the risks associated with fluid retention and edema, although these side effects are important to consider.[13,20,21]

Brain Natriuretic Peptide (BNP) has recently been recognized as an efficient screening method for heart dysfunction that has predictive and diagnostic value[22-25.] This hormone is secreted primarily from the left ventricle in response to increased volume or pressure overload in the heart[24]. BNP is produced as a prohormone and is subsequently processed into two parts: BNP, the active moiety, and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), the inactive moiety.[25,26] Although both hormones provide similar diagnostic information, comparisons suggest that NT-proBNP is the more sensitive diagnostic marker.[25-27]

The present study aims to address the current uncertainty in literature that exists with respect to the effect of TZD therapy on heart function in type 2 diabetes patients. As NT-proBNP is a reliable indicator of heart failure, this study assesses the within-person changes of this hormone that occur when patients with type 2 diabetes and no known heart failure, initiate TZD therapy.

Materials and Methods

Design

The present study included 76 consecutive consenting outpatients with type 2 diabetes who were prescribed either rosiglitazone (67% of patients) or pioglitazone (33% of patients) while visiting St. Paul's Hospital Diabetes Education and Treatment Center in Vancouver, British Columbia, Canada. Recruited patients had been diagnosed with type 2 diabetes according to the current American Diabetes Association criteria for diagnosis[28] and were not currently on a TZD, but could be using any combination of anti-diabetic therapies. Patients were prescribed TZD dosages depending on the patient's therapeutic requirement. When considering rosiglitazone, 53% of patients received 4 mg, 9% of patient received 8 mg and 5% of patient received 2 mg. When considering pioglitazone, 20% of patients received 30 mg and 13% of patients received 15 mg. Patients

with heart failure were excluded. Informed consent was obtained prior to enrolment in the study, and the St. Paul's Hospital Ethics Board approved the study protocol, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Prior to initiating TZD therapy (baseline), patients completed a non-fasting serum NT-proBNP assay. Three months later (follow-up), participants completed a second assay for NT-proBNP. A medical chart review was also performed at both baseline and follow-up in order to determine demographic information (age, gender, duration of diabetes) and to assess changes in diabetic parameters (A1C, BMI, serum creatinine).

Assays

Blood was drawn by venopuncture and separated for serum samples (Heparin/ EDTA) in glass tubes. Analysis was performed within 24 hours of sample collection. Samples were kept at room temperature for temporary storage. The Roche Elecsys 1010 bench top analyzer for heterogeneous immunoassay analyzed the samples (Roche Diagnostics Inc., Germany).[22] The system is an Electrochemiluminescense (ECL) machine that uses 2 polyclonal antibodies for detecting NT-proBNP.[22] The between run coefficient of variation for this assay platform ranges from 4.4-5.3%, as stated by the manufacturer.[22]

Analysis

Data was analyzed using a statistical software program (R, version 1.7.0). A two-tailed matched-pairs t-test was used to compare clinical parameters (NT-proBNP levels, A1C, BMI, and creatinine) at baseline and follow-up. Two-sample t-tests were performed to determine whether changes in NT-proBNP differed between females and males, and between patients who took pioglitazone and those who took rosiglitazone.

A Spearman rank correlation coefficient was calculated to assess association between change in NT-proBNP levels and the following: age, duration of diabetes, TZD dosage, baseline NT-proBNP, baseline A1C and baseline serum creatinine. A simple regression model was fitted in order to determine whether changes in NT-proBNP were related to concurrent diabetes medications such as metformin, sulfonylureas, or insulin. In all cases, statistical significance was established at $p<0.05$.

Results

Of the 76 patients who consented to participate in this study, 50 were included in data analysis. Twelve patients were excluded due to noncompliance in obtaining blood, while 9 discontinued TZD therapy during follow-up for various reasons such as noncompliance (n=2), stroke (n=1), high blood pressure (n=1), edema (n=2), dizziness (n=1), hypoglycemia (n=1), and arthralgia (n=1). Two patients were switched to insulin therapy during the follow-up period. Of the remaining 53 patients, 3 were excluded from analysis because their baseline NT-proBNP levels exceeded 1000 pg/mL.[19] Demographic data for the study population is presented in Table 1. The subjects (42% female, 58% male) ranged in age from 30 to 81 years.

Table 1. Demographic characteristics for study population

Baseline Characteristic	
n	50
Female (*n*)	21
Male (*n*)	29
Age	59.8±11.8*
Duration of Diabetes	11.4 ± 8.3*
Blood pressure (mmHg)	126±16/75±10
BMI	30.9 ± 8.7
Anti-Diabetic Medications	
Metformin+Sulfonylurea	38 (76%)
Metformin	6 (12%)
Metformin and Insulin	2 (4%)
Sulfonylurea	1 (2%)
Metformin,Sulfonylurea+Repaglinide	1 (2%)
Insulin	1 (2%)
Metformin, Sulfonylurea+Acarbose	1(2%)

* mean±SD

A comparison of NT-proBNP levels, A1C, BMI and creatinine at baseline and follow-up

are shown in Table 2 for all subjects. Although mean NT-proBNP and creatinine both increased slightly throughout this timeframe, neither of these trends was significant. On the other hand, A1C values did improve markedly, decreasing by 1.0±1.2% ($p<0.0001$). A significant mean increase in BMI of 0.6±1.5 kg/m^2 was also observed ($p<0.05$).

Table 2. Within-person changes in clinical characteristics

Characteristic	Before Treatment	After Treatment	Net Change	P Value
NT-proBNP (pg/mL)	143.8±203.9	150.6±186.2	6.8 ± 91.0	0.6
HbA1c (%)	8.7±1.1	7.7±1.5	-1.0 ± 1.2	< 0.0001
BMI (kg/m2)	30.9±8.7	31.5±8.9	0.6 ± 1.5	< 0.05
Creatinine (μmol/L)	86±24	88±25	2 ± 12	0.28

Data are means ± SD unless otherwise indicated; HbA1c : Hemoglobin A1c; BMI: Body mass index.

NT-proBNP levels of the female subgroup increased nonsignificantly from 145.9±202.6 pg/mL to 172.8±225.7 pg/mL, whereas mean NT-proBNP levels of the male subgroup decreased nonsignificantly from 142.2±208.4 pg/mL to 134.5±153.7 pg/mL during the therapy period. However, changes in NT-proBNP were not significantly differ-ent between males and females.

We assessed correlation between change in NT-proBNP and the following demographic and clinical parameters: age, duration of diabetes, baseline NT-proBNP, baseline A1C, baseline creatinine and dosage of TZD. Results are presented in Table 3. Results indicated no association between change in NT-proBNP and age, duration of diabetes, baseline creatinine, baseline HbA1c or dosage of TZD. A negative correlation between change in NT-proBNP and baseline NT-proBNP existed ($p<0.05$).

Table 3. Relationship between change in NT-proBNP and clinical characteristics

Characteristic	Correlation Coefficient	P Value
Age	-0.014	0.92
Duration of Diabetes	-0.078	0.60
Baseline NT-proBNP	-0.34	<0.05
Baseline HbA1c	0.032	0.83
Baseline Creatinine	0.28	0.057
Dosage of TZD prescribed	0.28	0.061

Throughout the study period, 67% of patients took rosiglitazone and 33% took pioglitazone. NT-proBNP levels of patients prescribed pioglitazone decreased from 105.3±175.4 pg/mL to 95.9±85.9 pg/mL, while NT-proBNP levels of patients who initiated rosiglitazone increased from 159.8±213.6 pg/mL to 176.5±219.4 pg/mL. Changes in NT-proBNP were not significantly different for those prescribed pioglitazone versus those prescribed rosiglitazone.

We assessed whether existing diabetes medications-those that the patient was taking prior to TZD prescription and continued to take throughout the treatment period - were associated with changes in NT-proBNP. When recruited, patients were on various combination or monotherapy regimes. For each type of existing medication, no significant association between taking the medication and change in NT-proBNP was evident.

Discussion

TZD medications are shown to have a number of cardiac benefits.[2,13,18-21] The present study aimed to assess the relationship between TZD therapy and levels of NT-proBNP, a proven marker of heart dysfunction, in patients with no history of heart failure. We also sought to determine whether baseline NT-proBNP levels can predict a positive or adverse cardiovascular reaction to TZD therapy.

Our analysis of 50 patients indicated that there was not a significant within-person change in NT-proBNP levels during 3 months of TZD therapy. This observation is in alignment with the current American Diabetes Association consensus, which states that the cardiovascular risk of TZD therapy is low for patients with no existing heart failure.[13] However, based on Haffner et al's finding that rosiglitazone therapy promotes a significant decrease in the prevalence of several inflammatory markers,[18] we might have expected to see a decrease in NT-proBNP levels after 3 months of therapy.

A comparison of change in NT-proBNP levels and baseline NT-proBNP shows a significant negative correlation between the two variables. That is, as baseline NT-proBNP increases, the magnitude of change in NT-proBNP throughout the 3 months of TZD therapy actually tends to decrease or become more negative. This finding suggests that TZD therapy may actually have a beneficial effect for people with elevated baseline NT-proBNP levels or subclinical cardiac dysfunction.

In 2003, Ogawa et al examined the relationship between TZD therapy and BNP levels. Ogawa's study investigated change in plasma BNP levels in 30 patients treated with pioglitazone for up to 48 weeks, terminating treatment when BNP levels rose above 100 pg/mL, a cutoff that is suggestive of left ventricular dysfunction.[29] The group found that the initiation of pioglitazone therapy was accompanied by a significant increase in BNP levels, and that patients with higher baseline BNP levels exhibited a more significant increase in BNP during the therapy period.[29] In fact, if patients had a baseline BNP exceeding 18.4pg/mL, levels always rose above 100 pg/mL during pioglitazone treatment.[29]

Direct comparison between the present study and Ogawa's was not possible, as they assessed levels of plasma BNP, while the present study measured serum NT-proBNP. However, results of the present study are unable to provide support for Ogawa et al's conclusions that TZD therapy causes an increase in BNP, and that elevated baseline BNP levels can predict the development of left ventricular dysfunction in candidates for TZD therapy. Instead, our results indicate that TZD therapy causes no significant change in ambient NT-proBNP levels, and that patients with elevated baseline NT-proBNP levels actually have relatively small or more negative changes in this hormone while on TZD therapy.

Two studies, one by Sambanis et al and another by Dorkhan et al, measured NT-proBNP levels and demonstrate findings in line with Ogawa et al. A study by Sambanis et al found that the addition of pioglitazone for 12 weeks to type 2 diabetes patients already receiving sulfonylurea plus metformin resulted in significant increases in NT-proBNP by 39%.[30] However, none of the patients developed edema or signs or symptoms of heart failure. The study concluded that pioglitazone does not affect heart function and even though increases in NT-proBNP are observed, this was thought to be a reaction to volume overload.[30] Dorkhan et al also observed significant increases in mean NT-proBNP levels in subjects in response to pioglitazone after 26 weeks.[31] Again, it was speculated that the increase in NT-proBNP could be a result of volume overload on the heart rather than impairment of cardiac function.[31]

The present study also evaluated the effects of TZD therapy on A1C, BMI and creatinine. In alignment with previous studies which have tested the safety and efficacy of TZD medication, we found that 3 months of therapy resulted in a significant 1.0 % decrement in A1C, and a significant 0.6 kg/m2 increase in BMI. No significant change in creatinine levels were observed throughout the therapy duration, suggesting that kidney function remained constant from baseline to follow-up.

We assessed the relationship between magnitude of within-person change in NT-proBNP levels and selected demographic and

clinical parameters. No correlation existed between change in NT-proBNP and age, sex, duration of diabetes, creatinine, or baseline A1C. Recent findings suggest that age, duration of diabetes, glycemic control, and BMI are all associated with the progression of heart failure.[32,33] Therefore, it might be expected that a greater age, duration of diabetes, A1C, or BMI at baseline would be associated with larger increases in NT-proBNP levels if TZD therapy were precipitating the development of heart failure within the study population. Instead, our results indicate that none of these factors were related to the magnitude of change in NT-proBNP levels throughout the 3 month therapy period.

We sought to determine the relationship between diabetes medications taken concurrently with TZDs and change in NT-proBNP levels. We found no significant relationship between taking either sulfonylureas, metformin, or insulin and change in NT-proBNP. Insulin and sulfonylureas have been implicated in the progression of heart failure,[34] while it has been suggested that metformin has cardioprotective properties,[35] however we failed to find any relationships between these medications and magnitude of change in NT-proBNP.

Finally, we also determined whether change in NT-proBNP levels was associated with the dosage of TZD taken throughout the follow-up period. TZD dosage was not significantly associated with change in NT-proBNP. As well, change in NT-proBNP levels was not significantly different between those receiving pioglitazone therapy and those receiving rosiglitazone therapy. In accordance with our results, pioglitazone and rosiglitazone appear to carry similar risks for the development of heart failure.[13]

An important limitation of the present study was that it was not placebo controlled. As well, it is possible that our sample size of 50 patients was not large enough to adequately represent the entire type 2 diabetes population, but these results provide a starting point for more comprehensive investigation and require confirmation in prospective, randomized, placebo-controlled trials.

In summary, results indicate that TZD therapy has no significant effect on NT-proBNP levels throughout 3 months of therapy in patients with no history of heart failure. The type or dosage of TZD taken does not appear to affect the magnitude of change in NT-proBNP levels throughout the duration of therapy. Additionally, most base-line clinical and demographic parameters do not appear to be related to the magnitude of change in NT-proBNP levels, with the excep-tion of baseline NT-proBNP and creatinine.

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