

Sulfonylurea therapy is associated with increased NT-proBNP levels in the treatment of type 2 diabetes[☆]

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Abstract

Background: We sought to determine N-terminal pro-Brain Natriuretic Peptide (NTproBNP) levels among a population of individuals with type 2 diabetes, and to correlate these levels with diabetes medications and patient demographics.

Methods: We analyzed data from 506 patients with type 2 diabetes. We compared NT-proBNP levels of these patients with those from the general population. We also sought to determine whether patients' NT-proBNP levels were correlated with diabetes medications, age, gender, creatinine, hemoglobin A1C levels, BMI, blood pressure, and lipid levels.

Results: Increasing doses of sulfonylureas were associated with increasing levels of NT-proBNP. However, patients on combined sulfonylurea and metformin therapy had lower NT-proBNP levels than those on sulfonylureas alone. Neither thiazolidinediones nor insulin were associated with NT-proBNP levels. The majority of patients with type 2 diabetes had similar NT-proBNP levels compared to a reference group from the general population. In no age category did NT-proBNP levels differ significantly between men and women. Levels of NT-proBNP were positively associated with age ($p < 0.0001$), systolic blood pressure ($p < 0.01$) and creatinine levels ($p < 0.0001$), and negatively associated with diastolic blood pressure ($p < 0.001$). Levels of NT-proBNP were not associated with A1C, BMI, triglycerides, and high density lipoprotein ($p = \text{NS}$).

Conclusions: Levels of NT-proBNP are associated with increasing sulfonylurea dosage, age, blood pressure, and creatinine levels. There is unlikely to be clinically significant differences in NT-proBNP levels between patients with type 2 diabetes and a normal population.

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1. Introduction

The epidemiological relationship between diabetes and cardiac dysfunction is highly significant. Cardiovascular disease is the primary cause of mortality in patients with

diabetes [1]. According to the Framingham Heart Study, patients with diabetes are at an increased risk for developing congestive heart failure (CHF). Results revealed that males with diabetes had twice the incidence, and females with diabetes had five times the incidence of CHF compared to nondiabetic controls [2].

At present, patients with diabetes lack a routine screening procedure for cardiac dysfunction. In addition, certain medications used to treat type 2 diabetes, such as thiazolidinediones, have been implicated in precipitating CHF [3]. More recently, sulfonylurea medication has been associated with acute ischemic events and all-cause mortality

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[4]. Although echocardiography is theoretically an effective screening technique for CHF, its limited accessibility and high cost renders it impractical [5–7]. Alternatively, researchers have recently suggested a more accessible and potentially cost-effective screening method: Brain Natriuretic Peptide (BNP).

BNP, a 32-amino acid polypeptide, has gained significant recognition as a marker of heart dysfunction. This hormone is synthesized in human cardiac tissue, and plays a key role in regulating body fluid levels and blood pressure [8,9]. It is secreted primarily from the left ventricle in response to an increase in blood volume or pressure overload in the heart [8,10–13]. Epshteyn et al. revealed that BNP levels greater than 79 pg/mL are 95% positive predictors (88% accurate), and levels less than 60 pg/mL are 90% negative predictors of CHF (79% accurate) [11].

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 [14–16]. Although both hormones provide similar diagnostic information, NT-proBNP may be more advantageous than BNP on a practical level, as it is more reproducible, economical, and stable at room temperature [6,15,17]. Additionally, in patients with CHF, plasma levels of NT-proBNP are higher than that of BNP. Such findings suggest that NT-proBNP is more strongly correlated with CHF, and consequently a more sensitive diagnostic marker than BNP [6,18].

It has been suggested that levels of NT-proBNP less than 125 pg/mL accurately exclude cardiac dysfunction, levels greater than 125 pg/mL are associated with an increased risk of CHF for normals under 75 years, levels greater than 450 pg/mL are associated with an increased risk of CHF for normals over 75 years, and levels greater than 1000 pg/mL are highly associated with CHF [7,19,20].

Although past studies have utilized single cut-off values to identify cardiac dysfunction, [10,21], more recent studies indicate that single reference intervals do not suffice. Findings reveal that levels of NT-proBNP appear to rise with age and are higher among women than men [7,15]. Thus, multiple reference intervals should be established in order to adjust for the independent effects of age and gender.

Although much research has examined NT-proBNP levels within the general population, few studies have examined levels of the hormone within a population of patients with diabetes. To date, findings are mixed: it is currently unknown whether patients with diabetes have higher NT-proBNP levels than the general population [22,23]. Additionally, no studies have examined the relationship between NT-proBNP levels and diabetes medications. Consequently, the goal of the present study was to compare age-specific levels of NT-proBNP among a large population of individuals with type 2 diabetes ($n=506$) with levels from a general reference population, and to examine associations between NT-proBNP levels and diabetes medications.

2. Method

2.1. Design

The present study was conducted at the Diabetes Teaching and Training Centre at St Paul's Hospital in Vancouver, British Columbia. We analyzed data from 506 consecutive consenting outpatients with type 2 diabetes who agreed to a non-fasting NT-proBNP assay, routine blood work, and a medical chart review (e.g., current medications, age, gender, BMI, hemoglobin A1C, duration of diabetes, lipids, serum creatinine, diabetic therapy regimen, diabetic complications, and blood pressure). Only blood work obtained within three 3 months (pre or post) of the NT-proBNP assay was included in the present study.

Patients were categorized as having type 2 diabetes based on the current Canadian Diabetes Association (CDA) criteria for diagnosis [24]. Only participants with NT-proBNP levels less than 1000 pg/mL were included in the present study. Patients with known CHF were excluded. An additional 53 consenting patients were excluded from the analyses due to non-compliance in obtaining blood work. The hospital ethics board approved the study protocol.

2.2. Assay

Blood was drawn by venopuncture and separated for serum sample analyses (Heparin/Ethylenediaminetetraacetic acid) in glass tubes. Analysis was performed within 24 h of sample collection. Samples were kept at room temperature for temporary storage.

NT-proBNP was analyzed using the Roche Elecsys 1010 bench-top analyzer for heterogeneous immunoassay (Roche Diagnostics Inc., Germany). The system is an ElectroChemiluminescence (ECL) machine that uses 2 polyclonal antibodies for detecting NT-proBNP. The between run coefficient of variation for this assay platform ranges from 4.4–5.3% [25]. The Roche NT-proBNP has been characterized with regards to precision, specificity, stability, and utility [26].

2.3. Statistics

Data was analyzed using a computerized spreadsheet (Excel, Microsoft Inc., California). We used a 2-sample *t*-test to compare mean levels of NT-proBNP in our study population with the reference group ($n=1411$) described in the Roche NT-proBNP assay package insert [20]. We examined gender differences in mean NT-proBNP levels using an analysis of variance (ANOVA). To examine the relationship between BNP and diabetes medications we used linear regression analysis. Last, multiple regression analysis was used to examine the relationship between diabetic parameters and log-

Table 1
Demographic and clinical characteristics for the study population

Characteristic	Patients
Mean±SD age (years)	62.7±10.6
Females/males	233 (46.0%)/273 (54.0%)
Mean±SD BMI (kg/m ²)	31.3±6.9
Mean±SD duration of diabetes (years)	9.2±8.7
Mean±SD HbA1C (%)	7.1±1.3
Mean±SD systolic blood pressure (mmHg)	127.0±16.8
Mean±SD diastolic blood pressure (mmHg)	73.6±8.9
Mean±SD creatinine (µmol/l)	87.8±29.0
<i>Drug therapies</i>	
Metformin	341 (67.4%)
Sulfonylureas	179 (35.4%)
TZD	73 (14.5%)
Insulin	83 (16.4%)

transformed NT-proBNP. Statistical significance was established at $p < 0.05$.

3. Results

Mean±SD demographic data for the study population of patients with type 2 diabetes is presented in Table 1. The 506 participants (46.0% female, 54.0% male) had a mean±SD age of 62.7±10.6, ranging from 23–88 years. Participants' mean±SD A1C was 7.1±1.3. Among patients, 123 (24.3%) maintained glycemic control via diet, 149 (29.5%) were on monotherapy, and 234 (46.2%) were on combination therapy.

As presented in Tables 2 and 4, levels of NT-proBNP increase with age in patients with type 2 diabetes. A comparison of NT-proBNP levels by age category between our data (patients with type 2 diabetes) and a reference group (a sample of people from the general population) [20] is presented in Table 2. Using a 2-sample *t*-test, results revealed that within the 45–54, 55–64 and >75 year cohorts, patients with type 2 diabetes did not exhibit significantly different levels of NT-proBNP compared to the reference population. Within the <45 year cohort, patients with type 2 diabetes exhibited significantly lower mean levels of NT-proBNP than the reference population ($p < 0.001$). Within the 65–74 year cohort, patients with type 2 diabetes exhibited significantly higher NT-proBNP levels compared to the reference population ($p < 0.05$).

Table 2
Levels of NT-proBNP by age category

	<45 years		45–54 years		55–64 years		65–74 years		≥ 75 years	
	Reference*	Diabetes	Reference	Diabetes	Reference	Diabetes	Reference	Diabetes	Reference	Diabetes
Mean (pg/mL)	67.8	25.6	64.6	90.0	82.1	70.5	110.8	149.9	242.8	249.9
SD	83.7	24.0	96.2	145.2	107.7	98.4	95.2	182.8	211.1	248.1
Median	41.4	17.0	39.6	36.0	57.7	38.5	83.4	77.5	191.1	156.0
<i>n</i>	56.0	27.0	472.0	70.0	455.0	190.0	308.0	142.0	120.0	77.0
<i>p</i> -value	0.0005		0.16		0.18		0.016		0.83	

* Reference data obtained from Roche [20].

Table 3
Relationship between log NT-proBNP and diabetes medications

Diabetes medications	<i>p</i> -value	
	Dosages of medications	Taking vs not taking medications
Metformin	NS	NS
Sulfonylurea	<0.05	<0.01
Insulin	NS	NS
TZD*	NS	NS
Metformin × sulfonylurea	NS	<0.01
Metformin × insulin	NS	NS
Metformin × TZD	NS	NS
Sulfonylurea × insulin	NS	NS
Sulfonylurea × TZD	NS	NS
Metformin × sulfonylurea × TZD	NS	NS
Metformin × sulfonylurea × insulin	NS	NS

* TZD = thiazolidinedione.

We used an analysis of variance (ANOVA) to examine gender differences in levels of NT-proBNP. The BNP data center at around 50 pg/mL with a median of 51 pg/mL and a few extremely large values close to 1000 [unit], resulting in a highly right-skewed distribution. The data were normalized using the log transformation to validate the application of the ANOVA. Results revealed that the mean log-transformed NT-proBNP values did not significantly differ between males and females with type 2 diabetes.

A linear regression model was used to examine the relationship between diabetes drugs and levels of NT-proBNP. Drug variables (alone and in combination with other medications), were entered as covariates and log-transformed NT-proBNP was entered as the response. Age and creatinine were adjusted for in the model. Results are presented in column 1 of Table 3. Only the relationship between treatment with a sulfonylurea and log NT-proBNP levels was significant ($\beta = 0.031$, $p < 0.05$). After controlling for age and creatinine, increasing doses of sulfonylureas are associated with increasing levels of NT-proBNP.

Subsequently, each drug variable was transformed into a dichotomous variable (taking or not taking the drug) and regression analyses were re-performed. Again, age and creatinine were adjusted for in the model. Results are presented in column 2 of Table 3. Sulfonylureas ($\beta = .68$, $p < 0.01$) and sulfonylurea/metformin combination therapy ($\beta = -0.65$, $p < 0.01$) were significantly associated with NT-proBNP levels. The model shows that the log NT-proBNP

Table 4
Correlation between NT-proBNP and diabetic variables

Variable	<i>p</i> -value
Age	<0.0001
Systolic blood pressure	<0.01
Diastolic blood pressure	<0.001
Creatinine	<0.0001

levels of a patient on sulfonylurea but not metformin is expected to be 0.68 higher than that of a patient who is not on sulfonylureas. However, the log NT-proBNP levels of a patient taking both metformin and sulfonylureas is expected to be only 0.03 higher than a patient not taking sulfonylureas.

A multiple regression model was used to examine the relationship between diabetic parameters and levels of NT-proBNP. Age, duration, A1C, BMI, blood pressure, lipids, and creatinine were entered as predictors and log-transformed NT-proBNP was entered as the response. Significant results are presented in Table 4. Age, systolic blood pressure, diastolic blood pressure and creatinine were significant. NT-proBNP levels tend to increase with age, systolic blood pressure and creatinine, but decrease with diastolic blood pressure. No significant association existed between NT-proBNP levels and duration of diabetes, A1C, BMI or lipid levels.

4. Discussion

NT-proBNP is an established biochemical marker of cardiac dysfunction. Although type 2 diabetes is a major independent risk factor for CHF [1], our findings based upon 506 participants suggest that, in most age groups, there are unlikely to be clinically significant differences in NT-proBNP levels between patients with diabetes and the general population. To date, this study is the largest study examining NT-proBNP levels in a group of patients with type 2 diabetes. Consequently, our results help to further our understanding of NT-proBNP's role as a marker of cardiac dysfunction and risk of developing CHF.

The majority of patients with type 2 diabetes (45 to 54, 55 to 64, and >75-year age groups) have similar NT-proBNP levels compared to the reference group described by Roche in their proBNP assay package insert. Although Roche reports little clinical and demographic information about the reference group aside from the fact that it excludes people with CHF, the mean NT-proBNP levels reported for the group are suggested to be indicative of normal NT-proBNP levels in the general population. The similarity between our study population — who all have type 2 diabetes — and this reference group suggests that people with type 2 diabetes and no CHF have NT-proBNP levels that are clinically similar to the general population.

Prior studies have compared BNP levels in people with diabetes to non-diabetic controls. Wu et al. compared 367 patients with diabetes and 1219 controls, and found no difference in BNP levels between the two groups [22].

The two groups were matched and separated into 3 categories: those with CHF, those without CHF, and those with a history of CHF. Results from all three categories revealed no significant difference in median levels of BNP between patients with type 2 diabetes and a control group.

On the other hand, Magnusson et al. (2004) found that patients with type 2 diabetes exhibited significantly higher median levels of plasma NT-proBNP (360.9 pgmol/L) compared to non-diabetic controls (302.7 pmol/L) [23]. Their study consisted of 253 patients with diabetes and 230 controls. They did not stratify either group by age. Also, as mentioned by Magnusson et al., these findings may be confounded by the fact that their type 2 diabetes cohort had higher BMI, heart rate, and blood pressure compared to their non-diabetic cohort. Similarly, in the present study, it is possible that the type 2 diabetes population varied from the reference group in terms of these clinical parameters. However, regardless of clinical differences that may have existed between our comparison groups, we failed to observe a significant difference in NT-proBNP levels in most age categories.

Within the less than 45-year age group, patients with type 2 diabetes have significantly lower NT-proBNP levels compared to the reference group. However, due to a small sample size (diabetes $n=27$, control $n=56$), it is difficult to draw definitive conclusions based on these findings. Future studies using larger samples within this cohort are likely to expand our understanding of NT-proBNP levels in young to middle-aged patients with type 2 diabetes compared to the normal population.

Conversely, within the 65 to 74-year age cohort, patients with type 2 diabetes have significantly higher NT-proBNP levels compared to the age-matched reference group. It is important to note that NT-proBNP levels are affected not only by the hormone's rate of synthesis, but also by the hormone's rate of clearance via glomerular filtration [23]. Based on interpretation of NT-proBNP levels reported for the Roche reference group, the cut-off for detecting CHF increases from 125 pg/mL to 450 pg/mL above age 75, reflecting the decline of glomerular filtration rate with age [7,20]. Renal dysfunction is also associated with reduced glomerular clearance and corresponding high levels of NTproBNP [14,15]. Consequently, it is possible that the 65 to 74-year cohort of patients with type 2 diabetes had a higher prevalence of renal dysfunction compared to members of the general population of the same age, as it is a complication of type 2 diabetes that develops over time. Nevertheless, the difference in NT-proBNP levels is small and unlikely to be of clinical significance. According to McCullough et al., among patients 65–85 years of age, NT-proBNP levels fall into a “gray zone” and are confusing and of minimal value to patients and clinicians [7].

In accordance with Magnusson et al., NT-proBNP levels were not associated with A1C in patients with type 2 diabetes [23]. In line with previous studies examining NT-proBNP,

our results reveal that NT-proBNP levels are significantly positively associated with serum creatinine levels [17].

Contrary to Magnusson et al. which found no correlation between NT-proBNP and age, our results demonstrate that NT-proBNP levels in patients with type 2 diabetes are independently and positively correlated with age [23]. This finding provides support for the claim that diagnostic cut-offs for NT-proBNP should be age-dependent [17]. As both patients with and without type 2 diabetes appear to have similar levels of NT-proBNP, with a positive association in both groups, results suggest that it is not necessary to create a separate diagnostic cut-off for patients with type 2 diabetes.

Although past literature suggests that NT-proBNP levels differ between males and females in the normal population [7,17], no such gender differences are found in the present study. Our results reveal that, in all age categories, males and females with type 2 diabetes have similar NT-proBNP levels.

We observe a significantly positive relationship between sulfonylurea therapy and levels of NT-proBNP. At present, the effect of sulfonylureas on cardiovascular risk is controversial. In the UK Prospective Diabetes Study, treatment with a sulfonylurea and metformin was associated with increased mortality [27]. However, at least one study has shown no link between vascular disease and patients treated with metformin and/or sulfonylureas [28]. A recent study found sulfonylurea monotherapy to be associated with increased all-cause mortality and death by acute ischemic event, but failed to find an association between metformin and these adverse endpoints [4]. Experimental models of cardiomyopathy have suggested an explanation for the possible effect of sulfonylureas on cardiac functioning. On a physiological level, sulfonylureas impair mitochondrial KATP channels; this leads to cardiac dysfunction [29]. Impairment of KATP has been implicated in inducing ventricular arrhythmias and increasing the risk of sudden death [30]. Although we are not aware of any studies examining the association between impairment of KATP channels and the secretion of BNP, this is a hypothesis that could be readily tested and would help to explain the association between BNP levels and sulfonylureas described in this paper.

Interestingly, our results indicate that a patient using a sulfonylurea but not metformin is expected to have log NT-proBNP levels 0.68 higher than a patient who is not using sulfonylurea therapy. However, if a patient is using sulfonylurea/metformin combination therapy, their log NT-proBNP levels are expected to be merely 0.03 higher than a patient not using sulfonylurea therapy. Similarly, a recent observational study found that metformin, either alone or in combination with sulfonylureas, was associated with less all-cause mortality than sulfonylurea therapy alone [31]. The ability of metformin to reduce hyperinsulinemia in people with type 2 diabetes may help to account for this observation [27]. From a clinical perspective, these findings suggest that the combination of metformin and sulfonylureas may be a preferable form

of therapy for patients with high baseline NT-proBNP levels.

Although theories suggest that high serum insulin levels promote the development of heart dysfunction, the present study finds no relationship between levels of insulin and levels of NT-proBNP [32]. Similarly, thiazolidinediones have been associated with an increased risk of CHF, however the present study finds no relationship between the dosage of thiazolidinediones and levels of NT-proBNP [3].

In conclusion, our results indicate that patients with and without type 2 diabetes have similar NT-proBNP levels. Consequently, in a clinical setting it is unlikely that the type 2 diabetes population requires a unique NT-proBNP screening and/or interpreting procedure. Additionally, as NT-proBNP levels in both patients with type 2 diabetes and controls increase with age, our results strengthen the argument that single algorithmic reference intervals do not sufficiently diagnose cardiac dysfunction. Last, our findings indicate that sulfonylureas, but not insulin and thiazolidinediones, are associated with elevated NT-proBNP levels. However, this finding has yet to be studied in detail, and since the present study is cross-sectional, we are unable to draw conclusions regarding causation. Future longitudinal studies involving pre/post drug therapy measurements of NT-proBNP will help to elucidate our understanding of the effects of sulfonylureas and other diabetes drugs on levels of NT-proBNP.

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