

Short Communication

Canmetformin Buffer the Deleterious Association between Psychological Distress and Glycemia in Patients with Type 2 Diabetes?

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Abstract

Background: Psychological distress is associated with hyperglycemia in persons with diabetes. Preliminary reports suggest that metformin may help buffer the effects of psychological distress on hyperglycemia. Many Cambodians who are currently over age 35 have elevated symptoms of psychological distress from having survived their country's genocide. This study investigated the associations among psychological distress, metformin use, and glucose levels in Cambodians with type 2 diabetes.

Methods: Patients with type 2 diabetes >1 year, aged 35-80, not using insulin, were recruited from a Cambodian Diabetes Association clinic. Participants provided a fasting finger prick blood sample and completed a psychological assessment.

Measures: A MiniMed Ultra-II point of care glucometer was used to determine fasting glucose. Participants completed the valid and reliable Khmer language version of the 25-item Hopkins Symptom Checklist (HSCL) which measures symptoms of depression and anxiety. The HSCL was administered via a computerized spoken format which allowed standardized administration and automated data entry.

Data Analysis: Multiple linear regressions were performed using SPSS v21.

Results: Participants, n=60, were M=55.7 (SD=9.6) years old, 60% female, 68.3 % were using metformin. Fasting glucose values were above target range, M=143.5 mg/dl (SD=48.1). Mean total scores on the HSCL exceeded the clinical cutoff (1.75) for likely psychiatric disorder, M=1.8 (SD=0.5). In linear regression with main effects in the model there was a significant interaction between psychological distress and metformin use on glucose, ($\beta=-1.47$, $t=-2.49$, $*p<.05$). Controlling for age, sex, antidepressant use and other oral hypoglycemic agents did not meaningfully change the findings. Conclusion: Metformin may buffer the deleterious association between psychological distress and glucose. These findings add to a small but provocative literature on the potential metabolic benefits of metformin specifically for patients with psychological distress.

INTRODUCTION

Psychological distress is common among persons with diabetes. The two most common forms of distress among persons with diabetes are symptoms of depression and symptoms of anxiety. Depression and diabetes are highly comorbid, with 30% of patients with diabetes reporting subclinical depressive symptoms and nearly 20% meeting criteria for Major Depressive Disorder (MDD) [1]. There is strong, consistent evidence that when depression accompanies diabetes, it is adversely associated with glycemic control [2], risk for long-term complications [3], and early mortality [4]. Data suggest that the relationship between diabetes and depression is reciprocal and that they may share

common biological precursors [5]. Living with the daily burden of diabetes symptoms and diabetes-related complications may cause depression [1]. Conversely, depressive symptoms, such as low levels of motivation and impaired cognitive function, may cause poor diabetes self-management (e.g., poor diet, limited physical activity, low medication adherence), thereby worsening diabetes control [6]. Depression may also directly worsen diabetes control by activating neuroendocrine and inflammatory responses (increased cortisol, catecholamines, and cytokines) [7]. Additionally, there is substantial support for shared biological substrates between diabetes and depression, including altered activity in both the hypothalamic-pituitary-adrenal (HPA) axis and metabolism of neurotransmitters [8].

Anxiety is also common comorbidity of diabetes. A systematic review [9] reported that 40% of patients with diabetes report subclinical anxiety symptoms and nearly 15% meet criteria for an anxiety disorder. A more recent systematic review and meta-analysis [10] also reported a positive association between diabetes and anxiety (both disorders and subclinical symptoms). Anxiety is associated with worsened glycemic control in diabetes [11]. Whereas the literature for the link between anxiety and diabetes is less well developed than for depression and diabetes, it is hypothesized that some of the same behavioral mechanisms, and some related biological mechanisms, worsen glycemic control when anxiety accompanies diabetes.

Metformin is commonly used in the treatment of type 2 diabetes due to its well-demonstrated ability to regulate glucose levels. It is the most commonly prescribed drug for diabetes globally [12]. Yet, metformin's other cellular and molecular mechanisms are less well understood. For example, there is a suggestion that metformin may impact hippocampal neurogenesis. The hippocampus is a brain structure that is part of the limbic system, which is involved in mood regulation and cognitive function. Imaging studies have revealed hippocampal atrophy in patients with severe MDD or post-traumatic stress disorder (see Bartsch 2015 for review of the hippocampus in mental disorder [13]). A medication that encourages hippocampal neurogenesis could be beneficial in the treatment of MDD and post-traumatic stress disorder [14]. In animal models; metformin stimulates hippocampal neurogenesis and improves cognitive performance [15]. Recently it has been proposed that metformin may have clinical utility for management of both diabetes and some psychiatric disorders [14].

Although evidence is mixed [16], several lines of evidence in humans converge to suggest that metformin may have beneficial effects on distress in the presence of glucose dysregulation. Some studies suggest that metformin may have antidepressant effects in persons with diabetes [17]. Others suggest that metformin may protect glycemia in persons experiencing psychological distress. In the Diabetes Prevention Program (DPP), use of antidepressants was associated with increased risk of conversion to type 2 diabetes in both the intensive lifestyle intervention and placebo arms of the trial, but not in the metformin arm [18], suggesting that metformin played a role in modulating the deleterious relationship between depression and glucose levels.

Depression, anxiety and diabetes are all global problems, particularly affecting the developing world [19]. Cambodia is a case in point. In Cambodia King et al. [20] found 5% rural and 11% semi-urban diabetes prevalence, and fully one quarter of all adults in the study had some degree of glucose intolerance. Cambodia also has high rates of post-traumatic stress disorder (62%) and major depressive disorder (51%) [21]. Due to a genocide that killed 1/3 of its population and traumatized survivors. This combination of factors, along with metformin being first-line treatment for type 2 diabetes in Cambodia, makes Cambodia an ideal setting to investigate the relationships among metformin, psychological distress, and glucose. Therefore, this study investigated the buffering effects of metformin on the association between psychological distress (i.e., depression and anxiety) and hyperglycemia in a sample of Cambodians with type 2 diabetes.

METHODS

Participants and procedures

Participants were a convenience sample of patients of the Cambodian Diabetes Association clinic in Siem Reap, Cambodia. Patients were invited to participate if they were between 35 and 80 years of age, had been diagnosed with type 2 diabetes for at least one year, were not taking insulin, and were not diagnosed with or treated for any long-term complications of diabetes including known myocardial infarction, stroke, nephropathy, or amputation.

Participants arrived to a morning research appointment at the clinic having fasted and withheld medication for 8 hours. After providing written informed consent, participants answered questionnaires, were assessed for anthropometrics, and provided a fasting blood sample.

Measures

Glucose. A MiniMed Ultra-II point of care glucometer was used to determine fasting glucose. Samples were obtained with standard finger prick procedure.

Psychological Distress. Participants completed the valid and reliable Khmer language version of the Hopkins Symptom Checklist (HSCL; [22]). The 25-item HSCL has subscales that measure symptoms of depression and anxiety; total scores above 1.75 indicate likely psychiatric disorder. The HSCL was administered via a computerized spoken format which allowed standardized administration and automated data entry.

Demographic and clinical characteristics. Demographics were collected during face-to-face interview by a trained research assistant. Medications were extracted from chart review and confirmed by the prescribing physician. Height and weight were measured using calibrated equipment and body mass index calculated as weight in kilograms divided by the square of height in meters.

Data Analysis

To describe the sample, means, standard deviations, and frequencies were calculated and zero order correlations were calculated among variables. Linear regression was performed, predicting fasting glucose from distress scores, metformin use, and their interaction term. When the effect was significant, a fully adjusted model was then run, controlling for covariates including age, sex, antidepressant use, and other oral hypoglycemic agents. Standardized regression coefficients are reported. Data processing and analysis was performed using SPSS 12 for Windows.

RESULTS

Subjects

Approximately 120 charts were reviewed for eligibility and approximately 80 patients were invited to participate before a sample of 60 participants was reached; the 20 not included either did not show up for their appointment or declined participation.

Participants, $n=60$, were $M=55.7$ ($SD=9.6$) years old, and 60% female. The majority, 68.3 %, was using metformin to control

their diabetes; 13% were taking metformin only, 15% were taking glyburide only, and 55% were using metformin and glyburide in combination. Participants were not taking any other anti-diabetic agents. Antidepressants were taken by 13.6% (all of them were taking amitriptyline). Fasting glucose values were normally distributed (skewness=0.9, kurtosis=0.3) and were above target range, $M=143.5$ ($SD=48.1$) mg/dl. Mean total scores on the HSL were normally distributed (skewness=0.9, kurtosis=0.3) and exceeded the clinical cutoff for likely psychiatric disorder, $M=1.8$ ($SD=0.5$). Scores on the subscales were: depression $M=1.9$ ($SD=0.5$), (skewness=0.7, kurtosis=0.3); anxiety $M=1.7$ ($SD=0.6$), (skewness=1.0, kurtosis=0.4). One participant was excluded as an outlier for an anxiety score (3.4) that was 1 SD above the next 3 highest scores. See table 1 for descriptive characteristics and correlations among study variables.

In linear regression with main effects in the model and controlling for antidepressant use, there was a significant interaction between total psychological distress and metformin use on glucose, ($\beta=-1.47$, $t=-2.49$, $*p<.05$). Controlling for age, sex, BMI, and glyburide use did not substantially change the findings, the effect for the interaction remained significant, $p<.05$. See figure 1. Given the small sample size, we addressed the possibility that statistical outliers might be exerting undue influence on the results by performing a follow-up analysis that excluded individuals scoring ≥ 2.7 on the Hopkins Symptom Checklist ($n=5$). The unadjusted ($\beta=-1.54$, $t=-2.19$, $*p<.01$) and adjusted ($\beta=-1.79$, $t=-2.24$, $*p<.05$) results remained significant for the interaction term. These follow-up analyses were consistent with the previous models. They also showed that among individuals using metformin there was no relationship between psychological distress and glucose, whereas among individuals not taking metformin, there was a significant positive association between distress and fasting glucose.

DISCUSSION

The main finding from this study is that metformin buffered the deleterious association between psychological distress and hyperglycemia in patients with type 2 diabetes. Among patients using metformin there was no relationship between distresses and fasting glucose, whereas among those not taking metformin higher distress was associated with higher glucose. This suggests that metformin confers glycemic protection for diabetic patients with psychological distress.

Patients with chronic psychiatric illness have high rates of overweight and obesity. Metformin is associated with modest weight loss in diabetic and nondiabetic obese patients. Controlled studies have also found metformin to be effective for preventing and treating weight gain due to antipsychotic medications [23-26]. Yet, our results remained significant even after controlling for BMI. This suggests that metformin buffered the effect of distress on glucose independent of any effect on BMI.

Our findings are consistent with reports that show that metformin can help depressed diabetic patients. For example, Guo [17] randomized 58 participants with diagnosed depression and type 2 diabetes to either metformin or placebo for 24 weeks. Chronic treatment with metformin for 24 weeks improved glucose metabolism, depressive symptoms, and cognitive performance. Furthermore, associations were observed between blood glucose and depressive symptoms. These findings suggest that chronic treatment with metformin has antidepressant behavioral effects. Guo et al. interpret their findings to mean that supplementary administration of antidiabetic medications may enhance the recovery of depression in persons with comorbid with type 2 diabetes through improvements in cognitive performance.

Unlike Guo et al., we did not find that metformin improves

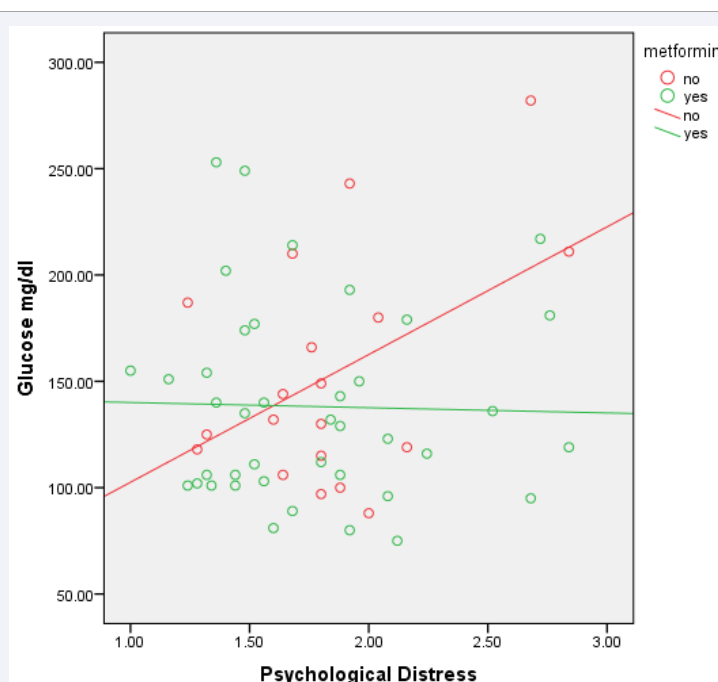


Figure 1 Relationship between psychological distress and fasting glucose depends on metformin use.

Table 1: Unadjusted correlations among study variables.

	M	SD	Correlations								
			1	2	3	4	5	6	7	8	
1 ^a Metformin Use	0.68	0.47	1								
2 Psychological Distress	1.81	0.47	-.08	1							
3 Fasting glucose mg/dl	143.50	48.09	-.11	.05	1.0						
4 Age	55.68	9.59	.02	.09	-.27*	1					
5 ^b Sex	0.60	0.49	-.04	.34**	.01	.13	1				
6 ^a Amitriptyline Use	0.13	0.34	-.16	.29*	-.16	.33**	.22	1			
7 ^a Glyburide	0.85	0.36	-.19	-.11	-.07	-.02	-.06	.03	1		
8 Body Mass Index	25.38	3.66	.24	.02	-.16	-.24	-.24	-.15	-.13	1	

Note: ** $p < .01$, * $p < .05$
^amedications: 1 = no, 2 = yes; mean values represent proportions
^bSex: 0 = Male, 1 = Female, mean values represent proportions

depression per se. That is, patients taking metformin had similar scores on psychological distress compared to those not taking metformin. Nor did we find that patients taking metformin had lower fasting glucose. Rather, we found that metformin mitigated the adverse association between distress and glucose. Therefore, our study cannot conclude that metformin has antidepressant effects per se. Indeed, not all literature supports metformin's antidepressant actions. Kashani and colleagues [27] investigated the effects of two diabetes medications (pioglitazone and metformin) in a sample of obese patients with polycystic ovarian syndrome (PCOS) and comorbid MDD. In a six-week, double-blind study, 50 patients with PCOS and MDD randomly received pioglitazone or metformin. Both agents were similar in reducing insulin resistance, but pioglitazone was superior to metformin in reducing depression in their nondiabetic sample.

Whereas we did not find that metformin had antidepressant effects per se, we did find that metformin mitigated the adverse effect of distress on glucose. The clinical implications are that patients with symptoms of depression or anxiety accompanying diabetes may uniquely benefit from metformin independent of its effects on weight.

LIMITATIONS

This study was on a small sample from a single geographic location. The design was cross-sectional and observational, so no conclusions about causality can be drawn. Future studies should examine a larger sample in an experimental design to isolate any effects of metformin on distress, glucose, and their relationships.

CONCLUSIONS

We found that metformin protects glucose from the deleterious effects of psychological distress. Whereas the literature on metformin and distress is mixed, our study indicates that it is premature to conclude that metformin is not a candidate for further testing on its effects on glucose in persons with psychological distress [16]. If larger, randomized, controlled studies confirm that metformin reduces distress and/or buffers the effect of psychological distress on glycemia, there may be a clinical role for metformin in clinical management of psychological distress accompanying diabetes. This would be a very important development given the high rates of comorbidity.

Conflict of Interest: The authors have no conflict of interest to declare.

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