Opioid use disorder and type 2 diabetes mellitus

Effect of participation in buprenorphine-naloxone substitution programs on glycemic control

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Abstract

Objective To measure the effect of buprenorphine-naloxone as opioid substitution therapy on glycemic control in patients with type 2 diabetes mellitus and opioid use disorder.

Design Retrospective cohort study and secondary data analysis.

Setting Northwestern Ontario.

Participants Patients with diabetes receiving opioid substitution therapy, as well as patients with diabetes only, who live in 6 remote First Nations communities.

Main outcome measures Glycated hemoglobin A_{1c} values during a 2-year time period in the 2 groups.

Results Over a 2-year period, there was an absolute decrease of 1.20% in mean glycated hemoglobin A_{1c} values in patients with diabetes who also received opioid substitution therapy, compared with patients with diabetes who were not being treated for opioid dependence, whose values rose by 0.02%.

Conclusion Patients with diabetes who also suffer from opioid use disorder achieve significant ($P = .011$) improvement in glycemic control when treated with buprenorphine-naloxone substitution therapy compared with other patients with diabetes. Treating opioid use disorder with buprenorphine-naloxone substitution therapy has an unintended positive effect on diabetes management.

EDITOR'S KEY POINTS

- The glycated hemoglobin A_{1c} levels in patients with diabetes were examined along a 2-year continuum. Patients with diabetes participating in a buprenorphine-naloxone substitution program were compared with those not participating in such a program.
- Participation in a buprenorphine-naloxone program was associated with a decrease in glycated hemoglobin A_{1c} level compared with the control group. The mean absolute decrease of 1.20% is clinically significant and statistically different compared with the control group ($P = .011$).
- While it is possible that some of the effect might be related to medications, such a large effect is likely owing to improved self-care and improved adherence to treatment of all health issues.

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Dépendance aux opiacés et contrôle du diabète de type 2

Le contrôle de la glycémie chez les patients qui participent à un programme de remplacement des opiacés par la buprénorphine-naloxone

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Résumé

Objectif Mesurer l'effet d'un traitement de remplacement des opiacés par la buprénorphine-naloxone sur le contrôle de la glycémie chez des diabétiques de type 2 qui présentent une dépendance aux opiacés.

Type d'étude Étude de cohorte rétrospective et analyse secondaire des données.

Contexte Le nord-ouest de l'Ontario.

Participants Des diabétiques participant à un traitement de substitution pour dépendance aux opiacés et des diabétiques ne participant pas à un tel programme. Tous ces patients vivaient dans 6 communautés isolées des Premières Nations.

Paramètres à l'étude Les niveaux d'hémoglobine glycosylée A_{1c} ont été mesurés dans les 2 groupes durant une période de 2 ans.

Résultats Sur une période de 2 ans, on a observé une diminution absolue de 1,20% du niveau d'hémoglobine glycosylée A_{1c} chez les patients diabétiques qui suivaient un traitement de substitution pour une dépendance aux opiacés, en comparaison d'une hausse de 0,02% chez ceux qui ne suivaient pas de programme de substitution.

Conclusion Les patients diabétiques qui présentent aussi une dépendance aux opiacés améliorent de façon significative (P=.011) le contrôle de leur glycémie lorsqu'ils suivent un traitement de substitution par la buprénorphine-naloxone, contrairement aux autres patients diabétiques. Le traitement de la dépendance aux opiacés à l'aide d'un programme de substitution par la buprénorphine-naxolone a un effet favorable non intentionnel sur le traitement du diabète.

POINTS DE REPÈRE DU RÉDACTEUR

- On a mesuré les niveaux d'hémoglobine glycosylée A_{1c} chez des diabétiques durant une période ininterrompue de 2 ans. On a comparé les diabétiques qui suivaient un programme de remplacement des opiacés par la buprénorphine-naloxone avec ceux qui ne participaient pas à un programme de ce type.
- Chez les participants au programme de buprénorphine-naloxone, on a observé des niveaux d'hémoglobine A_{1c} inférieurs à ceux des patients du groupe témoin. La diminution moyenne de 1,20% est importante sur le plan clinique et elle est statistiquement significative par rapport au groupe témoin (P=.011).
- Même s'il est possible qu'une partie de cet effet soit due à des médicaments, il est probable qu'un effet de cet ordre soit plutôt le résultat d'une amélioration de l'hygiène personnelle et d'une meilleure fidélité aux traitements de tous les problèmes de santé.

Cet article a fait l'objet d'une révision par des pairs.
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Opioid use disorders and type 2 diabetes mellitus (T2DM) might coexist in many patients. This overlap occurs in many First Nations communities in northern Ontario, where both diseases have high prevalence.[1]

Diabetes rates in Indigenous Canadian populations have ranged from 2.7% to 19%, with some estimates of age-standardized prevalence as high as 30%.[1] First Nations persons living on-reserve are at the highest risk of diabetes, with a prevalence of 15.3% for people aged 18 years and older, compared with 6.0% for non-Aboriginal populations.

The 2008 to 2010 First Nations Regional Health Survey reported that 6.8% of Ontario on-reserve respondents used opioids without a prescription.[2] Prescription opioid abuse prevalence has been estimated to be between 35% and 50% in several Nishnawbe Aski Nation communities.[3] The number of Indigenous people seeking treatment for prescription opioid use disorders in Ontario tripled between 2009 and 2014.[4] In response to this public health and social crisis, a number of communities in northwestern Ontario have initiated opioid use disorder treatment programs combining psychosocial interventions with buprenorphine-naloxone substitution.[5] There is a paucity of data available on whether participating in the buprenorphine-naloxone programs has an effect on glycemic control in patients with diabetes.

Both opioid use disorders and T2DM are chronic medical illnesses in which noncompliance with treatment is a common problem influenced by psychosocial factors.[6] Opioid exposure is consistently associated with poorer glycemic control, as indicated by significantly elevated glycated hemoglobin A_{1c} (HbA_{1c}) levels relative to control groups ($P<.05$).[7] Duration of addiction is a mediating factor, with substantially higher HbA_{1c} levels among patients who had been using opioids for 2 or 5 years versus those who had been addicted for 5 months or 1 year.[7]

Different treatment methods for opioid use disorders have varying effects on diabetes control. Methadone maintenance therapy (MMT) in patients without T2DM is associated with increased sugar intake, elevated body mass index, and changes in glucose metabolism akin to those observed in T2DM patients.[8] Conversely, acute administration of buprenorphine to laboratory animals is associated with reduced sugar consumption; this effect is reduced with chronic buprenorphine administration, with test animals consuming less sugar but a normal overall amount of calories.[8] This effect is also seen with opioid antagonists such as naltrexone.[8] A retrospective observational study comparing MMT and buprenorphine maintenance therapy with regard to incidence of T2DM diagnosis found that patients receiving MMT were significantly more likely to be diagnosed with T2DM, even after controlling for confounding variables in regression analysis ($P=.0458$). However, among patients who were diagnosed with T2DM, HbA_{1c} results were not significantly different between the MMT and buprenorphine maintenance therapy groups, nor were they considered to be elevated.[9]

METHODS

One of the authors (D.T.) noticed a trend of improved HbA_{1c} values in patients with diabetes treated with buprenorphine-naloxone in her First Nations community practice. This prompted a literature search and subsequent retrospective study.

The literature search was carried out using MEDLINE and EMBASE from 1982 to 2015 for the following terms and combinations: *buprenorphine and/or naloxone, naloxone, narcan, opioid antagonist,* and *naltrexone;* and *diabetes mellitus, type 2, diabetes control, t2dm control, diabetes mellitus control, hyperglycemia, non-insulin dependent diabetes,* and *glucose metabolism*. Naloxone was marginally associated with an increased risk of hyperglycemia. No articles focused on the effect of buprenorphine on glycemic control or treatment of patients with addiction.

Written permission was obtained from 6 First Nations communities in northern Ontario to participate in the study. The 6 communities being studied had buprenorphine-naloxone substitution programs ranging in size from 33 to 160 patients. The total population of the 6 communities was 4388 and included 526 patients receiving buprenorphine-naloxone and 573 patients with diabetes. A total of 62 patients had both opioid substitution therapy and diabetes, and these patients were the study group. The remaining 511 patients with diabetes functioned as the control group.

Using anonymized data from electronic medical records, we examined the HbA_{1c} levels in patients with diabetes along a 2-year continuum in patients participating in a buprenorphine-naloxone substitution program compared with those not participating in such a program. The initiation of the buprenorphine-naloxone programs roughly coincided with the adoption of electronic medical records in the communities. The 62 study patients who had diabetes and were participating in buprenorphine-naloxone substitution therapy were identified. A total of 511 control participants consisting of patients with diabetes who were not prescribed buprenorphine-naloxone were also identified. Hemoglobin A_{1c} levels from the beginning of the study period (July to December 2013), which were the earliest data in the electronic medical record and roughly correlated with the start of most of the community programs, were compared with HbA_{1c} levels from January to July 2015. Independent 2-sample *t* tests were performed for equal variances. The study was approved by the Sioux Lookout Meno Ya Win Health Centre Research Review and Ethics Committee.

RESULTS

The average change in HbA_{1c} level of the study group was an absolute decrease of 1.20%. It varied by community from an increase of 0.34% to a decrease of 2.30%, with 5 of 6 communities showing an improvement in this measure of glycemic control (**Table 1**).

In comparison, the control group of patients with diabetes and without buprenorphine-naloxone treatment experienced an average absolute rise in their HbA_{1c} results of 0.02%. This average control group change in HbA_{1c} level varied by community from an increase of 0.52% to a decrease of 0.50%, with half of the communities having a small increase and the other half a small decrease.

The absolute difference between the HbA_{1c} levels in the 2 groups was 1.22% (P=.011), which is both clinically and statistically significant.

DISCUSSION

In this study, participation in a buprenorphine-naloxone program was associated with a decrease in HbA_{1c} level compared with not participating in such a program. The decrease of 1.20% is clinically significant and favourably compares to the decrease associated with oral diabetes medications such as α-glucosidase inhibitors (1%), biguanides such as metformin (1%), dipeptidyl peptidase 4 inhibitors (0.75%), sulfonylureas (1.25%), and thiazolidinediones (1.25%).[10] It is interesting that the study group had a higher baseline HbA_{1c} level than the control group did (9.76% vs 8.90%) despite having a younger average age. This appears to reflect the burden of opioid use disorder on diabetes control shown by previous research.[7] By the end of the study this relationship was reversed and the study group's HbA_{1c} level was lower than that of the control group (8.57% vs 8.91%). Perhaps participation in buprenorphine programs will reduce disease burden and diabetes complications in the long term. This might have an even bigger effect considering the relatively young age of the patients with both comorbidities.

While it is possible that some of the effect might be medication-related, such a large effect is likely owing to improved self-care and improved adherence to treatment of all health issues, as previous research on the pharmacobiology of buprenorphine administration did not find such a large effect. It is conceivable that patients participating in these programs also have more contact with health care professionals in regard to substance use disorders and might therefore receive improved follow-up of other health issues such as diabetes.

Limitation

One limitation of this study was the difference in age between the study group and the control group. Those in the diabetes-only control group were older than those in the buprenorphine-naloxone–treated group by an average of 13 years. However, as all eligible study participants with diabetes were included, this age difference likely reflects the difference in prevalence of opioid use disorder among different age strata in the communities, with people aged 20 to 50 most predominantly affected. Our study also had a greater proportion of female participants than male, which reflects the different sex distribution of diabetes diagnoses in these communities.

Our control group was made up of patients with diabetes who were not prescribed buprenorphine-naloxone. This group would include participants without opioid use disorder but might also include participants with untreated or undiagnosed opioid use disorder. However, this inclusion does not change the positive effect that the treatment of opioid use disorder had on diabetes control, as all patients had the percentage of change in their HbA_{1c} level compared against their own baseline HbA_{1c} level. As this was a retrospective observational study, we did not control for the initiation of various diabetes medications. As the control group was substantially larger than the study group, we believe such an analysis would not change the results. Furthermore, we postulate that the change in glycemic control is related to positive lifestyle changes, including improved adherence to diabetes medications. Therefore, changes in diabetes medications prescribed would not obfuscate the results.

All of the patients in this study were First Nations Canadians living in remote communities, who are known to experience high rates of T2DM.[1] It is unknown if the results would be similar for other Indigenous populations, other ethnic groups, or urban populations.

Table 1. Patient demographic characteristics and change in HbA_{1c} levels in the 2-year study period

GROUP	N	MALE, N (%)	MEAN AGE, Y	INITIAL HBA_{1c}, %	FINAL HBA_{1c}, %	MEAN CHANGE IN HBA_{1c}, %
T2DM only	511	218 (43)	51.8	8.90	8.91	+0.02
T2DM and buprenorphine-naloxone	62	20 (32)	38.5	9.76	8.57	-1.20*

HbA_{1c}—glycated hemoglobin A_{1c}, T2DM—type 2 diabetes mellitus.
*P=.011 for the difference between groups.

Conclusion

This study demonstrates that patients with diabetes and opioid use disorder achieve improved glycemic control when enrolled in a community-based opioid substitution program. Both diseases have multiple long-term sequelae. Early investment in such community-based opioid use treatment programs might have many subsequent health and cost benefits.

Dr Tilbrook is a physician practising in Sioux Lookout, Ont. **Mr Jacob** is Health Director of Webequie First Nation in Ontario. **Mr Parsons** was Electronic Medical Records Technologist for Sioux Lookout First Nations Health Authority. **Mr Edwards** is a researcher, **Ms Loewen** is a research intern, and **Dr Kelly** is a research consultant for the Anishinaabe Bimaadiziwin Research Program.

Contributors

All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests

None declared

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