

Identification of Repurposable Drugs with Beneficial Effects on Glucose Control in Type 2 Diabetes Using Machine Learning

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Abstract:

Despite effective medications, rates of uncontrolled glucose levels in Type 2 diabetes remain high. We aimed to test the utility of machine learning applied to big data in identifying the potential role of concomitant drugs not taken for diabetes which may contribute to lowering blood glucose.

Success in controlling blood glucose was defined as achieving HgA1c levels <6.5 % after 90-365 days following diagnosis and initiating treatment. Among numerous concomitant drugs taken by Type 2 diabetic patients, α 1 adrenoceptor antagonist drugs were the only group of medications that significantly improved the success rate of glucose control. Searching the published literature, this effect of α 1 adrenoceptor antagonists has been shown in animal models, where this class of medications appears to induce insulin secretion.

In conclusion, machine learning of big data is a novel method to identify effective antidiabetic effects for potential repurposable medications already on the market for other indications. Because these α_1 adrenoceptor antagonists are widely used in men for treating benign prostate hyperplasia (BPH) at age groups exhibiting increased rates of type 2 diabetes, this finding is of potential clinical significance.

Keywords: Diabetes type 2, machine learning, α_1 adrenoceptor antagonist , glucose control, big data analysis

Introduction:

Diabetes Mellitus type 2(DM-2) is a chronic condition afflicting increasing numbers of individuals worldwide, and adversely affecting their health, quality of life and survival (1). In addition to dietary modifications, exercise and other lifestyle changes, the majority of DM-2 patients are treated chronically with several groups of medications (2). These include insulin, meglitinides, sulfonylureas, thiazolidinediones, dipeptidyl peptidase (DPP-4) inhibitors, glucagon-like peptide (GLP) 1 receptor agonists, and sodium transport protein 2 (SGLT 2) inhibitors. Yet, despite extensive efforts, balancing carbohydrate metabolism remains a challenge for many patients (1). In an effort to find new ways to identify medications that can help in

balancing DM-2, we have employed big data machine learning techniques, recently validated by us in successfully identifying repurposable anti-hypertensive drugs (3).

We present evidence that $\alpha 1$ adrenoceptor antagonists have a significant favorable effect on balancing DM Type 2 when combined with known anti diabetic drugs.

Methods:

From the electronic medical charts of Maccabi Health Services, the second largest health service organization in Israel insuring over 2 million members (4), we identified patients receiving their first- ever drug treatment for DM-2 after a diagnosis had been made . Medications utilized were identified from the electronically- recorded purchases of the patient. For these patients, initial blood glucose values were recorded before treatment. Weight, age, BMI and smoking status were extracted from the electronic medical charts, calculating their mean, median, maximum, minimum, and standard deviation. Mean HgA1c levels for these patients were calculated for the period between 90 to 365 days following the date of diagnosis. Patients with HgA1c levels < 6.5 were classified as successful treatment and based on this criterion 54% of the patients were successfully treated. The study was approved by Assuta Hospital Research Ethics Committee in Tel Aviv permitting access to the patients' files.

Machine Learning methodology:

“Classification” is a task of machine learning in which the data can be divided into separate categories or classes. The algorithm is designed to predict the correct class for each data item in the repository. In our case there were 2 classes: “treatment success” by achieving HgA1c levels $<$

6.5 within 90-365 days of treatment initiation, and “treatment failure” (all other cases). We used 2 types of machine learning algorithms: Decision trees and fully connected neural networks. The analysis was done employing Python. Statistical and machine learning analyses were performed with infrastructure from Scipy, Ssikit-learn.(5-8)

We systematically surveyed drug groups and compared HgA1c levels of treated and untreated diabetic patients with antidiabetic drugs. In an attempt to eliminate as much patient variability among the treated and untreated groups, we used propensity score matching to examine whether a specific drug treatment/ combination achieved independently higher success rates (9-10). Using this method, we trained a regression model to predict the probability of the patient’s treatment success when taking a given drug. The treated and untreated groups were constructed in such a way that the propensity scores of the groups were as similar as possible.

We used the following patient characteristics for the matching: weight, age, BMI and smoking status. Treatment groups were excluded according to rate of re-sampling and Kolmogorov -- Smirnof (KS) goodness of fit tests for all features (5-8). We chose a re-sampling rate of 20 percent, with p values of less than 0.0001 for a single feature, as our limit for group's exclusion. Specifically, if the KS test for one of the features we matched had p-value of greater than 0.001, we considered it to be insufficiently strong to prove treatment success. . Re-sampling was allowed in the matching process (i.e. the same patient could be matched to several patients from the original group). The basic concept behind matching is to try to match one group of observations with another group of observations in such a way that the items in the groups are as

similar as possible in all aspects except for the tested variable. In our case, given a group of patients that are treated with drug x, we aimed to match every patient with a patient that was identical to him/her in age, weight, BMI etc. except for the fact that the matched patient was not treated with drug x.

We performed an exhaustive search over all treatment groups, excluding drugs that were bought by less than 200 patients and identified 73 such groups. For each treatment group, we compared treatment success rates of the group of patients treated with that specific drug to a matched group of patients that were not treated with that specific treatment. Based on the entire data base, logistic regression was used for predicting the probability of treatment success with the matched drug and this constituted the propensity score. For each patient in the treated group we matched a patient untreated with that specific treatment with the closest propensity score.

Pearson's chi squared test was used to determine whether the success rates differed among groups. To accommodate for multi hypothesis testing, the p-values were corrected according to the Bonferoni correction. We present the 5 smallest chi square p-values including the Bonferoni corrected p.

Results:

A. Main Analysis(Tables 1-2)

We extracted 29540 patients diagnosed with type 2 diabetes between 2005 and mid-2016. Mean HgA1c levels for these patients were calculated for the period between 90 to 365 days following

diagnosis date. Patients with HgA1c levels < 6.5 were classified as successful treatment and 54% of the patients were successfully treated.

Alpha 1(α 1) adrenoceptor antagonists were the only drug class that yielded significantly better success rate in glucose control. Comparing a sub-group of patients from the above that was additionally treated with α 1 adrenoceptor antagonists (for benign prostate hyperplasia) with a matched group of patients that did not receive α 1 adrenoceptor antagonists showed a significantly higher success rates for the treated group:

61% success rate for treated group and 53% success for untreated group. $p < 0.0004$ and test statistic of 16.7).

Using propensity score matching, the treated group contained 1356 patients and the untreated group contained 1221 patients.

The α 1 adrenoceptor antagonists taken by the patients included alfuzocin (27%), doxazocin(18%) , terazocin(6%)and tamsulosin(49%), Tamsulosin and alfuzocin are selective 1- α 1 A adrenoceptor antagonists, whereas tetrazocin and doxazocin are non selective α 1 adrenoceptor antagonists . Because of the limited sample size, we could not perform a sub-analysis comparing antidiabetic potency among the different α 1 adrenoceptor agonists.

In further dividing the diabetic group according to anti-diabetic drug treatment, the largest group of patients (9121) were treated with biguanides. In repeating the tests for this subgroup only, we also found a statistically significant difference in diabetes treatment success rates favoring patients treated with α 1 adrenoceptor antagonists (409 treated, 380 not treated, $p = 0.02$, test stat. 5.23).

B. Additional Analyses

1. We examined the prevalence of DM-2 among patients concomitantly treated with drugs for BPH and found it to be 10%. Chi squared test for diabetes treatment success rates for patients with hypogonadism (male) did not show significant difference. ($p= 0.77$)
2. Chi squared test for diabetes treatment success rates for patients with enlarged prostate (male);

Out of 26537 patients diagnosed with enlarged prostate there were 5756 patients that did not receive $\alpha 1$ adrenoceptor antagonists . Out or these patients, 253 were diagnosed with Type 2 diabetes. Matched with a group of 246 Type 2 diabetes patients that were not diagnosed with enlarged prostate, there was not statistically significant difference of improved success rate ($p=0.06$) (Table 1).

Discussion:

Our analysis, using machine learning of big data, confers a significant therapeutic advantage to $\alpha 1$ adrenoceptor antagonists in controlling glucose levels in DM- 2 patients receiving anti diabetic drugs. Based on animal experiments one may hypothesize that this class of drugs is involved in the regulation of basal insulin secretion(13) resulting in stimulation of plasma insulin levels(14).To examine the validity of these findings, we systematically reviewed the published literature on potential effects of this group of medications on glucose metabolism. The effects of $\alpha 1$ adrenoceptor antagonists on

plasma concentrations of glucose and insulin were studied in rats. Infusion of the selective α_1 adrenoceptor antagonist prazosin slightly increased glucose levels and decreased insulin concentrations. (13) In contrast, a mouse study has shown increased basal plasma insulin levels with the α_1 adrenoceptor antagonist prazosin. (14). After hypothetically testing data from genome wide association studies, proteomics and metabolomics, Zhang et al hypothesized that alpha 2 (but not α_1 adrenoceptor antagonists) may be favorable for glucose control in type 2 diabetes (15).

An uncontrolled study reported on the effect of the α_1 adrenoceptor antagonists doxazocin in treating hypertensive patients with type 2 diabetes. Although there was no obvious improvement in glucose metabolism, doxazocin noticeably reduced insulin resistance (16). The effect of the α_1 adrenoceptor antagonist doxazocin on plasma insulin and blood glucose was studied on 10 newly diagnosed essential hypertension patients undergoing a glucose tolerance test. In addition to a lipid lowering effect over 6 months with doxazocin, there was a significant decrease in plasma insulin and blood glucose. The glucose to insulin ratio (the insulin sensitivity index) increased. The study suggested a favorable effect of doxazocin on insulin action (17). In a study on hypertensive patients, with or without non- insulin dependent diabetes mellitus, doxazocin was associated with a significant improvement in insulin –mediated glucose disposal and lower plasma insulin, but not in diabetic patients (18).

In mild hypertensive patients, the introduction of doxazocin was associated with significantly lower plasma insulin response to a 75g oral glucose load. In addition, insulin-mediated glucose uptake was significantly greater after doxazocin (19). Similar results, suggesting doxazocin-induced improvement in sensitivity to insulin were shown

by Huuponen et al (20). Of interest, in virtually all the above cited studies, oxazocin was given in an attempt to evaluate its antihypertensive efficacy in hypertensive patients also experiencing type 2 diabetes.

Our study is the first attempt to use machine learning, big data analytics to evaluate potential anti diabetic effects of non anti diabetic drugs taken concomitantly by diabetic patients. Out of almost 300 drug classes, only $\alpha 1$ adrenoceptor antagonists conferred an antidiabetic effect after controlling for a variety of potential confounders.

It is noteworthy that almost all of our patients received the $\alpha 1$ adrenoceptor antagonists for benign prostatic hyperplasia (BPH), a condition where this class of drugs is commonly used due to its proven ability to relax the smooth muscle of the urethra (21).

Several studies have investigated the relationship between BPH and type 2 diabetes.

Ozcan et al have shown a positive correlation between high prostate volume and diagnosis of diabetes mellitus in patients with BPH (18), a finding confirmed by Hammarsten (23), while Sarma et al did not find such an association (24).

Because $\alpha 1$ adrenoceptor antagonists drugs were taken almost exclusively for benign prostate hyperplasia(BPH) in men, all other analyses were conducted on men. Hence these data does not provide sufficient information to judge whether women would also benefit from $\alpha 1$ adrenoceptor antagonists, hence studies enrolling women to specifically test this hypotheses should be conducted.

Even by virtue of age, it is expected that 50% of males above 60 years of age will experience BPH (25), of whom an estimated 10-20% will have type 2 diabetes (26).

Hence the antidiabetic effects of $\alpha 1$ adrenoceptor antagonists have a potentially important clinical utility to millions of men exhibiting both conditions.

. Among other questions, future work will have to evaluate the relative efficacy of the different subtypes of $\alpha 1$ adrenoceptor antagonists, as well as potential risk of hypoglycemia when $\alpha 1$ adrenoceptor antagonists are used among patients with BHP not suffering from type 2 diabetes.

Conclusions:

Machine learning of big data is a novel method to identify effective antidiabetic effects for repurposing medications already on the market for new indications. The evidence emerging from our study, backed up by both animal and human experimental data, strongly suggest that $\alpha 1$ adrenoceptor antagonists should be rigorously tested for their potential favorable impact on diabetes control through carefully designed prospective studies. Because $\alpha 1$ adrenoceptor antagonists are widely used in for treating benign prostate hyperplasia at age groups exhibiting increased prevalence of type 2 diabetes, this finding is of potential clinical significance.

Disclosure:

The authors declare no conflict of interest associated with this study. No financial support was received to conduct this study.

Authors' contributions:

GK and GN conceived the project.

GK wrote the first draft.

GN performed the analysis.

KR oversaw the analysis.

VS received permission to use the database and critically reviewed the manuscript.

Data Repository link is not relevant for big data machine learning

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Table 1: Comparison of success in glucose control between patients with BPH treated and untreated with /without diabetes

	diabetes	prostate	Prostate drug	Total patients	Treatment success*	Treatment fail
Group1	+	+	-	253	151 (60%)	102
Group2	+	-	-	246	119 (48%)	127

*P=0.06

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