Using Clinical Data, Hypothesis Generation Tools and PubMed Trends to Discover the Association between Diabetic Retinopathy and Antihypertensive Drugs

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ABSTRACT

Diabetic retinopathy (DR) is a leading cause of blindness and common complication of diabetes. Many diabetic patients take antihypertensive drugs to prevent cardiovascular problems, but these drugs may have unintended consequences on eyesight. Six common classes of antihypertensive drug are angiotensin converting enzyme (ACE) inhibitors, alpha blockers, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers, and diuretics. Analysis of medical history data might indicate which of these drugs provide safe blood pressure control, and a literature review is often used to guide such analyses. Beyond manual reading of relevant publications, we sought to identify quantitative trends in literature from the biomedical database PubMed to compare with quantitative trends in the clinical data. By recording and analyzing PubMed search results, we found wide variation in the prevalence of each antihypertensive drug in DR literature. Drug classes developed more recently such as ACE inhibitors and ARBs were most prevalent. We also identified instances of change-over-time in publication patterns. We then compared these literature trends to a dataset of 500 diabetic patients from the UT Hamilton Eye Institute. Data for each patient included class of antihypertensive drug, presence and severity of DR. Graphical comparison revealed that older drug classes such as diuretics, calcium channel blockers, and β-blockers were much more prevalent in the clinical data than in the DR and antihypertensive literature. Finally, quantitative analysis of the dataset revealed that patients taking β-blockers were statistically more likely to have DR than patients taking other medications, controlling for presence of hypertension and year of diabetes onset. This finding was concerning given the prevalence of β-blockers in the clinical data. We determined that clinical use of β-blockers should be minimized in diabetic patients to prevent retinal damage.

Categories and Subject Descriptors

[**Applied Computing**]: Life and Medical Sciences – *Health informatics.*

Keywords

Data mining, text analytics, cohort discovery, intervention assessment, hypothesis generation

1. INTRODUCTION

According to the 2014 American Diabetes Association (ADA) Standards of Medical Care in Diabetes, hypertension control is an established measure to prevent DR [1]. Several studies [2-5] have compared the effects of different classes of antihypertensive drug—ACE inhibitors, ARBs, β-blockers, calcium channel blockers, and diuretics—on diabetic pathology. One meta-analysis of 11 prospective, randomized clinical trials compared various classes of antihypertensive drugs as potentially accelerating the progression of diabetes [5]. The analyses showed with significance that a higher percentage of patients taking "diuretics and/or β-blockers" developed new onset diabetes than the groups taking ACE inhibitors or ARBs.

Though the duration of diabetes and control of hyperglycemia typically correlates with the incidence and progression of DR, some studies have shown meaningful differences in retinal disease between different classes of antihypertensive drugs. For example, after a 5-year study, patients taking the ACE inhibitor enalapril and the ARB losartan demonstrated a 65% and 70% reduction [6], respectively, in the progression of severity of DR compared to a placebo. Another study compared ARB with β-blockers treatment in diabetic rat retinas. The animals treated with ARB showed improvement in DR pathology whereas the β-blocker did not. In another diabetic rat model [7] DR showed faster progression in animals treated with β-blocker atenolol than with an ARB.

Understanding the potential clinical impact of drug selection for hypertension control in diabetics is not just an academic exercise. Millions of diabetic patients have been treated for hypertension using β-blockers for decades. However, autonomic innervation to the retina is well described [8], and recent studies by Jiang, Zhang, and others [9, 10] have shown that β-adrenergic blockade *causes* retinopathy in knockout models and significantly exacerbates the progression and severity of DR in animal models of diabetes [9,11]. Thus, the previous mainstay of therapy for hypertension control in diabetic patients, β-blockers, may in fact worsen eye disease in these patients, relative to other blood pressure medicines. The relationship between blood pressure control and retinopathy in diabetic patients is not clear. For example, β-blockers have been shown to be both helpful and harmful [12, 5, 13-15]. Demonstrating this deleterious effect would have a profound effect on the management of hypertension in this very large and rapidly expanding cohort of patients.

The Hamilton Eye Institute retinal image data set includes retinal images and longitudinal clinical management data on over 500 diabetic patients, going back to the 1990s [16]. The HEI data represents a valuable data mining resource in which to explore the potential relationship between β-adrenergic blockade and DR incidence and progression *in silico*. Towards that goal, we report results of data-driven hypothesis generation, cohort discovery and intervention assessment in this paper. We mined medical and demographic features to identify microsegments of diabetic patients that on further analysis revealed the connection between antihypertensive drugs and diabetes.

We then investigated the gap between human studies of antihypertensive drugs and diabetes and in vitro or animal studies of DR. Large clinical trials such as the ACCORD Eye Study [17] did not differentiate between classes of antihypertensive drug but studied overall effects of hypertension control. Other clinical trials indicate that some β-blockers negatively affect diabetic pathology [2]. Thus the ADA recommends ACE inhibitors or ARBs for diabetic patients. In vitro studies and rat models indicate that β-blockers also accelerate progression of DR. However, human studies of the effects of different classes of antihypertensive drug on DR are limited, so the purpose of our clinical data analysis was to investigate this relationship between drug selection and retinopathy disease prevalence.

2. METHODS

Previous work explained the value of linking publicly available biomedical "knowledge bases" with clinical data for improved knowledge discovery with hypothesis generation [18]. Our efforts in this paper leveraged ideas and implementation in [18] to discover the association between hypertensive treatment and diabetic retinopathy. We describe the experiment in Section 2.1. We then posit that the clinical practice of medicine lags the science of medicine in published literature, and that lag between research and practice may be a critical causal factor for severity and (accelerated) incidence of retinopathy in diabetic patients.

We test our hypothesis by comparing quantitative trends regarding antihypertensive drugs and diabetic retinopathy. We first identified quantitative trends in the overall publication about the topic in the leading biomedical database PubMed/MEDLINE. Initial literature reviews revealed complex and even conflicting perspectives on proper hypertension treatment for diabetic patients. We discuss the search process in Section 2.2 and the trend analysis in Section 2.3. By quantitatively summarizing what has been published about DR and antihypertensive drugs, we then compare with actual hypertension treatment in a clinical dataset of 500 diabetic patients. The quantitative statistical comparisons are described in Section 2.4 and 2.5. These experiments help us draw interesting conclusions in Section 3.

2.1. Data-driven Hypothesis Generation

Today, in the Big Data era, physicians and clinical researchers are collecting on data about treatments, clinical pathways and trials. Their intuition and gestalt leads to a hypothesis – that then is validated using clinical trials that are funded by agencies such as the National Institutes of Health. But what if the data collected to answer one hypothesis is more valuable than the one hypothesis it was collected for?

The framework described in [18] was a hypothesis generation solution implemented to help researchers ask the right question. The framework is able to digest domain knowledge as simple ontologies (or Semantic Web standard compliant triples), integrate with clinical measurement data, correlate textual descriptions, lab measurements and lab meta-data to generate potential new hypothesis for the researcher.

For the effort in this paper, we started with a de-identified dataset consisting of 7600 patients, 31 different clinical lab measurements with over a 100 meta-variables. Not all patients went through all the lab tests and the possibility of missing and incomplete data was intentionally allowed for the hypothesis generation study. The dataset was originally collected to build a predictive model for how soon a patient should schedule follow-up eye check-up. On this dataset, we applied cohort discovery algorithms. We posed the question – what features (medical, demographic, etc.) dominate the cohort of patients with diabetes but no retinopathy and the cohort consisting of diabetic patients that suffer from retinopathy. The results were as follows. The healthy patients had a normal routine medical history, were diagnosed with hypertension and were prescribed Lisinopril as the drug of choice to treat their hypertension (with at least 80% support). Patients with retinopathy on the other hand, had pre-existing description of fluid and/or exudates in the eye exam and where taking insulin and oral medication for blood sugar control.

Although the results initially seemed to suggest the obvious that patients with retinopathy are more severely diabetic, a deeper investigation revealed the association between the medication for anti-hypertensive treatment and retinopathy. Particularly, the fact that all patients considered under this study were hypertensive. If 100% of the patient population was hypertensive, and the microsegment of patients that do not have retinopathy are taking Lisinopril (which is an ACE inhibitor), then why did we not see Lisinopril in the patient population with retinopathy? Interestingly, the choice of antihypertensive treatment amongst that population was the β-blocker treatment. This observation posed the question could beta-blockers be the reason, or an accelerant of severity in diabetic patients towards retinopathy? Is this observation an artifact of the recent adoption of ACE inhibitors over beta-blockers? Or is this because of the delay in adopting the science of medicine into clinical practice? We attempted to answer these questions by analyzing PubMed trends.

2.2. PubMed/MEDLINE Search Process

To identify trends in publication about DR and antihypertensive drugs, we searched for journal articles in PubMed, recorded select data for each search, and analyzed search results graphically and numerically. Queries in PubMed provided data about how many journal articles have been published about DR and each class of antihypertensive drug or each specific drug. We searched the NIH-managed database MEDLINE through PubMed because of the increased reliability and accessibility of MEDLINE articles. Each MEDLINE article has been reviewed by NIH and indexed with Medical Subject Heading (MeSH) terms. MEDLINE also utilizes MeSH substance headings for chemical or biological substances, including drugs. Thus by searching within the MeSH

headings and MeSH substance headings for each query, the articles retrieved by each query were relevant to each combination of drug and disease.

The general query format was the same for each query—a medication and a disease. Below is an example query of β-blockers, or "adrenergic beta antagonists," and diabetic retinopathy.

Example Query: Adrenergic Beta- Antagonists [nm] OR Adrenergic Beta-Antagonists [MeSH Major Topic] AND diabetic retinopathy [MeSH Topic]
We searched for medication as a "MeSH Substance Heading," designated by [nm] and as a "MeSH Major Topic," designated by [MeSH Major Topic]. We searched for disease as a MeSH Topic in most cases except for diabetes as a MeSH Major Topic to increase the specificity of thousands of search results. Thus each query retrieved articles explicitly indexed under the specified medication and disease. We created a query for combinations of each class of antihypertensive drug and a disease: either diabetes or one of the related vascular complications (retinopathy, nephropathy, or neuropathy).

Another PubMed feature is a filter to retrieve only publications from the last 5 or 10 years. We incorporated this filter into our searches, recording for each query the total number of results, number of results from the last 5 years, and number of results from the last 10 years.

2.3. PubMed Trend Analysis

After recording data for each PubMed query, we analyzed the results primarily by graphical comparison. The purpose was to determine which antihypertensive drugs were most prevalent in the literature about each disease. Also, for the DR literature, we analyzed change-over-time in publication patterns. For each class of antihypertensive drug, we compared the percent of articles published in the last 5 years (approximately June 2009-June 2014), of the 5 previous years (approximately June 2004-June 2009), and of articles published before June 2004.

Though DR was the primary topic of the project, we analyzed literature from diabetes and from related diabetes complications to determine any similarities or differences between DR and related diseases. Diabetic nephropathy and diabetic nephrology are both microvascular complications of diabetes like DR [1], so we incorporated these diseases into the PubMed queries and then graphically compared prevalence of each antihypertensive drug in the four groups of publications—the three microvascular complication groups and diabetes group. When comparing diabetes literature with literature about the complications, we excluded microvascular literature from the diabetes literature using the Boolean operator "NOT" in each diabetes PubMed search. Thus statistics for diabetes literature were not skewed by publications about the microvascular complications that otherwise would be indexed as a subgroup within the broader topic of diabetes; the diabetes group was mutually exclusive.

We then investigated which specific antihypertensive drugs within each drug class were most prevalent in DR literature. The list of drug names was developed from the initial literature review and from the Mayo Clinic fact sheets about each class of antihypertensive drug. The PubMed query used the same formula as earlier queries to retrieve articles indexed under the drug name and DR.

2.4. Comparison of Publication Trends with Clinical Data: Research vs. Clinical Practice

For each of the six classes of antihypertensive drug—ACE inhibitors, Alpha blockers, ARBs, β-blockers, calcium channel blockers, and diuretics—we compared the prevalence of each drug class in publications about DR and antihypertensive drugs with the prevalence of each drug class in a group of diabetic patients with hypertension. For example, we compared the percent of the patients in the dataset taking β-blockers with the percent of all MEDLINE publications about DR and antihypertensive drugs, indexed under β-blockers. 273 patients of a dataset of 500 were reported to have hypertension and were taking a specified antihypertensive drug, so our analyses focused on these patients.

2.5. Clinical Data Analysis: Incidence and Severity of DR

After comparing the prevalence of each drug class in the data and the literature, we analyzed the clinical data separately for the incidence of DR within groups taking each drug. Longer duration of diabetes is a known risk for developing DR, so we divided the data into groups of patients based on 5-year ranges of diabetes onset and, within those groups, evaluated the level of disease by antihypertensive drug class. In each group we also looked at the percent of patients with each level of DR severity—PDR, NPDR, moderate NPDR, and mild NPDR—from most severe to least severe.

Since many patients were taking drugs from multiple antihypertensive classes, these patients were categorized in groups for each class of drug they were taking. For example, a patient taking β-blockers and ARBs would count one patient towards β-blockers and one patient towards ARBs. In these analyses patients were not mutually exclusive, but when some drugs seemed to increase chance of DR, the patients were separated and compared in two groups—all patients taking the potentially harmful drug and all patients not taking that drug.

3. RESULTS

3.1. DR and Antihypertensive Drugs: Publication Trends

Comparison of each class of drug in publications about DR, diabetes, and other microvascular complications of diabetes revealed common trends between the four categories of publications. ACE inhibitor was the most prevalent class of drug across all four categories. ARB was the second most prevalent, except that in diabetic neuropathy literature, calcium channel blockers were second—present in almost 30 percent of publications. In diabetes, DR, and nephropathy literature, each of the three older classes of drugs was present in less than 15 percent of publications.

3.2. Comparison of Publication Statistics with Clinical Dataset

Newer drugs, ACE inhibitors and ARBs, were the most widely researched drugs in the context of DR, according to the PubMed trend analysis. However, the older antihypertensive drugs that were published about less were actually much more prevalent in

the clinical data. Approximately 20 percent of patients were taking calcium channel blockers, and 30 were taking diuretics and β-blockers. Though ACE inhibitors were the most prevalent drug in the data and the literature, only 10 percent of patients were actually taking ARBs, while 30 percent of the DR and antihypertensive literature was indexed under ARBs. Thus the older classes of drug were widely prescribed even though DR research focuses on the classes of drug developed more recently.

The prevalence of individual drugs within each drug class was also concentrated more towards ACE inhibitors and ARBs in the literature, but a variety of older drugs were taken by many patients in the data (Figure 1). In lists of the thirteen most prevalent drugs in the literature and the data, the list for the data included only two ACE inhibitors and one ARB. Conversely, the list for the literature included five ACE inhibitors and five ARBs. Thus more drugs within each class were being researched than were actually prescribed. Notably the most prescribed drug, Lisinopril, was prescribed in twice as many patients as the second most-prescribed drug, a β-blocker.

Thus the clinical data at least to some degree followed the ADA guideline that diabetic patients should take either an ACE inhibitor or ARB.

When incidence of DR was compared graphically by diabetes onset year, β-blockers had the highest incidence of DR in three out of five of the 5-year diabetes onset ranges. Calcium channel blockers also demonstrated a higher incidence of DR, especially at the 2001-2005-onset range.

For a more focused analysis of the relationship between β-blocker use and higher incidence of DR, we compared incidence of DR in all patients taking β-blockers and all patients not taking β-blockers (Figure 2). At each 5-year diabetes onset range, the β-blocker cohort had a higher incidence of DR than the non-beta-blocker cohort. However, paired t-tests failed to determine statistical significance, possibly because of the small sample size within each 5-year onset range.

Because of the small sample size in the 5-year diabetes onset ranges, we divided patients into larger groups and conducted 2x2 chi-squared analyses to analyze for statistical significance between incidence of DR in patients with and without β-blockers. We determined statistical significance (with $p < 0.005$) in the higher incidence of DR in β-blocker patients, controlling for both presence of hypertension and diabetes onset of 5 or more years from time of screening.

4. DISCUSSION

Comparison between what has been published about DR and antihypertensive drugs with the medication patterns in a clinical population revealed that though the literature is dominated by drugs developed more recently (ACE inhibitors and ARBs), older drugs are still widely prescribed in some clinical environments. However, the high incidence of DR in patients taking β-blockers indicates that perhaps β-blockers were not researched sufficiently in the context of DR. Though the ADA already recommends use of ACE inhibitors or ARBs, clearly not all clinicians follow this guideline.

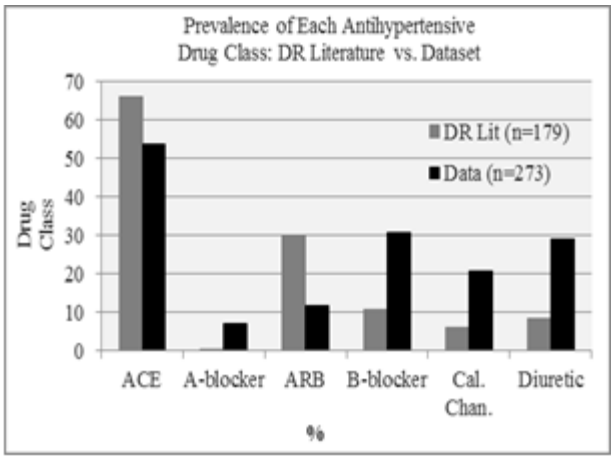

Figure 1. Comparison of prevalence of each drug class in DR literature vs. clinical data

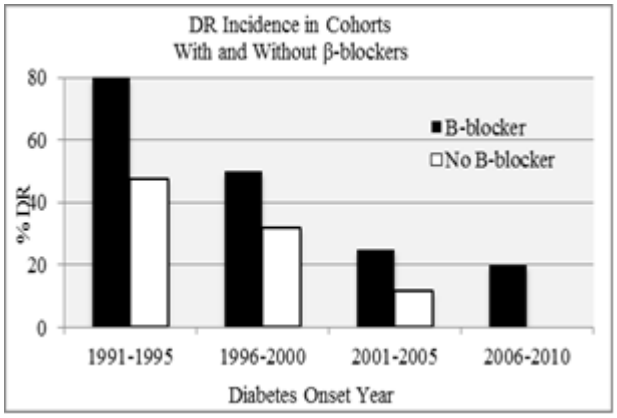

Figure 2. Incidence of DR in β-blockers patients vs. non- β-blockers patients over 5-year ranges

Sample sizes were too small to determine a meaningful relationship between severity of DR and class of antihypertensive drug. Thus a larger clinical dataset could provide more conclusive analysis of the progression of DR instead of only the presence of DR. More detailed medical history for each patient in the dataset would allow control of more variables that might affect DR. For example, duration of diabetes is a well-known risk for DR, but high glycemic levels—indicated by the HbA1c value—are another risk. A dataset including HbA1c values for all patients could help determine whether β-blockers cause an increase in glycemic levels that cause DR or if β-blockers are a risk independent from the progression of diabetes.

Automation of the PubMed search and trend analysis process could provide a "big picture" interpretation of literature about virtually any combination of diseases, medications, or treatment options. Already we used the process to compare publication patterns in antihypertensive drug literature between diabetes, DR, diabetic nephropathy, and diabetic neuropathy and were able to distinguish the overall similarities, with the exception of a higher emphasis on calcium channel blockers in neuropathy literature. Thus one use of the process is to compare what has been published about similar diseases in the context of a particular medication or treatment. These analyses, as demonstrated by the DR and antihypertensive drug comparison, can potentially

emphasize key areas for further investigation in data analysis, experimentation, or clinical trials. The literature search and analysis was done manually for this study. Our future efforts are towards automating and enriching the text analysis using recent advanced in Big Data technologies and algorithms and applying the automated methods to more clinical trial datasets.

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