Mean HbA1c Comparison among Diabetic Subgroups Treated with Oral Agents alone, Insulin alone and Combination of Both

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Abstract

Purpose: The goal of the paper is to determine if there is a significant difference in mean Hemoglobin A1c (a1c) among treatment-groups comprising Type 2 Diabetes patients receiving oral hypoglycemics agents alone, insulin alone, and a combination of oral agents and insulin, respectively.

Methods: Deidentified patient data were obtained from an ambulatory clinic EHR over a 5-year period, 2011-2015, representing a1c results of all active patients on either oral hypoglycemics, insulin, or both. The latter of at least two a1c results from the preceding 12 months in qualifying patients was used. Age and Gender data were collected for patient distribution comparisons among the groups.

Results: Of 3058 records, oral treatment group numbered 2084 or 68% of the total population; insulin group was 160 (5%) and combination treatment group was 814 or 27% of the population. Age and gender distribution were similar in all groups. There were statistically significant differences at 95% CI between the group means: 7.9, 8.9 and 9.3 for oral, Insulin and Oral+Insulin respectively, with p-values of Oral-Insulin P=3.8e-10; Oral- Oral+Insulin P <2.2e-16; and Insulin- Oral+Insulin P=0.0013.

Conclusions: Oral treatment group had the lowest mean a1c (statistically different) and the highest percent of patients with a1c under 8%, followed by Insulin group in both categories, then, combination group.

Keywords: HbA1c; A1c; Oral hypoglycemic agents; Insulin treatment; Combination insulin and oral agents; Type 2 Diabetes control

Introduction

While managing Type 2 diabetic patients in my practice, I noticed that those on oral agents alone had better Hemoglobin A1c (a1c) results compared to the group on insulin alone. The worst a1c seemingly was noted in the group treated with both oral agents and Insulin. The most frequently used oral regimen in my practice is Metformin with the addition of Glimepiride or Glipizide and pioglitazone as needed to get a1c under reasonable control. Insulin regimens were built around Lantus once or twice daily, with supplemental sliding scale Regular Insulin, usually Humalog or Novolin. Some patients were on both oral regimen (usually Metformin alone) and Insulin.

My practice setting afforded the opportunity to test my observation: a multi-location primary care ambulatory and inpatient practice organization (FQHC-type) staffed by multi-specialty healthcare providers including Physicians and Advanced Clinical Practitioners (Nurse Practitioners and Physician Assistants), running on the same, shared EHR. This structure provides authorized electronic access to the data on all the patients (including diabetics) in the entire practice, their treatment regimens and laboratory tests and results, as well as demographics. Additionally, qualified and interested staff is encouraged to do research on the data (on their own time); the organization has an IRB (Institutional Review Board) to review research proposals. I availed myself of these resources in the pursuit of my objective, including obtaining a determination from the IRB that this work is not considered Human Research and as such, is not subject to IRB review.

The question, “is the mean a1c for a group of diabetics on oral agents alone lower than that of the insulin-only group and or oral plus insulin treatment group?” is important because a1c level is recognized as the measure of the status of chronic glucose control in a diabetic. a1c levels are also correlated with certain clinical complications of Diabetes. These attributes have earned a1c a role as a benchmark for diabetic care [1]. The question may also have a relevance to health outcomes optimization, a contemporary healthcare management goal [2].

The null hypothesis for testing my observation is: there is no difference in mean a1c among different diabetic treatment groups taking either oral hypoglycemics alone, insulin alone or a combination of oral agents and insulin.
Materials and Methods

Data

Using i2i [3], I conducted a retrospective search and report on the database residing in an EHR (Electronic Health Records), “NextGen”, deployed at a primary care health provider organization. Search criteria were limited to: a) patients who were active (at least last 2 years with the clinic-system); b) patients who were seen at least once during the past 12 months at the time of data collection in 2015; c) and had a diagnosis of Type 2 Diabetes (with active exclusion of Gestational Diabetes, Type 1 Diabetes and Prediabetes) during the period from 2011 to 2015; d) or had Hemoglobin A1c (herein after, “a1c”) resulted at least 2 times at least three months apart during the past 12 months at the time of data collection in 2015; e) or were receiving anti-diabetic treatment with either oral hypoglycemics, insulin, or a combination. Patient’s age, gender and BMI were also collected.

The resulting report was in Excel format and read it into R (R programming language) platform [4] where data analyses were performed after stripping off all patient identifying data. As a first step, I performed EDA (Exploratory Data Analysis), resulting in the discarding of BMI data because manual weight entry, whence it is derived, was unreliable, leading to unacceptable values.

For a1c, only the latter of the two a1c results from d) above was retained. Where Mean Plasma Glucose (MPG) (usually co-reported with a1c) alone was resulted, it was converted to a1c using the formula widely reported and in use [5].

MPG=(35.6 × HbA1C) - 77.3.

In a private email correspondence for verification, the Laboratory serving the clinic-system affirmed the same formula.

All records without a1c data, as well as records with a1c less than 5.7 were removed; as were records without any treatment group.

Following original raw data munging, I constructed a database with the fields: Age, Gender, treatment group (as “oral”, “insulin” and “oral.insulin”, the latter designating combination of oral agent(s) and insulin) and a1c. I derived subsets of a1c and oral treatment, a1c and insulin treatment; and a1c and combined oral + insulin treatment data respectively for further analysis.

Population and group summary statistics were produced (Table 1), while Age Histogram and Gender Mosaic Plot visualized age and gender distributions respectively among the treatment groups (Figures 1 and 2).

A violin plot compared the treatment groups’ a1c moments (mean and SD) while revealing comparative a1c distributions (Figure 3).

Statistical method for means difference inference (using R)

Four different statistical methods were used to test group means difference; the results were compared for agreement [6]. The goal is to avoid normality violation, normality being the condition on which popular test methods are predicated. A greater than 30 sample size (achieved by each treatment group) can overcome the normality restrictions. This allows for the application of the Welch’s two-way t-test, with the additional advantage that it is appropriate for unequal sample sizes (as the groups demonstrate). Kruskal-Wallis Test by Rank and Wilcoxon rank sum test (also known as Mann-Whitney test) are non-parametric alternatives which can be used when data are not normally distributed. The treatment groups’ data are not all normally distributed, so the latter two methods were applied. The results from these three different methods were similar. Finally, since three groups are being compared, pairwise Wilcoxon test method was used to calculate pairwise comparisons between group means with corrections for multiple testing. The pairwise results matched the previous methods’ results.

Results

Table 1 Summary statistics including population and subsets by treatment type.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Oral</th>
<th>Insulin</th>
<th>Oral Insulin</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean a1c</td>
<td>7.9</td>
<td>8.8</td>
<td>9.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Median a1c</td>
<td>7.2</td>
<td>8.4</td>
<td>9.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Max a1c</td>
<td>18</td>
<td>16</td>
<td>16.9</td>
<td>18</td>
</tr>
<tr>
<td>% with a1c &lt;9</td>
<td>78</td>
<td>62</td>
<td>49</td>
<td>69</td>
</tr>
<tr>
<td>% with a1c &lt;8</td>
<td>66</td>
<td>43</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>n (sample size)</td>
<td>2084</td>
<td>160</td>
<td>814</td>
<td>3058</td>
</tr>
<tr>
<td>n as %population</td>
<td>68.1</td>
<td>5.2</td>
<td>26.6</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 P-value table constructed by pairwise mean comparisons using Wilcoxon rank sum test method.

<table>
<thead>
<tr>
<th>Rx</th>
<th>Oral</th>
<th>Insulin</th>
<th>Oral insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (mean=7.9)</td>
<td>3.80E-10</td>
<td>&lt;2.2e-16</td>
<td></td>
</tr>
<tr>
<td>Insulin (mean=8.8)</td>
<td>3.80E-10</td>
<td>0.0013</td>
<td></td>
</tr>
<tr>
<td>Oral Insulin (mean=0.3)</td>
<td>&lt;2.2e-16</td>
<td>0.0013</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1 Comparing gender distribution in each treatment group. Distributions appear similar, without apparent skew.

Figure 2 Comparing gender distribution in each treatment group. For each group, the Female (F) to male (M) ratio (vertical axis) is approximately the same. The horizontal axis compares each group’s numerical size population proportion.
Violin plot of a1c for each treatment group.

Figure 3 A violin plot of a1c for each treatment group.

The horizontal line marks the a1c mean (insulin 8.3; oral 7.9; oral.insulin 9.3). Each dot in a band in the center of the violin represents an a1c result; together the dots give an idea of the density distribution at various a1c levels. The oral treatment group shows a relatively sharp peak close to a1c 7 which is a clearly different distribution compared with the other groups roundly-peaking at around a1c of 8; an indication that there is a higher propensity for lower a1c in the oral group. A violin plot was chosen to reveal such comparative distributions [7].

Discussion and Conclusion

Study population

3058 records make up the study population (roughly matching the actual number of Diabetics in the entire organization’s practice). Of that number, 2084 (68.1%) belong to the Oral treatment group; 160 (5.2%) to the Insulin group and 814 (26.6%) to the combination oral plus insulin treatment group (Table 1). Age distribution (Figure 1) in each treatment group as well as Gender distribution (Figure 2), respectively are similar.

a1c statistics

Summary statistics for a1c data (units in %) (Table 1) show a population maximum of 18.0, with group maximum range of 16.0-18.0. Mean a1c was 7.9 oral group; 8.8 insulin group; and 9.3 oral + insulin treatment group (8.3 for the entire population). Pairwise mean comparison p-values (Table 2) at 95% confidence level are as follows: oral/insulin: P=3.80e-10; oral /oral.insulin: P<2.2e-16; and insulin /oral.insulin: P=0.0013. These p-values lead to the rejection of the null hypothesis, in favor of the alternate: the group means are statistically different, one from another. The inference is that the oral treatment group had a lower and statistically significant different mean a1c than the insulin group as well as the combination group. This indicates a validation of my initial observation. Note that the insulin group in turn had a lower mean a1c than the oral + insulin treatment group.

In the violin plot (Figure 3), the a1c means are visually compared. The plot also shows that the oral treatment group a1c distribution “sharply” peaks around a1c 7 while the other groups show rounded peaks closer to a1c 8; pointing to where the highest probability of locating a group’s a1c may be found [7]. This favors the oral group as more likely to have a lower a1c.

A standard Type 2 DM control measure is the percent of patients with a1c under 8%. Table I shows that oral group had the best score, followed by insulin group, then combination treatment group, at 66%, 43% and 31% respectively. Taken together, these findings strongly uphold the inference that the oral treatment group had the best a1c outcome over insulin group and over combination oral plus insulin treatment group for the study population. Keeping in mind that my study did not focus on new treatment initiation, there is a suggestion of conflict with the extrapolation of older study findings, which recommend starting newly diagnosed Type 2 Diabetics on insulin preferably, or on Metformin plus insulin alternatively, for best outcomes [8]. However, the 2017 Endocrinology Consensus statement recognizes using up to three different oral agents before adding insulin if the target a1c is not achieved [9]. It also emphasizes tailoring medication treatment to the patient’s
needs. A recent retrospective study comparing oral versus insulin therapy for newly diagnosed diabetics concludes that using oral agents alone for initiation of therapy performed well even with high initial a1c cases [10].

Given that there is no direct evidence for intrinsic medication-related factors driving my study’s outcome (although this should not be completely ruled out – that is, the regimens of themselves could have different efficacies), compliance is an obvious determinant. Compliance may be broadly broken down to compliance with medication treatment and compliance with diabetes-relevant lifestyle changes (dietary manipulation and physical exercise; impacting habits such as smoking, for example). What I learned by interviewing my patients is that there is a genuine fear of (use of) insulin, to the extent that better overall compliance can be extracted or negotiated if the only other option is initiating insulin treatment. The fear may lead to deliberate insulin under-dosing (to avoid hypoglycaemia—either experienced or heard about from others; this applies somewhat to oral agents use, too), although the patient may swear to dosage compliance initially. The latter may also be true when insulin under-dosing is driven by (un)affordability factors wherein stretching out the prescription is deemed the only practical way to sustain treatment. A few insulin users ignore prescription instructions in favor of ad-hoc insulin dosing contingent on how large a meal they intend to consume and or what the menu is. While compliance issues in general cut across all treatment groups, the foregoing are an extra burden for the insulin group. In a paper [11] which reported on the subject, many of the above compliance items were fleshed out; the paper also concluded that “nonadherence” to medication treatment was consistently higher with insulin than oral agents in the population studied. The most effective compliance improvement message and most dramatic a1c change, in my experience, come from directly targeting a specific dietary habit and item like the intake of extra sugar in the form of sodas, juices and other beverages; and or as a sweeter for common drinks such as coffee or tea.

One study limitation is that the patient population is over 80% Hispanic, so generalization to other populations may not be appropriate. In fact, the authors of the paper referenced above [11] find differential compliance with diabetic medication use related to ethnicity in their study which was focused on a Latino population. Another potential limitation is the fact that the oral agents used in the study do not include newer agents like the DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists. Type 1 DM and Gestational DM were excluded from the study. A more generic limitation is the fact that a written prescription (what is counted) may not have been filled by the patient and even after being picked up, may not have been taken. For example, a patient got, but would not take, their medication because of concerns about possible adverse interactions with beer ingested daily.

A practice implication is maximizing oral treatment before considering insulin. When additional treatment calling for insulin is indicated, the goal might be to eventually use insulin alone. The reader may wish to evaluate this suggestion within the context of the recommendations of “Standards of Medical Care in Diabetes” [12], which, nonetheless, also recommends tailoring the treatment regimen to the patient’s needs.

Future research to duplicate the findings here in a matched population, or a demographically different population, is in order and could be beneficial for optimized management of Type 2 Diabetes. There are many healthcare organizations providing care for Type 2 Diabetes that have (access to) statistically sufficient data, coupled with the availability of a plethora of statistical methodology, to conduct such research.

In conclusion, research results in this paper clearly affirm my earlier observations: the diabetic subgroup receiving oral treatment alone had lower (better) mean a1c than the subgroup receiving insulin alone as well as that receiving both oral agent(s) and insulin. Furthermore, the percent of the group with a1c under 8% was highest (best) in the oral agents alone compared to both the insulin only group and the combination oral plus insulin group respectively, a reflection of another statistical finding in the paper: the a1c of the oral treatment group was more likely to cluster in the lower end of the range when compared to the other treatment groups.

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