Electronic Disease Surveillance for Sensitive Population Groups – The Diabetics Case Study

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Abstract. Diabetics are quite susceptible to infectious diseases and can easily spread them under certain circumstances. Their blood glucose levels are increased after infection and this can cause a hyperglycemic crisis. Our study indicates that this increase results in glucosylated hemoglobin elevation, even when a diabetic is monitored closely and his/her blood glucose is under tight control. Thus, it is important to detect infections at the very early stages of disease progression in order to aid the patient. For this purpose, an electronic Disease Surveillance System could be developed to collect and analyze blood glucose data. Generally, we could extend the use of blood glucose data to the implementation of disease surveillance systems for the general population.

Keywords. disease surveillance, early detection, diabetics, blood glucose.

Introduction

Over the centuries many incidents of pandemics have been reported that resulted in a significant number of deaths. A current example is the avian influenza that, according to World Health Organization (WHO) reports, has caused almost 61% fatality among the total number of cases reported from 2003 to September 2007 [1]. Another kind of threat is bioterrorism, where the threat is still biological but it is caused solely by humans [2]. In order to confront these situations, a number of disease surveillance systems have been developed that utilize a variety of indicators to detect possible disease outbreaks.

Groups of ‘vulnerable’ individuals such as patients suffering from chronic diseases (diabetes, chronic heart and renal failure), elderly people and infants could be considered as Sensitive Population Groups (SPGs). For example, diabetics are quite susceptible to infections that can be easily spread under certain circumstances and seem
to be affected more compared to normal subjects [3, 4]. Therefore, the development of
Electronic Disease Surveillance Systems (eDSSs) for SPGs is an issue that should be
addressed. These systems could also aid health care professionals by providing them
with early indications of any possible infectious disease outbreak.

Infectious diseases are a common cause of high blood glucose (BG) and
hyperglycemic crisis in diabetics [5]. Generally, infection and any type of illness,
surgery, or injury causes stress on the body that needs more energy to combat this
situation. The body reacts by releasing counter-regulatory hormones that signal to the
liver to release extra glucose in order to provide body with the requested energy. These
hormones also inhibit the effect of insulin, and as a result there is over a certain period
of time an increase in BG that is more difficult to control [6]. However, the detailed
mechanism for BG elevation after infections has not been fully described yet [5].

Glycosylated hemoglobin (HBA_{1c}) is a reliable indicator of BG regulation,
especially in diabetics. It represents the average BG level of the past 4 weeks
approximately, strongly weighted toward the most recent 2 weeks. It is almost entirely
insensitive to BG levels more than 4 weeks before. In non-diabetics, the formation,
decomposition and destruction of HBA_{1c} reach a steady state with about 3.0% to 6.5%
of the total hemoglobin, but most diabetics have a higher HBA_{1c} level. The actual
HBA_{1c} level can be used as an indicator of the recent average BG level. Although
HBA_{1c} varies among individuals with the same average BG, it is very stable for any
given individual. Thus, a change of 1.0% in HBA_{1c} is definitely meaningful [7].

The target of this study was to demonstrate the need for developing DSSs for SPGs
through the diabetics’ case study. A simple system could be implemented using sensors
for data collection, a simple network infrastructure for transmitting them to a central
repository and an algorithm for data analysis; the same system could trigger alarms
based on the analysis results. Given the fact that diabetics (especially type-1 diabetics)
measure their BG daily, we claim that BG could be used as an indicator for the early
detection of infections at the early stages of disease progression, i.e. during the
incubation period. This period precedes symptoms onset which is the main time point
that the subject is made aware of his/her infection. Specific indicators for other SPGs
could be studied as well.

In order to establish a basis for further research it was considered necessary to find
strong correlations between BG and infections. For this purpose the Diabetes Control
and Complications Trial (DCCT) archives were used as the data source: DCCT was a
full-scale multi-center clinical trial, which recruited 1441 type-1 diabetic patients and
was conducted by the National Institute of Diabetes and Digestive and Kidney Diseases
(NIDDK) [8]. Among the numerous detailed data that were collected, HBA_{1c} values
and disease data were further assessed.

**Methods**

In DCCT patients were randomized into two arms: the conventional and the intensive
therapy arm; data were collected mostly during the follow-up visit that was scheduled
every three months.

In both arms adult males and females (age ≥18 years) were studied separately; the
first 48 months of their involvement was the period of interest. A patient that was
randomized to the conventional therapy arm was considered diseased if he/she reported
a disease of more than five days at the follow-up visit. For the second arm, the
recording of even one disease incident was considered adequate. Moreover, for both arms, it was decided that the 6-month periods before and after disease documentation should be free of any other disease, and women pregnant at any point during or close to these periods was excluded from the analysis.

Accordingly, the HBA1c values of the selected patients were assessed at specific time intervals: the follow-up visit of disease documentation (diseased value) and the 6-month periods before and after this visit (non-diseased values). The non-diseased HBA1c values were averaged for both periods. According to DCCT protocol, HBA1c values were collected every three months (at the follow-up visit) for the conventional therapy arm and every month for the intensive therapy arm. So, the non-diseased average was the result of two and five (the ones close to the diseased value were excluded) values correspondingly.

Sample distribution was tested for normality with the Shapiro-Wilk test, and the null hypothesis that the diseased HBA1c values are equal to the non-diseased values was tested with paired t-test for both sexes and arms. All p values were based on two-sided testing, and differences were considered significant at p<0.05. All statistical analyses were performed with SPSS software (version 14.0 for Windows, SPSS Inc., Chicago, IL).

Results

The age range for all patients was 18-39 years; some other descriptive statistics are presented in Table 1. Figure 1 displays information on the HBA1c grouped values (see abbreviations listed under the figure) distribution for both arms and sexes. The box plots and the outliers shown in this figure offer a quick overview for each group of values.

<table>
<thead>
<tr>
<th>Table 1. Descriptive statistics for all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Conventional Arm</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Intensive Arm</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Males</td>
</tr>
</tbody>
</table>

*Insulin-dependent Diabetes Mellitus duration until patients’ involvement

<table>
<thead>
<tr>
<th>Table 2. Shapiro-Wilk test for Normality</th>
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</thead>
<tbody>
<tr>
<td>HBA1c Grouped Values</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Female Diseased</td>
</tr>
<tr>
<td>Female Average Before</td>
</tr>
<tr>
<td>Female Average After</td>
</tr>
<tr>
<td>Male Diseased</td>
</tr>
<tr>
<td>Male Average Before</td>
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<tr>
<td>Male Average After</td>
</tr>
</tbody>
</table>
The Shapiro-Wilk test showed that all sample distributions were normal except from females receiving intensive therapy (Table 2). In this case, all distributions of diseased and non-diseased average values appeared to be right-skewed. So, the

<table>
<thead>
<tr>
<th></th>
<th>HBA1c</th>
<th>Mean</th>
<th>SDev</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseased – Average Before</td>
<td>0.288</td>
<td>0.719</td>
<td>0.163</td>
<td>0.412</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diseased – Average After</td>
<td>0.273</td>
<td>0.851</td>
<td>0.126</td>
<td>0.421</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diseased – Average Before</td>
<td>0.267</td>
<td>0.722</td>
<td>0.151</td>
<td>0.384</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diseased – Average After</td>
<td>0.225</td>
<td>0.681</td>
<td>0.115</td>
<td>0.335</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intensive Arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diseased – Average Before *</td>
<td>0.007</td>
<td>0.081</td>
<td>-0.009</td>
<td>0.023</td>
<td>0.342</td>
</tr>
<tr>
<td>Diseased – Average After *</td>
<td>0.016</td>
<td>0.076</td>
<td>0.001</td>
<td>0.031</td>
<td>0.021</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseased – Average Before</td>
<td>0.169</td>
<td>0.450</td>
<td>0.077</td>
<td>0.261</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diseased – Average After</td>
<td>0.115</td>
<td>0.563</td>
<td>0.001</td>
<td>0.230</td>
<td>0.049</td>
</tr>
</tbody>
</table>

* normalized values
logarithmic transformation (base-e logarithm) was used to correct the skew and normalize the distribution. It also appeared that the distribution for diseased females in the conventional arm was not normal either, but it was considered normal since there were only a few outliers and the dependent was quite normal, as appears in Figure 1.

The null hypothesis was tested with t-test and the results are presented in Table 3. All patients that were treated conventionally appeared to have increased HBA1c levels at the follow-up visit they reported a disease incident compared to the average values for the 6-month periods before and after this visit. Particularly, females had a slightly greater increase in their diseased HBA1c levels and a better recovery to lower non-diseased HBA1c values compared to males.

The results for the intensive therapy arm were rather different. The null hypothesis was equally rejected for the male patients as well as for the patients of the conventional therapy arm. However, normalized diseased female values showed no significant difference compared to the normalized average values before but a significant decrease after the disease.

Discussion

Assuming that there could be some hormones pathways in adolescent subjects that could affect HBA1c levels, only adults over 18 years were included in the analysis. The same assumption was made for pregnant women, who were excluded from this study. It could be argued that some other factors (physical activity, alcohol consumption, food intake) should be considered as well, but unfortunately there were no detailed recordings of them. Additionally, the recorded disease data was limited only to the number of disease incidents per patient for the intensive therapy arm, so in this case it was the only criterion for assessing whether a patient was ill or not. On the other hand, in the case of the conventional therapy arm, the days for each disease incident were also recorded. So, the criterion was modified: a reported disease incident that lasted less than 5 days was not considered important because it would be less capable of altering HBA1c values.

The results showed that HBA1c values rose after infection despite the tight BG control, and returned to non-diseased levels when the initial cause ceased. This was observed in all cases except the intensively treated females.

As mentioned above, infection causes release of counter-regulatory hormones and this results in BG elevation, but the detailed underlying mechanism has still to be determined. Moreover, the exact timing of BG elevation during the disease progression requires more clarification. It could be expected that both mechanism and timing follow quite different patterns in SPGs case and, especially, in diabetics who were the target group of this study. Particularly, a number of relevant questions could arise such as:

- Is it possible to observe a meaningful increase in HBA1c after infections?
- How well is BG regulated with insulin intake during disease episodes?
- Is BG a reliable indicator since it is affected by many other factors?
- What are the different patterns of BG elevation per individual and infection?

Our study indicated a meaningful increase in HBA1c after infections but this should serve only as a basis for further research. Ukaparol et al. [9] have partially answered the same question by their study in animals. Regarding the second question, there are findings that BG is increased in patients with postoperative infections even with tighter
glucose control [10, 11] (our analysis resulted in similar findings), but more targeted research is needed. Despite the fact that BG is affected by many other factors, such as food intake, insulin, physical activity and alcohol, the DCCT data analysis indicated that BG cannot be easily regulated after infection even when the patient is closely monitored for the other factors. A potential direction for future investigation is stated through the last question which is also our idea for the next steps in the field.

Electronic disease surveillance systems can offer early warnings for a disease threat and/or possible outbreaks. An eDSS for diabetics could employ biological sensors for collecting BG data and transmit them to a central data repository and their Electronic Health Record. Then an algorithm could analyze the incoming values in respect to each subject’s profile, identify epidemic threats for a bigger group of diabetics (or the general population) and trigger alarms if necessary. Naturally, the use of BG data and the implementation of similar systems for non-diabetics should be studied as well.

As stated above, the results of our study indicate that before developing an eDSS for diabetics more research is required. So, the next step is a pilot study with diabetics. The target of this study will be the collection of the necessary data that will be used in studying the different patterns and physiology mechanisms after infections in diabetics. A future plan is to investigate whether it is possible to apply the same strategies for the general population. Apparently the diabetics’ case study could act as the force for electronic disease surveillance not only for the general population but also for other sensitive population groups. However, a dedicated study should be performed per case in order to derive safe conclusions.

References