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Research Article

False Low HbA1c Levels Under Treatment with Ribavirin

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Abstract

Background: With increasing numbers of patients treated for hepatitis C, it will become more common that patients with diabetes will undergo those treatments as well. Up to now, only few data analysing HbA1c levels in diabetic patients under treatment for hepatitis C exists. Therefore, we compared changes of HbA1c levels during hepatitis C treatment in regimes with or without ribavirin

Methods: 14 patients in a ribavirin containing and 20 in a non-ribavirin containing regimen were followed for their glycemic control before, during and after treatment. HbA1c and fructosamine were measured at week 0, 4, 8, and 12 while under therapy, and 4 and 12 weeks after end of treatment.

Results: A significant decrease in HbA1c was shown in ribavirin treated patients, while no differences were found in the non-ribavirin containing group (ΔHbA1c week 0 to 12: ribavirin: -2.1±1.26 % / non-ribavirin: -0.25±0.1%; p <0.001). After treatment, HbA1c values returned to baseline levels. Fructosamine levels remained stable in both treatment groups.

Conclusion: Ribavirin leads to inadequately low HbA1c levels. Therefore, interpreting quality of glucose control via HbA1c measurement under ribavirin containing treatment is not encouraged in patients with diabetes.

Introduction

Since discovery of HbA1c in the late 60ies and its implementation into clinical practice in the 70ies and 80ies of the last century, this parameter has become a hallmark of diabetes care [1]. After its international standardisation between 1990 and 2000, other laboratory parameters for measurement of chronic glycaemic control are used rarely and only by specialists. However, limitations of HbA1c measurement are often unknown to physicians, even as this parameter is used very regularly.

Proteins with long half-lives, as haemoglobin, are continually glycated until they become degraded, so grade of glycation increases with elevation of plasma glucose and age of red blood cells [2]. As HbA1c represents the percentage of glycated to overall haemoglobin molecules, a shortened half life span of erythrocytes may therefore decrease HbA1c levels irrespectively to mean glucose levels [3].

Hepatitis C is a common infectious disease, which can be treated and cured nowadays. One of the drugs used for the treatment is ribavirin. It is a guanosine (ribonucleic) analogue used to stop viral RNA synthesis and viral mRNA capping and acts as a nucleoside inhibitor [4-7]. Hemolysis has been reported as side effect of Ribavirin. So far, only one case report showed the decrease in HbA1c during treatment with pegylated interferon and ribavirin [8]. Since newer treatment options for Hepatitis C do rarely include interferon, we wanted to study the effect of ribavirin containing treatment regimens on HbA1c levels in patients treated with Direct Acting Agents (DAA) for Hepatitis C.

Methods

From January to September 2016, patients in whom a treatment with DAA was initiated were asked to participate in

the study. Informed consent was obtained from all patients, and approval by ethic committee obtained (EKNZ UBE-2017-01118). Two groups of were conducted, one with a DAA regime containing Ribavirin and one with DAA only. As the study was prospective but purely observational, decision about the antiviral treatment was not influenced by participation in the study, but solely based on virological, clinical and radiological parameters.

All patients with hepatitis C treatment and willing to participate were included. As the principle of reduction in HbA1c levels occur in all patients and may even be more stable (without Ribavirin) in non-diabetic patients, we included patients with and without Diabetes mellitus, and diabetic treatment was independent of the study.

Exclusion criteria were change of diabetes treatment 8 weeks before or during the study. However, the two treatment groups were fairly matched (see baseline characteristics). At baseline, week 4,8,12 and 4 and 12 weeks after HCV treatment, HbA1c, fructosamine and hemoglobin were measured. Quantification of HbA1c was performed within three days by ion-exchange high performance liquid chromatography using the D-10TM HbA1c short program (Bio-Rad Laboratories, Hercules CA, USA). Primary endpoint was the difference in HbA1c decrease between group 1 and group 2.

Descriptive statistic was made for all patients at baseline, with the continuous data expressed as mean ± SD and categoric data expressed as counts. Baseline characteristics of the groups were compared with student's t-test and X^2 Test. Comparison for quantitative data between the groups was made with Wilcoxon-Mann-Whitney-Test. Regression analysis was made for correlation between decrease of hemoglobin and HbA1c by ANOVA. For regression analysis, only values from baseline until week twelve in patients with ribavirin were used.

As secondary endpoint, we wanted to know if physicians are aware about the limitations of HbA1c as laboratory parameter. We therefore conducted a survey using a questionnaire with five open questions: 1. HbA1c shows mean glucose values of what time period? 2. What exactly is measured by the test? 3. What is a normal value for HbA1c (diabetics)? 4. What circumstances may lead to false low HbA1c values? 5. What circumstances may lead to false elevated HbA1c values?

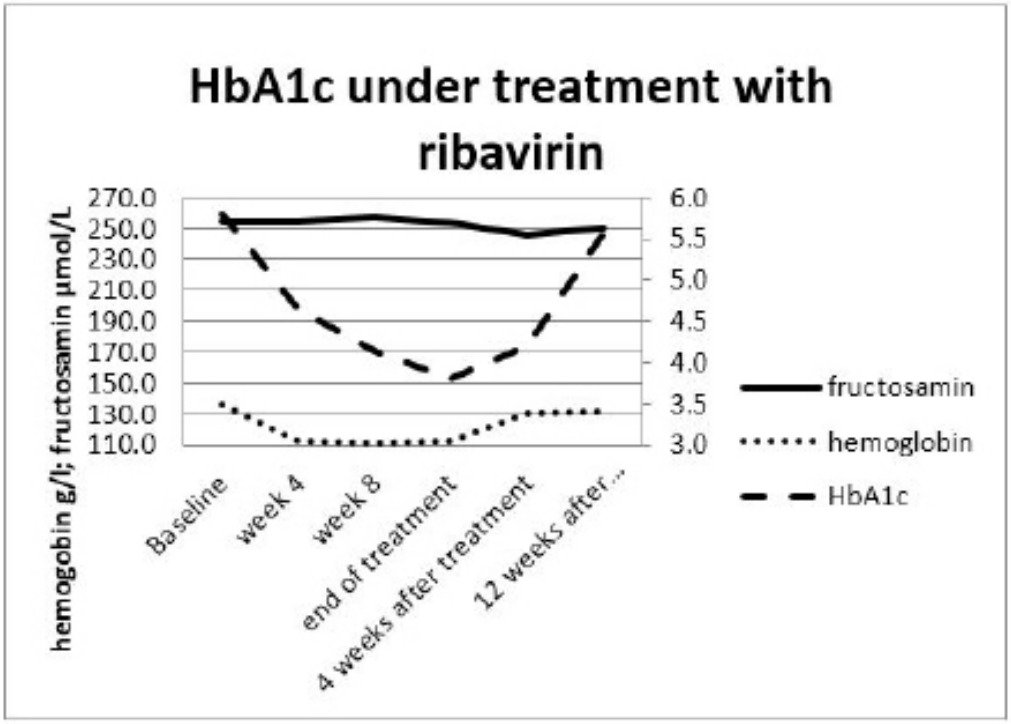
Results

34 patients were included in the study, 14 in the ribavirin containing (group 1) and 20 in the non-ribavirin containing group (group 2). 6/28(21%) patients were diabetic, and three additional patients had a HbA1c levels between 5.8 and 6.3%. Paritaprevir / ombitasvir / ritonavir / dasabuvir was used as DAA treatment in five patients of group1 and none in group 2 respectively (5 vs 0). Paritaprevir/ombitasvir/ritonavir was used in 3 vs 1 patients, sofosbuvir/ledipasvir in 1vs10, sofosbuvir/daclatasvir in 3 vs 3, sofosbuvir/pegylated interferon in 1vs 0 and elbasvir/grazoprevir in 0 vs 4 patients. (Table 1 baseline characteristics).

	Ribavirin-group (%)	Non Ribavirin Group	p-value
Age	51	54	0.4
Male	6/14 (42.8)	11/20 (55)	0.48
Diabetes	3/14	3/20	0.62
Caucasian	13/14	20/20	0.22
BMI>30	7/14	5/20	0.13
F4/cirrhosis	9/14	8/20	0.16
F3 fibrosis	4/14	4/20	0.56

Table 1: Baseline characteristics.

While in group 2 no significant decrease in HbA1c could be seen, it was significant (-2.1±1.26 %points) in group 1 ($p<0.001$). This decrease was correlating to the decrease of haemoglobin ($R^2=0.61$, $p=0.001$) (Figure 2). Different to HbA1c, fructosamin remained stable during the treatment in both groups (p>NS). After the end of ribavirin treatment, the values of hemoglobin as well as HbA1c returned to pre-treatment levels (Figure 1).



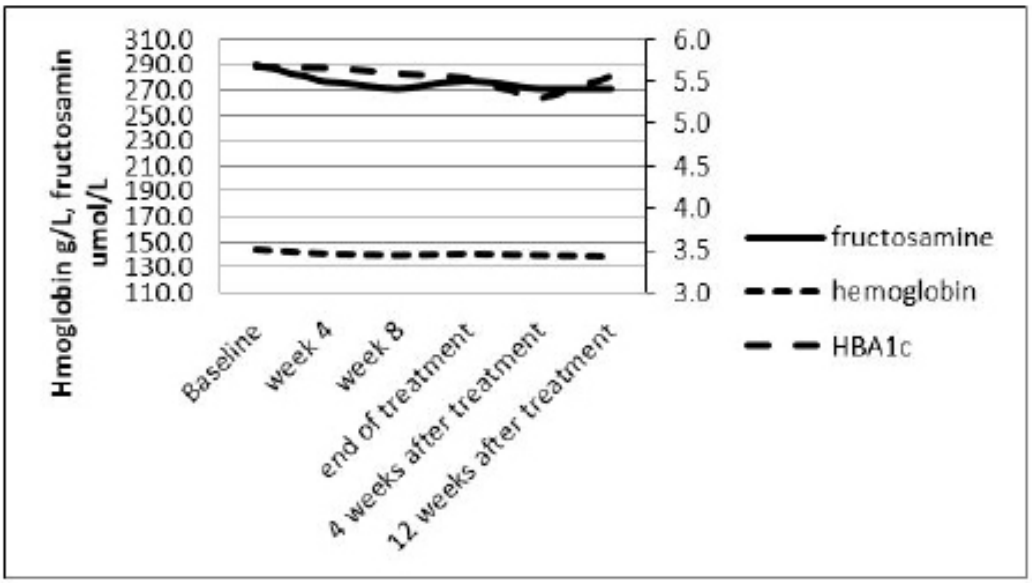


Figure 1: HbA1c, fructosamine and haemoglobin levels a) with and b) without ribavirin treatment.

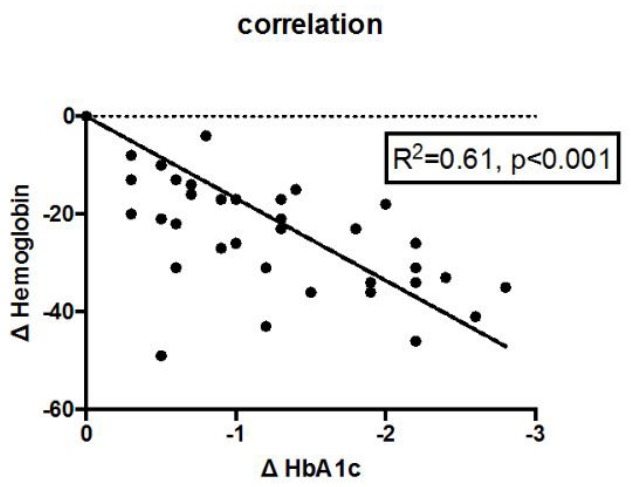


Figure 2: Correlation Between Δ Hb and ΔHbA1c.

Concerning the survey about knowledge of physicians, 53 participated: 28 residents, 4 students and 20 senior physicians, all working in a department of internal medicine in two Swiss hospitals. For question one, two and three, correct answers where given in 85, 85 and 55 % respectively. However, for question four and five concerning limitations of the parameters, correct answers where given only in 11 and 19 % respectively. With exception of question 1 (HbA1c shows mean glucose values of what time period?), no differences between junior and senior physicians were present (Figure 3).

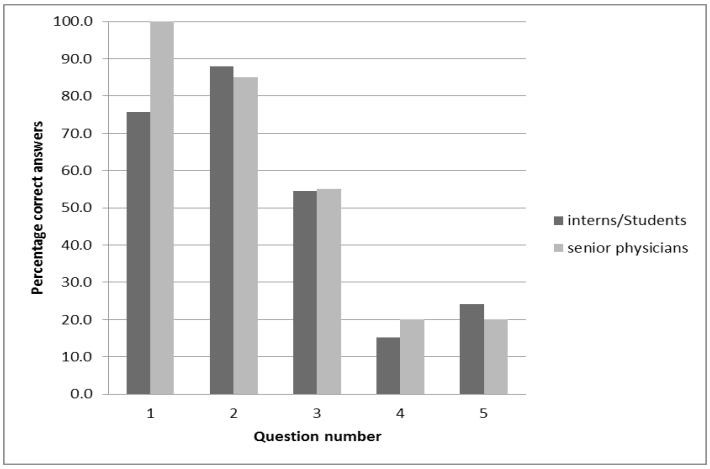


Figure 3: Percentage correct answers in questionnaire.

Discussion

HbA1c has become standard parameter for evaluation of quality of glycemic control in patients with diabetes [9]. Consequently, other parameters, as fructosamine, have become less important and are rarely used anymore. However, most clinicians are not aware of limitations of these laboratory parameters [10]. In our survey, less than 20% of physicians answered correctly on questions about limitations of the test. Even the reference HbA1c range for classifying diabetes was only clear to half of the physicians. However, if we opened the possibility form strict 6.5 % to somewhere between 6 and 7 %, 90% of the physicians answered correctly.

This might reflect our general inadequate high confidence in laboratory tests, ignoring important limitations. HbA1c measures the percentage of glycosylated haemoglobin molecules. Therefore, the parameter is prone to misinterpretation in situations of decreased or prolonged life span of erythrocytes [11]. It is known that Hemolysis can decrease Hb1Ac levels, and it is also known that ribavirin can induce Hemolysis during treatment. However, up to date only one case report showed a decrease in HbA1c under ribavirin treatment [8]. Our results do not show a false low HbA1c value per se, as there is no analytical interference in the test, but the values do not reflect the mean glycemic levels of the last three months. We could confirm this decrease in our study.

Moreover, we clearly showed a correlation between Hemolysis and HbA1c decrease and confirmed that no improvement in glycemic control was achieved, as fructosamine levels remained stable despite an impressive reduction of HbA1c. As this was a unique situation with expected Hemolysis during treatment we could calculate the decrease of hemoglobin and HbA1c. Even if, due to individual variation, the correlation was not very strict, with a R^2 of 0.61, we estimated that for a decrease in hemoglobin of 10 g/L, HbA1c decreased about 1 % point. This is the first study that measured the drop of HbA1c in correlation to Hemolysis over time. We are aware that other factors as age, ethnicity, mean cell hemoglobin concentration, renal insufficiency and BMI might influence HbA1c level, but as we measured HbA1c for each patient consecutively during treatment, these effects will not have influenced our results.

Even with newer, direct acting antiviral agents for the treatment of hepatitis C, almost 40 % of patients were treated with ribavirin, and 20% of the patients treated for hepatitis C were diabetic. Therefore, it is important to emphasise the limitations and possible errors of this measurement. We recommend that under treatment with ribavirin, glycemic control is only measured with serum glucose levels. Alternatively, fructosamine could be used to estimate the long term control. However, most clinicians are not familiar with this test, and treatment of hepatitis C rarely encompasses more than 12 weeks. Therefore, misinterpretations could surpass the benefits of fructosamine, even if theoretically it might sound reasonable to be used. We propose that measurement of HbA1c should be omitted for at least 3 months after termination of ribavirin treatment. While in one study, a decrease in fasting glucose during treatment with direct antiviral agent was observed

[12], we did not observe an improvement of glycemic control in our study. In the study by Pavone et al, HbA1c was measured as well, but no difference was made between ribavirin and non-ribavirin containing regiments. We therefore assume that the decreases in HbA1c found were rather biased by use of ribavirin.

Conflict of Interest:

All authors: No conflict of interest.

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