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CLINICAL PATHOLOGY AND MEDICAL LABORATORY

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Telp/Fax. (031) 5042113, 085-733220600 E-mail: majalah.ijcp@yahoo.com, jurnal.ijcp@gmail.com
Website: http://www.indonesianjournalofclinicalpathology.or.id

Accredited No. 36a/E/KPT/2016, Tanggal 23 Mei 2016
INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND
MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

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FRUCTOSAMINE AND GLYCATED ALBUMIN IN PATIENTS WITH TYPE 1 DIABETES MELLITUS DURING RAMADHAN FASTING

(Fruktosamin dan Albumin Glikat di Pasien Diabetes Melitus Tipe 1 yang Menjalankan Puasa Ramadhan)

Vinzy Yulina¹, Sidarti Soehita¹, Muhammad Faizi², Budiono³

ABSTRAK
Puasa Ramadhan dapat meningkatkan kebahayaan kekompilasi dalam pasien Diabetes Melitus (DM) tipe 1, yang dapat dicegah dengan kendali glikemik yang baik. Pemeriksaan fruktosamin dan albumin glikat digunakan untuk menggambarkan rerata kadar glukosa darah selama 2-3 minggu sebelumnya, sehingga lebih sesuai digunakan untuk menggambarkan kendali glikemik selama puasa Ramadhan (1 bulan). Tujuan penelitian ini adalah membandingkan dan membuktikan adanya kenasaban antara kadar fruktosamin dengan nilai albumin glikat sebelum, pertengahan dan akhir bulan puasa Ramadhan di pasien DM tipe 1 di RSUD dr.Soetomo Surabaya. Penelitian ini menggunakan desain analitis observasional di 13 pasien DM tipe 1 berusia 9–18 tahun yang menjalankan puasa Ramadhan. Pemeriksaan fruktosamin menggunakan metode nitroblutetrazolium (NBT) dengan alat Cobas Integra. Nilai albumin glikat dihitung sebagai persentase kadar albumin glikat (menggunakan metode enzimatis) terhadap kadar jumlah keseluruhan albumin serum (menggunakan metode bromcresol purple), dengan alat Proline R-910. Hasil analisis mengunakan p statistic t-berpasangan dan kenasaban Pearson. Tidak didapatkan perbedaan bermakna antara kadar fruktosamin pertengahan dibandingkan sebelum (p=0,307), akhir dibandingkan sebelum (p=0,249) dan akhir dibandingkan pertengahan bulan puasa Ramadhan (p=0,362). Tidak didapatkan perbedaan bermakna antara kadar fruktosamin pertengahan dibandingkan sebelum (p=0,478), akhir dibandingkan sebelum (p=0,285) dan akhir dibandingkan pertengahan bulan puasa Ramadhan (p=0,247). Kenasaban positif bermakna didapatkan antara kadar fruktosamin dan nilai albumin glikat sebelum (p=0,0001, r=0,952), pertengahan (p=0,0001, r=0,948) dan akhir bulan puasa Ramadhan (p=0,0001 dan r=0,963). Kadar fruktosamin dan nilai albumin glikat dapat digunakan sebagai tolok ukur kendali glikemik di pasien DM tipe 1 yang menjalankan puasa Ramadhan.

Kata kunci: Fruktosamin, albumin glikat, DM tipe 1, puasa Ramadhan

ABSTRACT
Fasting Ramadhan may increase the risk of complications in type 1 Diabetes Mellitus (DM) patients, which can be prevented by good glycemic control. Examination fructosamine and glycated albumin is used to describe the average blood glucose level over the previous 2-3 weeks, so it is more suitable to be used to describe the glycemic control during Ramadhan fasting month (one month). The purpose of this study was to compare and prove the correlation between fructosamine level and glycated albumin level at before, middle, and the end of Ramadhan fasting month in type 1 DM patients in the Dr. Soetomo Hospital. This study used an observational analytical design in 13 type 1 DM 9–18 year-old patients fasting Ramadhan. Fructosamine level examination used nitroblutetrazolium (NBT) with Cobas Integra. Glycated albumin value is calculated as a percentage of glycated albumin levels (using the enzymatic method) from total serum albumin level (using bromcresol purple), with Proline R-910. Results were analyzed by paired t-test statistics and Pearson's correlation. There were no significant differences between the mean of fructosamine level compared at middle and before (p=0.307), the end and before (p=0.249), middle and the end of Ramadhan fasting month (p=0.362). There were no significant differences between the mean of glycated albumin values compared at middle and before (p=0.478), the end and before (p=0.285), middle and the end of Ramadhan fasting month (p=0.247). There was a significant positive correlation

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between the fructosamine level and glycated albumin value at before (p=0.0001, r=0.952), middle (p=0.0001, r=0.948) and the end of Ramadhan fasting month (p=0.0001, r=0.963). Fructosamine level and glycated albumin can be used as parameters of glycemic control in patients with type 1 DM fasting Ramadhan.

Key words: Fructosamine, glycated albumin, type 1 diabetes mellitus patients, fasting Ramadhan

INTRODUCTION

Diabetes Mellitus (DM) type 1 is a glucose metabolic disorder characterized by chronic hyperglycemia due to pancreatic β cell damage, either by an idiopathic process or autoimmune process so that the insulin production is reduced or stopped. Ramadhan fasting can directly affect glycemic control in patients with type 1 DM because of changes in eating patterns, types of foods, therapeutic doses of insulin and daily lifestyle for the month. However, Ramadhan fasting does not cause complications in healthy people. Ramadhan fasting can also increase the risk of complications in patients with diabetes, such as hypoglycemia and hyperglycemia with or without KAD (ketoacidosis diabetic). Thus, good glycemic control in patients with type 1 diabetes who are having Ramadhan fasting is very important to prevent those complications.

Parameters that can be used to assess short-term glycemic control is blood glucose, fructosamine and glycated albumin for the medium-term glycemic control, as well as hemoglobin A1c (HbA1c) for the long-term glycemic control. Blood glucose examination, however, only illustrates instantaneous glucose level at the time of the examination conducted. HbA1c examination is used to describe only the mean blood glucose level over the previous 2–3 months, so it less able to describe glycemic control during Ramadhan fasting (for one month). Meanwhile, examination of fructosamine and glycated albumin is used to describe the mean blood glucose level over the previous 2–3 weeks, so it is more appropriate to use to describe glycemic control during Ramadhan fasting.

Examination of fructosamine level, moreover, describes total glycation of serum protein (absolute value), which can be affected by variations in serum protein levels, the large differences between individuals, as well as the effects of serum protein, other than albumin (such as globulin). This is in contrast with examination of glycated albumin values calculating the ratio of glycated albumin levels and total serum albumin, thus not influenced by variations in serum albumin levels, but less influenced by variations in individuals.

Therefore, this research aimed to compare both the levels of fructosamine and the values of glycated albumin during the middle and at the end of the Ramadhan fasting month to those before the Ramadhan fasting month. This research also aimed to analyze a correlation between the levels of fructosamine and the values of glycated albumin before, middle, and end of the Ramadhan fasting month in patients with type 1 diabetes in the Dr. Soetomo Hospital, Surabaya.

METHODS

This research used an observational analytical design in 13 patients with type 1 diabetes aged 9-18 years, who had been having Ramadhan fasting. The diagnosis of type 1 diabetes was made based on diagnosis criteria according to World Health Organization (WHO) in 2006 and International Society for Pediatric and Adolescent Diabetes (ISPAD). The criteria for the diagnosis of diabetes were a fasting blood glucose level of ≥126 mg/dL, a blood glucose level 2 hours after oral glucose tolerance test (OGTT) of ≥200 mg/dL, or patients with classic symptoms of hyperglycemia or hyperglycemia crisis with a random blood glucose level of ≥200 mg/dL or a HbA1c level of ≥6.5% (HbA1c <6.5% with the diagnosis of DM). The diagnosis of DM type 1, furthermore, were confirmed if there was one or more diabetes-associated autoantibodies, or the levels of C-peptide decreased. Diabetes-associated autoantibodies include glutamic acid dehydrogenase 65 autoantibodies (anti-GAD), tyrosine phosphate-like insulinoma antigen 2 (IA2), insulin autoantibodies (IAA), islet cell autoantibodies (ICA), as well as β cell-specific zinc transporter 8 autoantibodies (ZnT8) and one or more of these autoantibodies usually can be found in 85–90% of type 1 DM cases. The diagnosis then was established by supervisors of the Children Endocrinology in the Department of Pediatrics at the Dr. Soetomo Hospital. Ramadhan fasting is defined as a worship refrain or abstain from eating, drinking and all the things breaking the rules, starting at sunrise (dawn) to sunset characterized by prayer time of maghrib (iftar/breaking of the fast) during Ramadhan (for 1 month).

Next, the levels of fructosamine and the values of glycated albumin were examined three times, ie before, middle and end of the Ramadhan fasting month in 2015. The levels of fructosamine were examined using
nitroblutetrazolium (NBT) method with Cobas Integra instrument, while the values of glycated albumin were calculated as a percentage of glycated albumin (using an enzymatic method) towards the levels of total serum albumin (using bromcresol purple method) with R-910 Proline instrument. The results then were analyzed using paired t-test statistic and Pearson correlation test. The p value obtained was less than 0.05, indicating that there were significant differences or correlations.

RESULTS AND DISCUSSION

The number of the research samples aged 9–18 years with type 1 DM, who had been having Ramadhan fasting was 13 patients, consisting of 7 females (53.8%) and 6 males (46.2%). The age range of the samples was 9-18 years. The long period of the samples suffering from type 1 diabetes mellitus was 1-9 years. The range of HbA1c levels before the Ramadhan fasting month was 6.9 to 16%. All of these samples (100%) showed positive results of anti-GAD. All of these samples also showed lower levels of C-peptide than normal ones, except for one sample whose level of C-peptide in line with the reference value.

The levels of HbA1c in all of the research samples before the Ramadhan fasting month, moreover, were ≥6.5% (with a range of 6.9 to 16%), thus meeting the criteria for the diagnosis of DM. The diagnosis of type 1 diabetes for them was confirmed because the anti-GAD in all of those samples was positive with the decreased levels of C-peptide, lower than the normal ones. Nevertheless, there was a research sample with positive anti GAD and the level of C-peptide that was still in line with the reference value.

The levels of HbA1c in all of the research samples before the Ramadhan fasting month, moreover, were ≥6.5% (with a range of 6.9 to 16%), thus meeting the criteria for the diagnosis of DM. The diagnosis of type 1 diabetes mellitus was confirmed because the anti-GAD in all of those samples was positive with the decreased levels of C-peptide, lower than the normal ones. Nevertheless, there was a research sample with positive anti GAD and the level of C-peptide that was still in line with the reference value.

The levels of C-peptide increasing and reaching the normal limit usually can be found in patients with type 1 DM at clinical remission phase, called as “honeymoon period”. This phase usually occurs in 75% of patients with type 1 diabetes from 6 months after the diagnosis to a year or more. After this phase, the levels of C-peptide generally will decline gradually, and a significant reduction usually occurs 5-10 years after the diagnosis. A research conducted by Lombardo et al. in 2002 in Italy even showed that the honeymoon period occurred in 80% of patients with diabetes mellitus type 1, lasted more than one year after the diagnosis in 41.7% of patients, and lasted up to 2 years or more after the diagnosis in 16.4% of patients.12, 13 Similarly, the results of this research also showed that the research samples with the levels of C-peptide still in line the reference value were just diagnosed with type 1 diabetes for 1 year.

All of the research samples, furthermore, also had the levels of total serum albumin before, middle, and end of the Ramadhan fasting month in line with the reference value (3.5- 5.0 g/dL). A research conducted by Baker et al.13 indicated the results of fructosamine levels as glycemic control would be influenced by the levels of albumin protein, less than 3 g/dL. Another research conducted by Dominiczak et al.14 stated that the research subjects with hypoalbuminemia (a total serum albumin of <3.5 g/dL) had significant lower levels of fructosamine than the research subjects with normal serum albumin (3.5-5.0 g/dL).14, 15 In this research, the levels of total serum albumin in the research subjects before, middle and end of the Ramadhan fasting month were less than 3.5 g/dL, so they would not affect the results of the examination of fructosamine levels as medium-term glycemic control parameters.

In addition, the reference level of fructosamine was 205–285 mol/L. The levels of fructosamine in all of the samples before, middle and end of the Ramadhan fasting month are shown in Table 1. The results of the statistical analysis showed that there was no significant difference in the mean levels of fructosamine between in the middle of the Ramadhan fasting month and before the Ramadhan fasting month (p=0.307), between at the end of the Ramadhan fasting month and before the Ramadhan fasting month (p=0.249), as well as between at the end of the Ramadhan fasting month and in the middle of the Ramadhan fasting month (p=0.362).

The reference values for glycated albumin, moreover, was 11-16%. The values of glycated albumin in all of the research samples before, middle, and end of the Ramadhan fasting month are shown in

| Table 1. The levels of fructosamine before, middle and end of the Ramadhan fasting month |
|--------------------------------------|--------------------|------------------|----------------|
| **Fructosamine levels**              | **Range (µmol/L)** | **Mean (µmol/L)** | **Standard deviation (µmol/L)** |
| Before Ramadhan fasting month        | 254–757            | 519.3            | 148.4          |
| Middle of Ramadhan fasting month     | 267–679            | 488.5            | 107.2          |
| End of Ramadhan fasting month        | 267–679            | 474.4            | 123.1          |
The results of the statistical analysis showed that there was no significant difference in the mean values of glycated albumin between middle of the Ramadhan fasting month and before the Ramadhan fasting month \((p=0.478)\), between before the Ramadhan fasting month and at the end of the Ramadhan fasting month \((p=0.285)\), as well as between at the end of the Ramadhan fasting month and in the middle of the Ramadhan fasting month \((p=0.247)\).

The previous research conducted on 591 patients with type 2 diabetes who had been having Ramadhan fasting. The results of the previous research showed that there were no significant changes in fructosamine levels after Ramadhan fasting compared with before Ramadhan fasting on those patients with type 2 diabetes. In contrast, the results of several studies show that Ramadhan fasting on patients with type 2 diabetes may improve glycemic control than before the Ramadhan fasting. For instance, a research conducted by Gustaviani et al.\(^6\) on fructosamine levels of 24 patients with type 2 diabetes who had been having Ramadhan fasting showed a significant reduction in fructosamine levels after the Ramadhan fasting compared with before the Ramadhan fasting and the fructosamine levels after the Ramadhan fasting even were still higher than the normal ones.

Similar results were also shown by a research conducted by Mafauzy et al.\(^7\) on 22 patients with type 2 diabetes who had Ramadhan.\(^6,7\) Nevertheless, there still was no research using glycated albumin values as glycemic control parameters in patients with diabetes who still had Ramadhan fasting. As a result, it can not be compared with this research.

The results of the statistical analysis, furthermore, showed that there was a significant positive correlation between the levels of fructosamine and the values of glycated albumin before the Ramadhan fasting month with a \(p\) value of 0.0001 and a \(r\) value of 0.952 (see Figure 1), in the middle of the Ramadhan fasting month with a \(p\) value of 0.0001 and a \(r\) value of 0.948 (see Figure 2) and at the end of the Ramadhan fasting month (\(p=0.247\)).

Table 2. The values of glycated albumin before, middle and end of the Ramadhan fasting month

<table>
<thead>
<tr>
<th>The Values of Glycated Albumin</th>
<th>Range (%)</th>
<th>Mean (%)</th>
<th>Standard deviation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Ramadhan fasting month</td>
<td>11.76–47.32</td>
<td>33.33</td>
<td>10.13</td>
</tr>
<tr>
<td>Middle of Ramadhan fasting month</td>
<td>12.95–44.12</td>
<td>32.18</td>
<td>8.38</td>
</tr>
<tr>
<td>End of Ramadhan fasting month</td>
<td>13.21–43.93</td>
<td>30.95</td>
<td>8.57</td>
</tr>
</tbody>
</table>

Figure 1. Correlation of fructosamine levels and glycated albumin values before the Ramadhan fasting month.

Figure 2. Correlation of fructosamine levels and glycated albumin values in the middle of the Ramadhan fasting month.

Figure 3. Correlation of fructosamine levels and glycated albumin values at the end of the Ramadhan fasting month.

**CONCLUSION AND SUGGESTION**

Based on the results of this research, it may be concluded that there was a decrease in the mean levels of fructosamine and the mean values of glycated albumin from before, middle, to the end of the Ramadhan fasting month. However, there was no significant difference in the levels of fructosamine and the values of glycated albumin between both in the middle and at the end of the Ramadhan fasting month and before the Ramadhan fasting month on patients with...
month with a p value of 0.0001 and a r value of 0.963 (see Figure 3).

In addition, the results of this research had similar results with a research conducted by Beck et al.\(^\text{16}\) on 26 children and adolescents with type 1 diabetes who did not do Ramadhan fasting. The results of the previous research indicated that there was a positive correlation between fructosamine levels and glycated albumin values with a r value of 0.86. The results of the previous research also showed that the correlation between fructosamine levels and glycated albumin values was better than the correlation between both and HbA1c levels. The correlation of fructosamine levels and HbA1c levels showed r value of 0.56, while the correlation of glycated albumin values and HbA1c levels indicated r value of 0.57.\(^\text{16}\)

**CONCLUSION AND SUGGESTION**

Based on the results of this research, it may be concluded that there was a decrease in the mean levels of fructosamine and the mean values of glycated albumin from before, middle, to the end of the Ramadhan fasting month. However, there was no significant difference in the levels of fructosamine and the values of glycated albumin between both of in the middle and at the end of the Ramadhan fasting month and before the Ramadhan fasting month on patients with type 1 DM. There was a significant positive correlation between the levels of fructosamine and the values of glycated albumin in patients with type 1 diabetes before, middle, and end of the Ramadhan fasting month. As a result, both parameters can be used as glycemic control parameters in patients with type 1 diabetes who are fasting for Ramadhan. Further research is needed to be performed in a wider population.

**REFERENCES**