UDC 61

CORRELATION BETWEEN B-HYDROXYBUTYRATE (B-OHB) CONCENTRATION AND BICARBONATE LEVEL IN EARLY REGULATION OF BLOOD SUGAR ON DIABETIC KETOACIDOSIS PATIENTS IN RSUD DR. SAIFUL ANWAR MALANG, INDONESIA

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ABSTRACT
One of the acute complications of diabetes mellitus is diabetic ketoacidosis (DKA). DKA is characterized by glucose levels ≥14mmol/l (≥250mg/dL), acidosis pH <7.3, bicarbonate (HCO3) <18mEq/L, ketonemia, ketonuria. Currently in RSUD dr. Saiful Anwar, there is a β-hydroxybutyrate (β-OHB) examination by using a POCT ketone meter to facilitate clinical diagnosis and monitoring of DKA patients. The aim of this research is to analyze the correlation between the level of β-*OHB* and HCO_3 on initial insulin regulation in DKA patients. The research method used is observational analytic, cross-sectional in which the data is retrieved in time series. A total of 15 subjects are included in the inclusion criteria. Research shows that there is a correlation between HCO_3 and β-OHB levels after initial insulin regulation ($p = 0.012$ and $r = -0.628$). There were significant differences in the levels of HCO_3, β-OHB before and after insulin regulation with p-value of 0.001 and 0.015, respectively. There is a match between HCO_3 and β-OHB after insulin regulation ($p = 0.250$). It can be concluded that HCO_3 and β-OHB in the administration of initial insulin regulation correlate strongly. Thus, β-OHB can be used instead of HCO_3.

KEY WORDS
Diabetic ketoacidosis, β-hydroxybutyrate, bicarbonate, insulin.

Diabetes mellitus (DM) is a case often found in emergency departments (ED). The World Health Organization (WHO) predicts an increase in the number of people with diabetes mellitus in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030. On the other hand, the International Diabetes Federation predicts an increase in the number of people with DM in Indonesia from 9.1 million in 2014 to 14.1 million in 2035 (Soelistijo, 2015).

One of the acute complications of DM is diabetic ketoacidosis (DKA). Patients with blood sugar level above 250 mg/dL should be suspected of having hyperglycemia crisis (Kitabchi et al., 2009). DKA is characterized by hyperglycemia where serum glucose level is ≥ 14 mmol/l (≥ 250 mg/dL), acidosis with pH <7.3, serum bicarbonate levels <18 mEq/L, ketonemia or ketonuria (Manning et al., 2015). The condition of metabolic acidosis does not occur in patients with diabetic ketoacidosis but also in a variety of other conditions such as sepsis, alcoholic, liver disorders, kidney disorders. Thus, there are many things that can complicate arterial blood gas analysis for DKA patients (Rosen, 2017). In addition to using arterial blood gas analysis, RSUD dr. Saiful Anwar Malang (RSSA) now has an examination

of ketone objects using a POCT ketone meter to facilitate clinicians in diagnosing and monitoring DKA patients.

The study objective is to analyze the correlation between β-hydroxybutyrate (β-OHB) and bicarbonate (HCO_3) levels at the initial insulin regulation in diabetic ketoacidosis patients in RSSA.

METHODS OF RESEARCH

This research is observational analytic, cross-sectional in which the data is retrieved in time series to analyze the correlation between the levels of β-OHB and HCO3 at the initial blood sugar regulation in DKA patients in RSSA. Inclusion criteria were all patients aged ≥ 18 years, hyperglycemia with glucose levels> 250 mg/dL, metabolic acidosis blood pH <7.35 HCO_3 less than normal <18, anion gap more than normal> 10, positive ketone serum> 3mmol/L , normal potassium level as well agree to give informed consent.:Exclusion criteria include alcohol consumption, drug poisoning or chemical liquids (salicylate, methanol, toluene, ethylene glycol, phenformin, isoniazid, iron, paraldehyde), uremia, lactic acidosis (sepsis, liver disorders, kidney disorders), ketoacidosis (alcoholic patients, hunger), high-fat diet, fasting and starvation, lactation, ketogenic diet, referral DKA patients who have received insulin therapy. Arterial blood gas analysis (HCO_3) and serum β-OHB were done to all patients with inclusion criteria before therapy. Patients were managed in accordance with the DKA RSSA clinical pathway, after random blood sugar (RBS) fell 10% from the initial RBS value, the patient was taken back to analysis of arterial blood gas (HCO_3) and serum β-OHB.

Table 1 – Patient Characteristics

Characteristics	Total	(%)
Gender:		
Male	6	40
Female	9	60
Age Group:		
18 – 30	0	0
31 – 45	7	46.67
46 – 60	4	26.67
≥ 61	4	26.67

Table 2 – Central Size of Tendency

Variable	Average	SD	Median	Min	Max
HCO_3(before)	6.467	3.5310	4.600	2.4	13.3
HCO_3(after)	9.360	4.7933	9.400	3.7	21.7
β-OHB (before)	5.207	1.4385	5.300	3.1	7.0
β-OHB (after)	3.787	1.9075	4.200	0.4	7.0
RBS (before)	569.33	113.215	570.000	406	849
RBS (after)	446.80	111.489	431.000	283	729
DeltaRBS	122.53	38.139	114.000	75	190
DeltaTime	4.233	1.2010	4.200	2.6	6.9

Table 3 – Shapiro-Wilk distribution data

Variable	Statistics	dF	Sig
HCO_3(before)	0.891	15	0.069
HCO_3(after)	0.895	15	0.081
β-OHB (before)	0.901	15	0.100
β-OHB (after)	0.967	15	0.817
RBS (before)	0.948	15	0.500
RBS (after)	0.927	15	0.246
DeltaRBS	0.899	15	0.091
DeltaTime	0.961	15	0.705

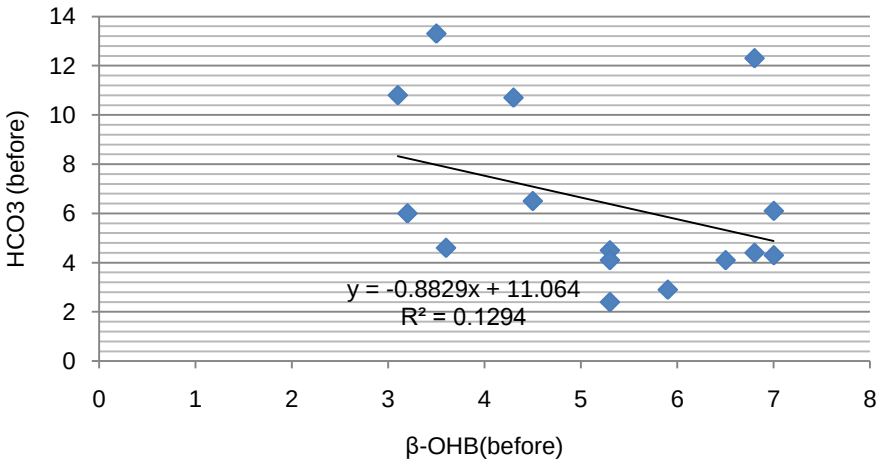

Figure 1 – Conform Linearity of HCO_3 - β-OHB before giving initial insulin regulation

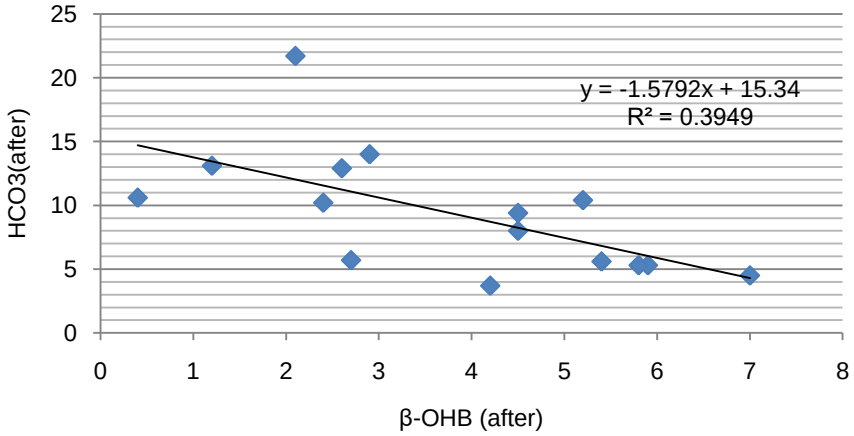

Figure 2 – Conform Linearity of HCO_3 - β-OHB after giving initial insulin regulation

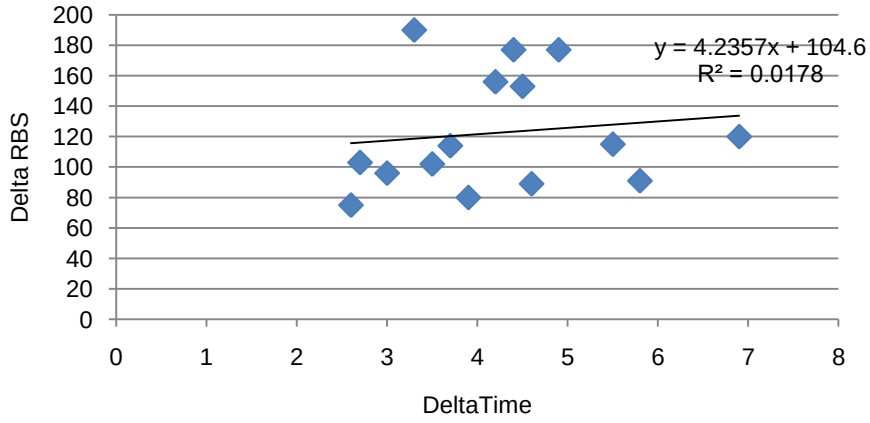

Figure 3 – Delta RBS and Delta Conform Linearity after the initial insulin regulation

Table 4 – Correlation of variables with Pearson test

Variable	r	p	N
HCO_3 - *β-OHB* (before)	0.360	0.188	15
HCO_3 - *β-OHB* (after)	0.628	0.012	15
Delta RBS – Delta Time	0.133	0.636	15

Table 5 – Analysis of differences in the levels of variables before and after initial administration of insulin with a paired T-test

Variable	p
HCO_3 before - after	0.001
β-OHB before - after	0.015
RBS before - after	0.000

Table 6 – The suitability analysis of changes in β-OHB and HCO_3 levels after administration of initial insulin was tested by the McNemar test

HCO_3	*β-OHB*	
	Good	Poor
Good	12	3
Poor	0	0

	HCO_3 - *β-OHB*
N	15
Sig	0.250[b]

RESULTS OF STUDY

There were 15 patients who met our inclusion criteria. Data were taken for 6 months from July to December 2018. In this study, the number of patients who were male reached 40% and 60% for female patients. The majority of patients were in the age group interval of 31-45, followed by the age group 46-60 and ≥ 61 of 26.67%.

All data had the fulfilled linearity test. Data distribution in this research is normal distribution because there is only small amount of data to be assessed using Saphiro-Wilk. Insignificant HCO_3 (before) data was found, and then the HCO_3 (before) data was transformed resulting in a normal distribution.

Based on the calculation of data analysis with the Pearson test, it was found that there was no significant correlation between HCO_3 and β-OHB before the initial regulation of insulin with a p-value = 0.188 and r = - 0.360. Meanwhile, between HCO_3 and β-OHB after the initial regulation of insulin calculation analysis using the Pearson test found a significant correlation with the p-value = 0.012 and r = - 0.628. Based on the calculation of data analysis with the Pearson test, it was found that there was no significant correlation between Delta RBS and Delta Time with p-value = 0.636 and r = 0.133.

Differences in the levels of HCO_3, β-OHB, RBS before and after insulin regulation using the Paired T-test had significant differences with p-value of 0.001, 0.015 and 0.000, respectively.

For the sake of analysis, numerical data of β-OHB and bicarbonate levels (HCO_3) were converted into categorical data in the form of good and poor categories both in the form of a decreasing in level of β-OHB or increasing in level of HCO_3 from the levels before administration of insulin. It was poor in the form of a constant β-OHB/HCO_3 level or an increase in β-OHB level or a decrease in HCO_3 level from the initial level before the administration of insulin. The suitability analysis of changes in β-OHB and HCO_3 levels after administration of initial insulin was tested by the McNemar test. was found to be compatible with p-value = 0.250.

DISCUSSION OF RESULTS

According to the multi-center research by Fritsch et.al in Europe, it was found that DKA was significantly higher than female patient. Meanwhile, epidemiological data in the United States showed that 50% of DKA patients were women with migrant background (Westerberg, 2013). Women have higher risk to get diabetes because they physically have the opportunity to experience an increase in body mass index putting them in the risk of becoming obese. People who get obese have bigger calorie input in which the pancreatic beta cells will

experience fatigue and they will not be able to produce adequate insulin in balancing the intake of calories in the body. In the end, the glucose level in the blood will increase (Kaban, 2007). Comparing to women, men tend to have more physical activities and they exercise routinely. This is because men have bigger physic and stronger muscles (Ortiz *et al.,* 2010).

The majority of patients were in the age group interval of 31-45 with a percentage of 46.67%, followed by the age group of 46-60 and ≥ 61 with a percentage of 26.67%. DKA is often found at younger people but it can occur at all ages and even at extreme ages. The research on 4807 DKA episodes obtained the frequency of > 70 years old was 14%, age 51 - 70 years old was 23%, age 30-50 years old was 27%, age <30 years old was 36% (Weterberg, 2013).

At the earlier stage of DKA before therapy, the patient is usually in the state of metabolic acidosis caused by the process of ketogenesis due to lack of insulin. The research data showed that HCO_3 and β-OHB before administration of insulin were correlated but not significant. The purpose of therapy on DKA patient is to decrease the ketogenesis. The decrease in ketogenesis will eventually be followed by resolution of acidosis conditions as the result (Wallace & Matthews, 2004).

Other studies have also found that patients with DKA had a significant correlation between β-OHB and bicarbonate, decreased level of β-OHB followed by an increase in bicarbonate level with r = −0, 24139 and p = 0.0161.:This research shows that capillary ketonemia was directly related to the severity of acidosis and serum bicarbonate level as well as pH during the DKA therapy. This is also in accordance with the observations of other authors. Measurement of capillary ketone level allows an immediate assessment of a patient's metabolic conditions. In addition, it is also the main diagnostic parameter for starting treatment for ketoacidosis decompensation (Rodriguez-Merchan et al., 2011).:This is in line with data from the research where it shows that HCO_3 and β-OHB have a correlation after administration of insulin.

Based on the analysis research data, the differences in the levels of HCO_3, β-OHB, RBS before and after insulin regulation using the Paired T-test had significant differences with p-value = < 0.05. The function of insulin includes energy storage and metabolism especially in liver tissue, adipose, and skeletal muscle. Insulin works in the liver for glucose uptake and it is converted to glycogen and it also inhibits the damage to glycogen (glycogenolysis) and suppresses gluconeogenesis. The effect of this mechanism is to store the glucose in the form of glycogen. Decreasing insulin level results in hyperglycemia. When pancreatic beta cells are present, hyperglycemia can trigger an increase in insulin and return to normal glucose concentration. Along with the process of the disease, hyperglycemia can no longer trigger an increase in insulin activity. Although there is an increase in intravascular glucose, the absence of insulin will make the cell unable to use glucose as a fuel source.:The body responds to this by breaking down proteins and adipose to produce intracellular fuels that can be used. The body loses the normal physiological effects of insulin causing secretion of catabolic (counterregulatory) hormones and resulting in hyperglycemia and ketonemia (Jalili & Niroomand, 2016). The administration of insulin is expected to reduce ketogenesis so that the metabolic acidosis in patients will improve. This is in line with research results in which the level of HCO_3, β-OHB, RBS before and after initial insulin regulation had significant differences (p = <0.05).

The research data obtained through the calculation of data analysis using the Pearson test found that there was no correlation between delta RBS and delta time with p-value = 0.636. In this research, before the administration of insulin the initial levels of β-hydroxybutyrate (β-OHB), bicarbonate (HCO_3) and RBS were varied and not at the same value. In addition, many factors influence the patient's condition. It has been mentioned in the literature review that metabolic acidosis and ketogenesis conditions can occur in patients other than DKA. In this research, exclusion factor was narrowed down to facilitate data retrieval.

Based on the data of research conformity analysis using McNemar test it was obtained p value> 0.05 which means there was no difference (accordingly) between changes in levels of β-hydroxybutyrate (β-OHB) and bicarbonate levels (HCO_3) after initial regulation of insulin.

This is in accordance with the theory that giving insulin will cause a decrease in ketogenesis which will be followed by decreased metabolic acidosis as a result (Wallace & Matthews, 2004). The research results showed that the mean value of β-hydroxybutyrate (β-OHB) before insulin regulation was 5.207 and it had improved after the administration mean insulin β-hydroxybutyrate (β-OHB) to 3.787. This corresponds to the value of bicarbonate (HCO_3) which also experience improvement from 6.467 (before mean HCO_3) to 9.360 (after HCO_3).

CONCLUSION

There is a significant correlation between the levels of HCO3 and *β-OHB* after the administration of initial regulation of insulin. There is a significant difference between the levels of β-*OHB,* HCO_3, RBS before and after the regulation of insulin in patients with diabetic ketoacidosis. There is suitability between the levels of HCO_3 and *β-OHB* after the administration of initial regulation of insulin. Examination of β-hydroxybutyrate capillary blood ketones (β-OHB) is recommended for diagnostic and therapeutic monitoring in patients with diabetic ketoacidosis. It is expected that the research will encourage the patients with hyperglycemia to come to the emergency room at RSUD dr. Saiful Anwar for further examination. Measurement of capillary blood ketones provides an increase in DKA management. In an emergency, the retrieval technique is easier to use because it is less invasive than measurements of arterial blood gas analysis. The results can be obtained faster and it allows for monitoring every hour of the patient's condition. Measurement of capillary blood ketones is also more cost efficient compared to arterial blood gas analysis. Hence, measuring capillary blood ketones reduce the cost of treatment, shorten the time of examination and increase the comfort of patients. β-OHB can be used to diagnose and monitor DKA therapy.

In this research, the exclusion factor was narrowed down due to the difficulty in data collection. This research has also obtained various values of *β-OHB*, HCO_3, and RBS when patients came. In the future, it is suggested to do further research by using appropriate exclusion criteria.

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