Severity of pediatrics ketoacidosis before and during COVID-19 pandemic

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SEVERITY OF PEDIATRIC KETOACIDOSIS BEFORE AND DURING COVID-19 PANDEMIC

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LIST OF ABBREVIATIONS

ADA – American Diabetes Association

COVID-19 – Coronavirus disease-19

DKA – Diabetic Ketoacidosis

DM – Diabetes Mellitus

ED – Emergency Department

ER – Endoplasmatic reticulum

FPG – Fasting plasma glucose

GDM – Gestational Diabetes Mellitus

HbA1c – Glycated hemoglobin A1c

IDDM – Insulin-dependent Diabetes Mellitus

MAD – Median absolute deviation

MODY – Maturity onset Diabetes of the young

NIDDM – Non-insulin-dependent Diabetes Mellitus

OGTT – Oral glucose tolerance testing

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

WHO – World Health Organization

1. INTRODUCTION

Roughly with the declared start of the new Coronavirus disease-19 (COVID-19) pandemic on March 11th, 2020, there were major changes in everyday life, starting with prophylactic hygiene measurements, self-isolation, lockdowns and new psychological attitude and social thinking (1). Quickly it became obvious, that this new challenge did not only affect everyday activities, but also exceptional, health related situations apart from an active COVID-19 infection.

When the pandemic started, physicians and scientists saw a reduced number of patients with non-COVID related issues seeking the consultation of health care workers (2). The reason for that is manifold, including closure of ambulant centers for consultation, or patients actively cancelling their scheduled appointments (3). But it also could be observed that the numbers of emergency patients in the emergency department (ED) drastically declined (4). In many specialized fields in medicine an increased level of severity of a newly diagnosed disease can be seen upon first time presentation of a patient (5). This is suspected to have two major reasons. The first one is aggravation of a disease due to an ongoing or previous COVID-19 disease (6, 7). The second reason is the noticeable delay in patient presentation with patients trying to avoid hospitalization due to their expectation of a higher risk for acquiring a COVID-19 infection during medical treatment (8).

Research indicates, that might be true for Diabetes Mellitus Type I (T1DM) as well, both in frequency of appearance, as well as in severity (9–11). This might be of special importance, since first time diagnosis of T1DM is often made not in an early state, but instead in about 40% of cases of new onset T1DM it is diagnosed, when the patient presents at the emergency department in the state of Diabetic Ketoacidosis (DKA) (12). In Germany this percentage is estimated to be between 16% and 26.3% (13). The aim of this research is to find out, if an aggravated severity of DKA since the beginning of the pandemic holds true for the REGIOMED hospital Coburg as well.

1.1. Diabetes Mellitus

Diabetes Mellitus (DM) is a group of disorders of the glucose metabolism, leading to elevated levels of blood glucose in affected patients. There are several diseases with different pathophysiologic and genetic ground in the broad spectrum of DM and therefore can be treated with different measures.

According to the American Diabetes Association (ADA) there are four categories for classification of Diabetes Mellitus (14):

1. Type I Diabetes Mellitus
2. Type II Diabetes Mellitus (T2DM)
3. Gestational Diabetes Mellitus (GDM)
4. Specific types of Diabetes due to other causes

To categorize the different types of DM the underlying pathophysiology is relevant. Previous classifications according to age or treatment modality and classifications into insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent Diabetes Mellitus (NIDDM) are not used anymore due to their limitations.
DM can also occur in patients with other underlying diseases, mostly endocrinopathies affecting insulin action, like Cushing's disease or insulin secretion, like chronic pancreatitis (15).

1.2. Glucose Homeostasis

In the healthy patient there is always a tightly regulated level of glucose in the blood. In the fasting state the blood glucose is 80-90 mg/dl, within an hour after a meal the values are between 120-140 mg/dl. Two hours after consumption of carbohydrates the glucose level is restored to base level. Several hormones and organs prevent hypoglycemia, which might lead to slowness of thought, weakness, seizures, coma and death. Additionally, a hyperglycemia, which might lead to either short term or long term consequences, is prevented (16).

Chronic consequences in DM from permanently elevated blood glucose include atherosclerosis of large and middle-sized arteries (macrovascular disease), increasing the risk of suffering from stroke, myocardial infarction and peripheral arterial disease. Damage to small blood vessels (microvascular disease) leads to peripheral neuropathy and retinal and kidney damage (17).

The only blood glucose lowering hormone produced by the human body is insulin, produced by the pancreas. The pancreas consists mainly of two tissues, the pancreatic acini and the islets of Langerhans. The acini secrete digestive juices via the main pancreatic duct into the duodenum. The islets of Langerhans on the other side consist mainly of alpha, beta and delta cells. Alpha cells make up 25% of the islet cells and are responsible for glucagon production. Glucagon triggers glycogenolysis and gluconeogenesis from amino acids in order to increase blood glucose. Delta cells produce somatostatin, while beta cells, being 60% of the islet cells,

are producing insulin and amylin. Somatostatins effect in glucose homeostasis is the inhibition of both, glucagon and Insulin secretion (16, 18).

Initially the pancreatic β-cells produce a 86-amino-acid chain precursor of insulin, the so called preproinsulin, which is subsequently cleaved into proinsulin. Proinsulin is the prohormone to insulin and consists of an insulin chain, as well as its incapacitating C-peptide. The final step to formation of the active insulin is proteolytic removal of the C-peptide when insulin secretion is needed. Both of the structures are secreted into the blood via exocytosis (15, 16, 18, 19).

The proteolytic activation and release of insulin into the bloodstream is mainly triggered by an increased level of glucose in the blood. An increased influx of glucose into the β-cells through GLUT-2 transporters leads to phosphorylation and subsequent glycolysis of the newly formed glucose-6-phosphate. The resulting ATP causes depolarization of the cellular membrane by binding to specialized K^+ channels. As a consequence, voltage dependent Ca^+ channels open and the influx of Ca^+ leads to co-secretion of insulin and C-peptide. After secretion, when first passing through the liver 50% of the Insulin is removed from circulation. Insulins overall short half life time of six minutes allows rapid clearing from the organism (15, 16, 18).

Insulins secretion can be potentiated by other factors, incretins like GLP-1 and GIP. They increase the insulin response in beta cells to glucose to nearly double the secretion when blood glucose is elevated. This also shows with amino acid consumption, which in combination nearly doubles the insulin response of the beta cells, while consumed alone they only cause slight secretion (15, 16, 18).

The secreted insulin exerts its manifold effects on storing carbohydrates as glycogen, carbohydrate, protein and fat metabolism after binding to the insulin receptors. More than ¾ of the cells in the human body respond to insulin exposure with increased glucose uptake, foremost muscle cells and fat cells. If the muscles are exercised in the time following a meal, the muscle will use the abundance of glucose as an energy source. If the glucose cannot be used for muscle movement, it will be stored in the form of muscle glycogen (16).

In the liver insulin causes rapid storage of glucose by trapping glucose in the liver by triggering phosphorylation and initiating conversion into glycogen for later maintenance of blood glucose level. This affects around 60% of glucose in a meal. If there is more glucose available, then the liver is able to store in form of glycogen, the excess is converted into fatty acids. Furthermore, the abundance of insulin in the liver exerts its influence on the enzymes responsible for glycogenolysis, preventing them from converting the storage form of glycogen

back into glucose. Gluconeogenesis also gets inhibited via effect on liver enzymes and decreased release of substrate, amino acids, from muscles (16).

If the available amount of glucose exceeds the livers storage capacity for glycogen, the excess glucose gets converted into fatty acids. Those fatty acids are used to form triglycerides, which are released into the blood and transported bound to lipoproteins. Upon arrival on the fat cells, the activating influence of insulin is required for enzymes to cleave the triglycerides into fatty acids, which are able to penetrate the adipocytes cell wall. Inside the fat cell reconversion into triglycerides is again necessary for storage. The necessary glycerol for that is synthetized inside the adipocyte from glucose, whose entry into the cell was promoted by insulin. Furthermore, insulin maintains the stored triglycerides by inhibiting their hydrolysis (16).

In contrast, between episodes of eating, the blood glucose levels fall and consequently the secretion of insulin from the pancreatic β-cells is lowered. The resulting reduction of available insulin leads to a stop of the previous processes for the storage of glucose and glycogen gets reversed into glucose, which gets released back into the blood (16).

In case of low blood glucose, the body does not only react with decreased insulin secretion, but actively takes actions to increase the glucose levels. For one this can be achieved in stressful situations by epinephrine, which causes glycogenolysis in the liver and release of fatty acids from the adipocytes, as an alternative source of energy. After several hours of growth hormone and cortisol influence the glucose usage of the bodies cells is reduced in favor of fat usage (16).

A way faster and very potent hormone the body uses to elevate the blood glucose is glucagon. Glucagon secretion is an answer to blood glucose levels falling underneath fasting levels. Consequently, there is reduced secretion with rising glucose levels. Glucagon quickly leads to glycogenolysis of the vast glycogen storage in the hepatocytes. There it also encourages gluconeogenesis. For this it stimulates the livers uptake of amino acids, which function as substrate for new formation of glucose. Following the consumption of protein rich food, the resulting amino acid load also stimulates glucagon secretion, the glucagon increasing their transformation into glucose. In addition, it inhibits storage of fat in the liver, thereby increasing the circulating amount of alternative energy sources (16, 18).

Somatostatin is a somewhat paradoxically appearing hormone from the delta cells, since it inhibits both, insulin and glucagon. It is secreted in response to elevated blood glucose, amino acids and fatty acids. Apart from its effects on insulin and glucagon it also slows GI motility and absorption from the GI tract. It is proposed, that this intents to prolong the availability of nutrients and also slow their usage, thereby optimizing usage of ingested foodstuff (16, 18).

One of the last two pancreatic hormones influencing glucose homeostasis is Amylin. This hormone is barely understood; it is secreted together with insulin and also inhibits insulin secretion while causing insulin resistance in skeletal muscle. The last hormone is the pancreatic polypeptide, which is even less understood and causes a feeling of satiety and has influence on digestive processes (16, 20).

1.3. Diabetes Mellitus Type I

The diagnosis of DM without determination of the underlying pathology and therefore without classification is made according to the following criteria of patient presentation, Fasting Plasma Glucose (FPG), Oral Glucose Tolerance Testing (OGTT) and glycated hemoglobin A1c (HbA1c). The ADA defines a FPG of over 126 mg/dl as a diagnostic criteria for DM. FPG is the measurement of plasma glucose after an at least 8 hours long fasting period with no other intake than water. In the OGTT the patients blood glucose is measured after a fasting period, before he drinks a solution of 75g of glucose dissolved in 300ml of water. A blood glucose level of 200 mg/dl or higher after a 2-hour waiting period signals a manifested DM. A measurement of a HbA1c value of 6.5% or more also justifies diagnosis of DM. All three tests can both be used for screening and diagnosis. The OGTT diagnoses more cases of DM, than can be found with FPG and HbA1c testing. The test results of the three tests do not necessarily show perfect concordance. The results of FPG and OGTT should be held in a higher account than HbA1c (14, 17, 21, 22).

Healthy results of FPG should be under 100 mg/dl, while 2 hours after ingestion of the glucose solution the blood sugar level in the OGTT should be less than 140 mg/dl. In a healthy person the HbA1c is defined below 5.7% glycation. The possible results between the healthy values and those diagnostic for DM define a prediabetic state, a state which is associated with increased risk of suffering from cardiovascular diseases and possible progression to fulminant DM (17, 18, 21).

In T1DM the underlying pathology is an immune-mediated destruction of pancreatic beta cells through T-lymphocytes. This usually leads to complete – or nearly complete – lack of insulin secretion. For symptoms to develop up to 80% of beta cells have to be destroyed, keeping the patient symptom free for a long period of time, with a sudden onset. The rest of the pancreatic cells is not affected. The cause for islet cell destruction is multifactorial, has a genetic predisposition and usually cannot be determined (15, 16, 18, 23).

Newly discovered T1DM is not as common as T2DM and affects mainly the age groups of five to seven years and teenagers. The incidence of T1DM is rising globally. To differentiate Type I Diabetes from Type II Diabetes the laboratory search for antibodies against pancreatic tissue can be helpful in the early stages of the disease. Islet cell antibodies, beta-zinc transporter, glutamic decarboxylase, tyrosine phosphatase-IA2 protein are antibodies which each can be found in 50% of newly diagnosed T1DM patients. Generally in 60%-80% of patients with new manifestations some kind of antibodies can be found (18).

Apart from antibodies specific genes regarding the major histocompatibility complex can be found, which are not diagnostic and widespread in the healthy population, but increase the susceptibility to T1DM. Certain loci for HLA-DQ and HLA-DR are the class II molecules providing the biggest risk factor, HLA-DP also has associations with T1DM. Still the genetic predisposition only leads to 50% of identical twins being affected and the vast majority of people with these genes never develop Diabetes. Apart from HLA-associated genes, there are other loci which increase the risk for T1DM, these include the genes for insulin itself, as well as changes in the genetic code for receptors having influence on excessive T-cell response (17, 18).

Viral infections are thought to be a possible trigger of T1DM autoantibodies; namely coxsackievirus infections and congenital rubeola, as well as mumps, cytomegaly and mononucleosis infectiosa are suspected (17, 18, 23).

The lack of insulin due to destroyed beta cells leads to increased glycogenolysis, increased gluconeogenesis and increased lipolysis. Both increased gluconeogenesis and glycogenolysis lead to hyperglycemia which exceeds resorption capacities of the kidneys. Glucosuria is present when blood glucose is over 180 mg/dl. Osmotic diuresis with consequent loss of water and electrolytes, especially sodium and potassium in the huge amount of urine results. Consequently, the patients experience excessive thirst and show polydipsia. Potassium excretion is accelerated when dehydration begins, due to the resulting action of the renin-angiotensin system. The lipolysis in the fat tissue leads to free fatty acids and ketone bodies in the blood. The lack of insulin inhibits anabolic processes and triggers catabolism of proteins. The musculature can only take up tiny amounts of glucose without insulin and depends on metabolism of the abundant free fatty acids. To compete with the catabolism and resulting weight loss, patients develop an increased appetite and ingest more foodstuffs than usual. This does not stop the weight loss. In children it leads to failure to thrive (15, 17, 18, 23).

The metabolic stress on the body and the loss of water and electrolytes in the urine increases the secretion of stress hormones. What is intended for low energy states and as a protection mechanism in starvation with secretion of epinephrine, cortisol, glucagon and growth hormone leads to a worsening of the situation. A possible remaining secretion of insulin and its effect on tissues are decreased, glycogenolysis and gluconeogenesis on the other hand are promoted. So are lipolysis and ketogenesis (16–18, 24).

1.4. Diabetic Ketoacidosis

Besides the classic triad of complication of T1DM, polydipsia, polyuria and polyphagia due to insufficient insulin action, the most severe acute complication is the DKA. Being a consequence of inappropriate insulin effect, DKA occurs mainly in Type 1 diabetics. Nevertheless, it can also occur in Type 2 diabetics when there is relative lack of insulin, for example during infections or after great trauma, when stress hormones diminish insulins effect, or insufficient insulin application (17, 18).

Ketosis itself is not necessarily a sign of diabetes or impeding ketoacidosis; in states of starvation or changing to a no-carbohydrate-dieting it is the bodies physiologic reaction to rely on fat metabolism. In these cases, the body is usually capable of insulin production and even small amounts of insulin are enough to regulate muscle catabolism and lipolysis, preventing wasting and uninhibited production of free fatty acids and ketone bodies in the liver. Furthermore, it enables the body to better use ketone bodies in the periphery. Acidosis and overt ketosis are therefore prevented (16, 17).

The DKA is characterized by the lowering of the pH and loss of bicarbonates due to increasing presence of ketone bodies. The ketogenesis triggered by lack of insulin mainly yields the ketone bodies β-hydroxybutyrate, acetoacetate and acetone. Marked hyperglycemia with averages of 500 mg/dl is present (16–18, 24).

Patients present lethargic with an altered mental status, nausea, vomiting and dehydration. The accumulated ketoacids cause abdominal pain. Comatose state is only observed in 10% of patients with DKA. Neither dehydration, nor the acidosis or ketosis are the reason for a comatose state, coma in DKA is caused by hyperosmolarity. Dehydration is noticeable, but the real dehydration often is obscured, since intravascular volume gets maintained by intracellular dehydration. The same holds true regarding loss of potassium. Extracellular potassium can be normal, while intracellular potassium is strongly depleted due to acidotic shift

of potassium outside of the cell. This provides a huge risk factor when lowering blood glucose, due to insulins effect to increase potassium influx into the cell during therapy. Additionally, rehydration increases kidney perfusion which leads to more potassium excretion due to the ongoing aldosterone effect, the combination leading to severe hypokalemia (16, 17, 23, 24).

With increasing severity of the acidosis respiratory compensation and therefore decreasing CO2 values in the blood can be observed. Roughly with a pH of 7.2 a typical breathing pattern starts to show; Kussmaul breathing. This is characterized by very deep breathing with a rapid frequency. Even though acetone is only produced in small quantities, it can be smelled in the patient breath early in the course of the disease (17, 23, 24).

2. OBJECTIVES

The aim of our study was to analyze, if there is a difference in severity of DKA comparing the pediatric patients presenting with this disorder before the COVID-19 pandemic.

We hypothesized that the patients presentation with DKA are more severe during the pandemic and that the average state of the patient is worse than the pre-pandemic group. The patients free from COVID-19 influence were expected to have significantly better laboratory values. Additionally, we expected to see higher blood glucose and HbA1c levels in the COVID-19 era.

3. PATIENTS & METHODS

3.1. Ethical approval

The Plan of Research was approved by the Institutional Review Board of the Medical School REGIOMED Coburg on March 18th, 2022.

3.2. Study design

This retrospective observational study was conducted at the pediatric department of the REGIOMED hospital Coburg, teaching hospital of the Medical School REGIOMED, University of Split, School of Medicine. We studied the whole population of pediatric patients presenting with DKA. Medical data is available in digitalized form, the databank is accessible via the Orbis system (Orbis®, Dedalus Healthcare, Bonn, Germany) used by REGIOMED.

The main outcome of this study is the assessment of the severity of DKA, before COVID-19 pandemic, compared with the severity during the pandemic. As secondary outcomes we investigate, if the laboratory parameters for pH, bicarbonates, blood glucose and HbA1c have worsened during the pandemic. Subgroups according to gender are studied for the same parameters as well.

We included the whole population of patients aged less than 18 years old, presenting with diabetic ketoacidosis in the REGIOMED hospital Coburg.

Our exclusion criteria are defined as treatment of the ketoacidosis before first in house blood sampling, multiple episodes of DKA in one calendric year, diagnosed eating disorder before or after investigated period, and alcoholic ketoacidosis.

For the time period before the beginning of the COVID-19 pandemic (Group A) the years from 01.01.2012 – 31.12.2019 were chosen. The sample for the pandemic group (Group B) was selected from the official beginning of pandemic situation by the World Health Organization (WHO) on 11th March 2020 – 11th March 2022. The period in between was excluded, to prevent inclusion of behavioral changes due to the first available information from 31st December 2019 on regarding a new pneumonia spreading in and out of Wuhan (25). The first lockdown period in Germany was declared from 22.03.2020 – 04.05.2020. On the 2nd of November a “lockdown light” was declared, to which successively more restrictions were added. It evolved into a hard lockdown on January 6th which ended in May 2021 (26, 27).

3.3. Data collection

For the blood gas analysis the machine used was a ABL800flex (Radiometer GmbH, Krefeld, Germany). We did not differentiate between capillary blood and venous blood for the

first blood gas analysis regarding pH, bicarbonates or base excess. These can be interchanged while still yielding precise results (28–30).

Blood glucose, HbA1c, sodium and chloride were taken from the first laboratory blood sampling.

We collected the patients data for Gender, Age at presentation, Year of presentation, pH, Bicarbonate, Base Excess, Blood Glucose, HbA1c, Sodium, Chloride, Urine Acetone, Blood Acetone.

3.4. Measure of severity

Assessment of severity was done according to the current S3 guideline for the therapy of DM, see Table 1 valid for Germany at the time of conduction. Mild ketoacidosis is defined if pH is <7.3 and bicarbonate is <15mmol/L while moderate ketoacidosis is defined with pH <7.2 and bicarbonate <10mmol/L. The severe ketoacidosis comprises all results with pH <7.1 and bicarbonate <5mmol/L (13).

When the pH and the bicarbonate values could not be grouped in the same category of severity, we used the pH value alone to determine the grade of severity.

Table 1. Classification of diabetic ketoacidosis

Parameter	**Grade of severity**		
	Mild	Moderate	Severe
pH	<7.3	≤7.2	≤7.1
Bicarbonate	<15 mmol/l	≤10 mmol/l	≤5 mmol/l

Source: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. [Internet]. Berlin: AWMF. S3-Leitlinie Therapie des Typ-1-Diabetes; 2018 Mar 28 [cited 2022 Jun 18]. Available from: URL: https://www.awmf.org/uploads/tx_szleitlinien/057-013l_S3-Therapie-Typ-1-Diabetes_2018-08.pdf.

3.5. Sample

In the period from 1st January 2012 to 31st December 2019, 76 pediatric patients got diagnosed with DKA in the department of pediatrics in the REGIOMED hospital Coburg. In 12 cases the blood gas analysis was not done with capillary blood, but with venous blood, these were used without difference from capillary analysis.

Of those original 76 presentations with the diagnosis of DKA 27 had to be excluded. Nine due to a history of more than one ketoacidosis in the year of presentation. Furthermore three patients were relocated from hospitals in the upper Franconian area without a pediatric ward and had to be excluded since the respective clinics already started the treatment, one more patient already initiated insulin treatment at home by himself. Another patient had to be excluded due to a diagnosed eating disorder. In 11 cases the digitalized data was incomplete regarding the main outcomes, pH and bicarbonates, for those the paperwork was taken from REGIOMED archives to fill in the data, one patient file could not be found, therefore this case had to be excluded due to missing data.

12 patients could not be classified according to the current S3 guidelines, since their pH/bicarbonate values were above those qualifying for a mild ketoacidosis in our used guideline. They were excluded as well. In some literature DKA is categorized with other values where a presentation with a pH of 7.35 already qualifies for mild ketoacidosis, so would many of the afore mentioned patients (24). This left us with 49 cases in group A we could assess for severity.

HbA1c Data was missing in one case, so was a glucose value, sodium/chloride values were missing in 13 cases. 48, 48 and 39 cases were available respectively after removal of disqualified cases.

From 11th of March 2020 to 11th March 2022 the diagnosis “diabetic ketoacidosis” was made in 26 patients. In four cases we had to fill in incompletely digitalized data regarding pH and bicarbonates with the information from the archived paperwork. Six sets of data had more than one episode of DKA per year and had to be excluded. In this group also one patient had to be excluded due to previous treatment, who was referred from another hospital. Seven cases could not be classified according to the used S3 guideline and were excluded. In group B we therefore could assess 12 cases regarding severity.

In 2020-2022 data for glucose and HbA1c was available for all 12 included cases, five times data for chloride was missing.

After deduction of disqualified cases 12 sets of data were usable for glucose and HbA1c and seven times for the anion gap.

3.6. Statistical analysis

For processing our collected Data JASP Version 0.16.3 (JASP Team, University of Amsterdam, Amsterdam, The Netherlands) and Microsoft® Excel® for Microsoft 365, Version 2206 (Microsoft Corporation, Redmond, WA, USA) is used.

Distribution of normality is calculated with Shapiro-Wilk test. For our hypothesis, that DKA is more severe in group B we use the Mann-Whitney U test due to a deviation from normality, so we do when comparing HbA1c values, pH, bicarbonates and glucose are compared with independent sample t-test. When observing these values according to gender the appropriate test according to distribution of normality is taken.

To test, if the equal variance assumption can be confirmed, Levenes test is used. Due to unequal variances in the female bicarbonate values, Welchs test is used here.

For our study the statistical significance is determined as $P<0.05$.

4. RESULTS

4.1. Severity of DKA

In our sample in 17/49 cases (34.69%) in group A the patients presented with severe ketoacidosis. In group B the incidence of severe form was 5/12 cases (41.66%). The distribution of severity can be seen in Figure 1.

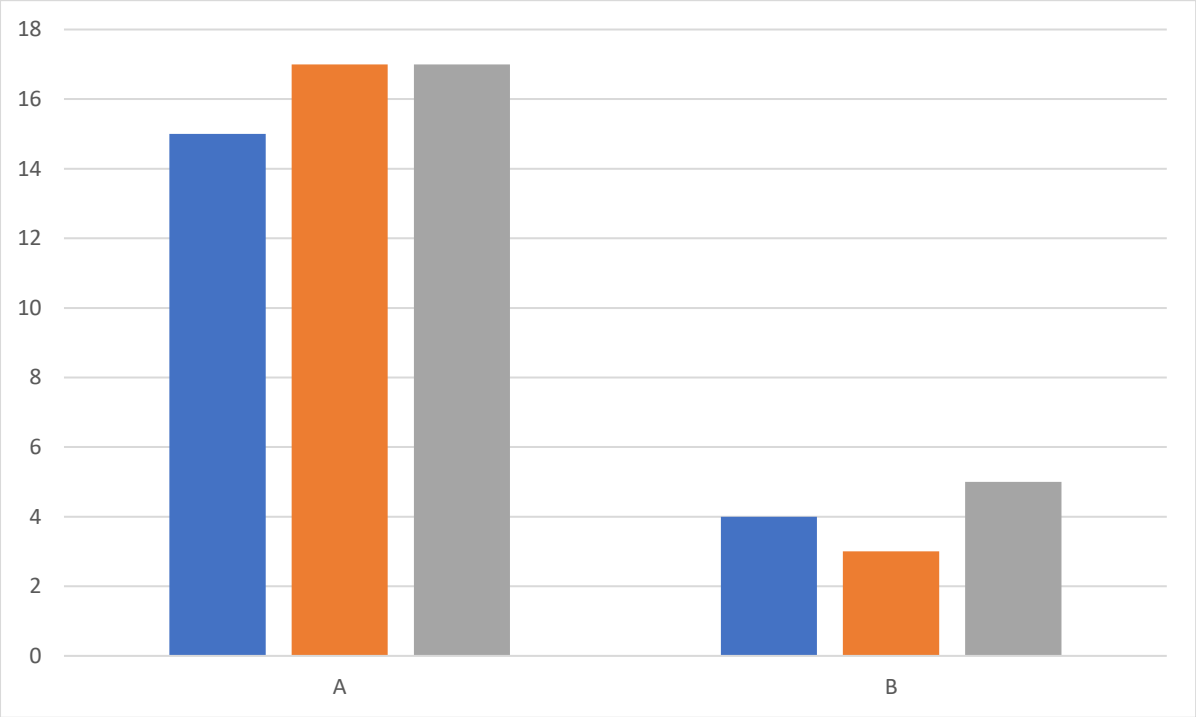


Figure 1. Distribution of severity
Legend
- Mild ketoacidosis
- Moderate ketoacidosis
- Severe ketoacidosis

As shown in Table 2 the distribution of severity of DKA shows deviation from normality when testing with Shapiro-Wilk test with $P<0.05$ in both groups. Both groups, group A (49 participants) and group B (12 participants) present with a median of 2 and a median absolute deviation (MAD) of 1 in both groups.

The Mann Whitney U test in Table 3 shows no statistically significant difference in the classification of severity ($P=0.435$).

When comparing the distribution in groups A and B divided for gender, the severity is not normally distributed in any subgroup with Shapiro-Wilk $P< 0.05$ for both genders in both groups. Comparing the severity between females in group A and B it can be seen, that the female median for severity in group A is 2 with a median absolute deviation of 1, in group B the female samples present with a median of 1 and a MAD of 0 with a very low number of only

seven cases. In the male cases in group A the median is 2 with a MAD of 1 as well. In group B the male cases show a median of 3 and a MAD of 0 with five cases as well (Table 2).

When we ran a Mann-Whitney U test to compare the severity of the females in group A with the severity of those females in group B no significant difference with *P*= 0.957 could be seen. This was also done with the male cases in group A compared to group B, here the Mann-Whitney U test showed a significant increase in severity in the pandemic group, with *P*=0.031, see Table 3.

Table 2. Comparison of Severity

	Severity		**Severity female**		**Severity male**	
	A	**B**	**A**	**B**	**A**	**B**
N†	49	12	20	7	29	5
Median	2.000	2.000	2.000	1.000	2.000	3.000
Mean	2.041	2.083	2.350	1.714	1.828	2.600
Std. Deviation	0.815	0.900	0.671	0.951	0.848	0.548
MAD	1.000	1.000	1.000	0.000	1.000	0.000
Shapiro-Wilk	0.796	0.781	0.773	0.732	0.769	0.684
P-value of Shapiro-Wilk	< .001	0.006	< .001	0.008	< .001	0.006
Minimum	1.000	1.000	1.000	1.000	1.000	2.000
Maximum	3.000	3.000	3.000	3.000	3.000	3.000
25th percentile	1.000	1.000	2.000	1.000	1.000	2.000
50th percentile	2.000	2.000	2.000	1.000	2.000	3.000
75th percentile	3.000	3.000	3.000	2.500	3.000	3.000

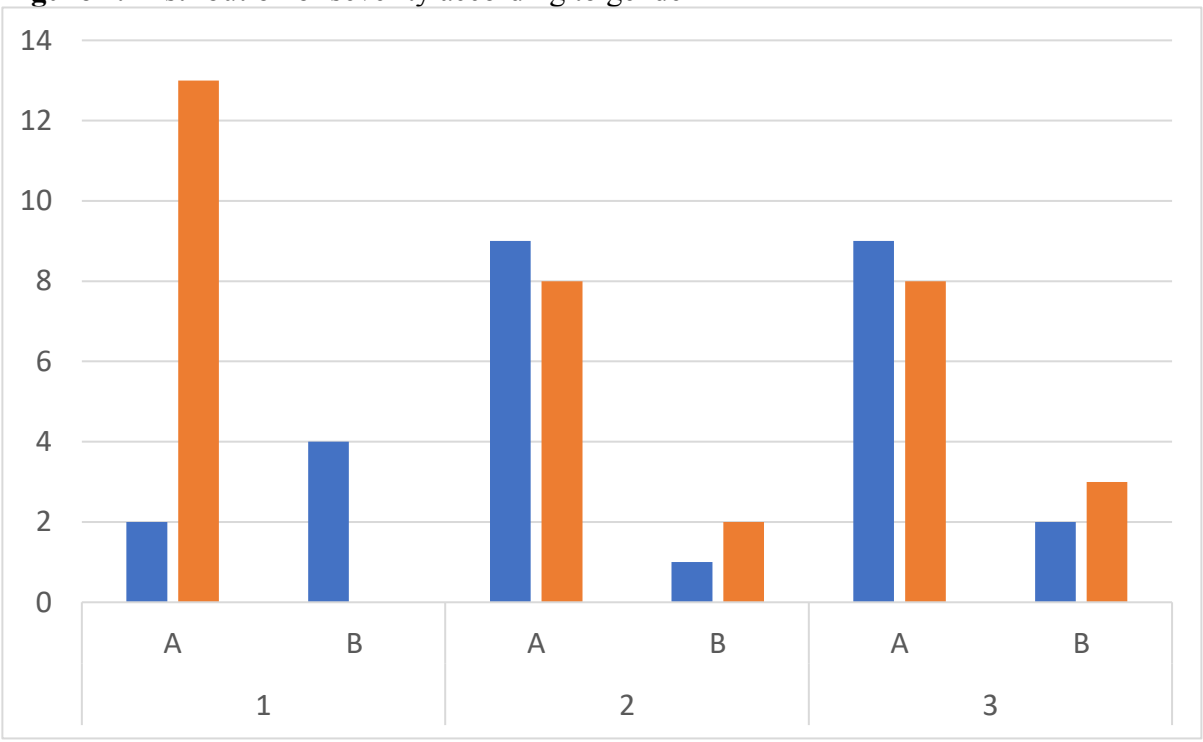
Legend
*Categorization of severity:
Mild ketoacidosis=1
Moderate ketoacidosis=2
Severe ketoacidosis=3
†Number of cases

Table 3. Difference in severity

	W	df	p
Severity	285.000		0.435
Severity female	98.500		0.957
Severity male	36.000		0.031

Note. For Mann-Whitney U test, the alternative hypothesis specifies that group *A* is less than group *B*.

Figure 2. Distribution of severity according to gender



Legend
1=mild ketoacidosis
2=moderate ketoacidosis
3=severe ketoacidosis
■ female
■ male

4.2. pH

The general distribution of the pH at time of presentation, without categorization into severity according to the guidelines was normal in both groups with *P*=0.068 and a mean pH of 7.14 in group A and *P*=0.527 and a mean pH of 7.115 in group B. Independent sample t-test did not show a significant difference in pH between these groups. When comparing pH presentation in the ER according to gender in group A the males presented with a mean pH of 7.143 and in group B the male mean pH is 7.115. For male cases only, the t-test also does not

detect a significant difference. In the female patients the mean pH changes from group A from 7.122 to 7.125 is also not significant. This can be seen in Table 4 and Table 5.

Table 4. Comparison of pH

	pH		pH male		pH female	
	A	**B**	**A**	**B**	**A**	**B**
N*	49	12	29	5	20	7
Median	7.158	7.135	7.180	7.100	7.139	7.208
Mean	7.143	7.115	7.157	7.101	7.122	7.125
Std. Deviation	0.109	0.137	0.114	0.051	0.100	0.179
MAD	0.072	0.076	0.080	0.047	0.055	0.086
Shapiro-Wilk	0.956	0.942	0.929	0.929	0.971	0.880
P-value of Shapiro-Wilk	0.068	0.527	0.051	0.589	0.769	0.227
Minimum	6.900	6.800	6.900	7.029	6.935	6.800
Maximum	7.300	7.300	7.300	7.152	7.292	7.300
25th percentile	7.080	7.064	7.100	7.076	7.047	7.046
50th percentile	7.158	7.135	7.180	7.100	7.139	7.208
75th percentile	7.230	7.209	7.238	7.147	7.182	7.236

Legend
*Number of cases

Table 5. Difference in pH

						95% CI for Mean Difference	
	t	**df**	***P***	**Mean Difference**	**SE Difference**	**Lower**	**Upper**
pH	0.755	59	0.227	0.028	0.037	-0.034	∞
pH male	1.072	32	0.146	0.056	0.052	-0.032	∞
pH female	-0.053	25	0.521	-0.003	0.054	-0.096	∞

Note. For T-test, the alternative hypothesis specifies that group *A* is greater than group *B*.

4.3. Bicarbonate

Analyzing the second part which makes up the categorization of severity, bicarbonate levels, in Table 6 we saw a non-normal distribution in group A with *P*=0.043 in the Shapiro-Wilk test. Median values for both groups are 10.3mmol/L. Due to the deviation from normality we ran a Mann-Whitney U test, see Table 7. The results from the Mann-Whitney U Test showed

no worsening of the parameters. When looking at the female and male cases separately, the bicarbonate values showed normal distribution in all subgroups. The therefore conducted independent t-test did not show any significant changes according to gender (Table 8). Levenes test showed an unequal variance between the female groups A and B, therefore a Welch test (Table 9) was run as a substitute. Here no significant difference could be found (*P*=0.617).

Table 6. Comparison of bicarbonate values

	HCO3†		**HCO3† female**		**HCO3† male**	
	A	**B**	**A**	**B**	**A**	**B**
N*	49	12	20	7	29	5
Median	10.300	8.800	9.150	11.600	11.300	8.600
Mean	10.639	9.550	9.415	9.886	11.483	9.080
Std. Deviation	3.345	3.005	2.431	3.760	3.656	1.777
MAD	2.400	2.900	1.700	2.600	2.500	0.400
Shapiro-Wilk	0.952	0.956	0.946	0.911	0.968	0.837
P-value of Shapiro-Wilk	0.043	0.729	0.316	0.405	0.507	0.156
Minimum	5.700	4.500	5.800	4.500	5.700	7.500
Maximum	20.300	14.200	13.900	14.200	20.300	12.100
25th percentile	8.100	7.950	7.475	6.950	8.600	8.200
50th percentile	10.300	8.800	9.150	11.600	11.300	8.600
75th percentile	12.700	11.950	10.825	12.500	13.700	9.000

Legend
*Number of cases
† values in mmol/L

Table 7. Difference in bicarbonate values

					95% CI for Hodges-Lehmann Estimate	
	W	**df**	**p**	**Hodges-Lehmann Estimate**	**Lower**	**Upper**
HCO3	337.500		0.218	0.844	-0.900	∞

Note. For Mann-Whitney U test, the alternative hypothesis specifies that group *A* is greater than group *B*.

Table 8. Difference in bicarbonate values according to gender

						95% CI for Mean Difference	
	t	df	p	Mean Difference	SE Difference	Lower	Upper
HCO3 f*	-0.382	25	0.647[a]	-0.471	1.233	-2.577	∞
HCO3 m†	1.427	32	0.082	2.403	1.684	-0.449	∞

Note. For independent t-test, the alternative hypothesis specifies that group *A* is greater than group *B*.

[a] Levene's test is significant ($P < .05$), suggesting a violation of the equal variance assumption

Legend

*female

†male

Table 9. Difference in bicarbonate values in females

						95% CI for Mean Difference	
	t	df	p	Mean Difference	SE Difference	Lower	Upper
HCO3 f*	-0.309	7.831	0.617	-0.471	1.522	-3.308	∞

Note. For Welch's test, the alternative hypothesis specifies that group *A* is greater than group *B*.

Legend

*female

4.4. Blood glucose

In our study there was a normal distribution of glucose in both groups. Group A had a mean glucose concentration of 512.575 mg/dl, group B had a slightly higher mean concentration of 544.25 mg/dl. The independent t-test showed no significant difference (P=0.276). We again examined the values separated for gender and compared the pre-pandemic and pandemic groups, for both groups both genders showed normal distribution. Shapiro-Wilk test shows a male P=0.985 in group A and P=0.952 in group B and a female P=0.927 in group A and P=0.947 in group B. We ran an independent t-test to compare the glucose values subdivided according to gender. Neither the male, nor the female values had a significant change. These results can be seen in Tables 9 and 10.

Table 10. Comparison of blood glucose values

	Glucose		Glucose male		Glucose female	
	A	**B**	**A**	**B**	**A**	**B**
N*	48	12	28	5	20	7
Median†	506.500	548.500	496.000	589.000	522.000	535.000
Mean†	512.575	544.250	493.379	564.000	539.450	530.143
Std. Deviation	176.382	93.974	141.551	110.492	217.213	86.569
MAD	98.500	76.500	95.000	115.000	140.000	92.000
Shapiro-Wilk	0.954	0.962	0.985	0.952	0.927	0.947
P-value of Shapiro-Wilk	0.058	0.813	0.947	0.751	0.138	0.704
Minimum†	223.000	410.000	223.000	436.000	260.000	410.000
Maximum†	1038.000	711.000	795.000	711.000	1038.000	637.000
25th percentile†	397.750	466.250	406.250	474.000	368.250	470.000
50th percentile†	506.500	548.500	496.000	589.000	522.000	535.000
75th percentile†	599.250	614.250	595.000	610.000	617.750	594.500

Legend
*Number of cases
†Values in mg/dl

Table 11. Differences in blood glucose values

						95% CI for Mean Difference	
	t	**df**	***P***	**Mean Difference**	**SE Difference**	**Lower**	**Upper**
Glucose	-0.599	58	0.276	-31.675	52.920	-∞	56.784
Glucose m*	-1.055	31	0.150	-70.621	66.969	-∞	42.925
Glucose f†	0.109	25	0.543	9.307	85.219	-∞	154.874

Note. For independent t-test, the alternative hypothesis specifies that group *A* is less than group *B*.

Legend
*male
†female

4.5. HbA1c

To see, whether there was a change in HbA1c values we assessed them as well, both in general and according to gender. The assessment for normality of distribution can be seen in Table 12. Normal distribution is given with *P*=0.794 in group A, but not in group B with *P* <0.001. Therefore, comparison of the median values, 11.3% in group A and 10.65% in group B was done with Whitney-Mann U test. No change could be observed. When taking into account only the female subgroup in Shapiro-Wilk test there is *P*=0.736 in group A for a normal distribution and *P*=0.007 in group B, showing a deviation from normality. After running Whitney-Mann U test no worsening effect could be confirmed (Table 13).

In the male only subgroup, both group A and B there was normal distribution with a *P*=0.861 and *P*=0.419 respectively. The conducted t-test failed to show a difference in Table 14.

Table 12. Comparison of HbA1c values

	HbA1c*		**HbA1c* male**		**HbA1c* female**	
	A	**B**	**A**	**B**	**A**	**B**
N†	48	12	28	5	20	7
Median‡	11.300	10.650	11.200	10.900	11.350	10.400
Mean‡	11.333	12.000	11.121	10.620	11.630	12.986
Std. Deviation	1.953	4.633	1.963	0.687	1.950	6.026
MAD	1.400	0.800	0.850	0.500	1.650	2.100
Shapiro-Wilk	0.985	0.611	0.980	0.902	0.969	0.725
P-value of Shapiro-Wilk	0.794	< .001	0.861	0.419	0.736	0.007
Minimum‡	6.700	8.300	6.700	9.800	7.300	8.300
Maximum‡	15.300	26.000	15.300	11.400	15.000	26.000
25th percentile‡	10.125	9.875	9.825	10.000	10.725	9.850
50th percentile‡	11.300	10.650	11.200	10.900	11.350	10.400
75th percentile‡	12.775	11.825	12.000	11.000	13.225	13.250

Legend
*Glycated hemoglobin
†Number of cases
‡HbA1c values in %

Table 13. Differences in HbA1c values

					95% CI for Hodges-Lehmann Estimate	
	W	df	*P*	Hodges-Lehmann Estimate	Lower	Upper
HbA1c†	327.00		0.767	0.400	-∞	1.400
HbA1c† f*	77.500		0.671	0.300	-∞	1.900

Note. For Mann-Whitney U test, the alternative hypothesis specifies that group *A* is less than group *B*.
Legend
*female
†Glycated hemoglobin

Table 14. Difference in HbA1c values in men

						95% CI for Mean Difference	
	t	df	p	Mean Difference	SE Difference	Lower	Upper
HbA1c* m†	0.559	31	0.710	0.501	0.898	-∞	2.023

Note. For t-tests, the alternative hypothesis specifies that group *A* is less than group *B*.
* Glycated hemoglobin
†male

5. DISCUSSION

In our research, our initial assumption, that after the beginning of COVID-19 pandemic the patients presenting with DKA arrive in the pediatric department in the REGIOMED hospital Coburg in a worse state then before, did not hold true.

With the beginning of the COVID-19 pandemic many studies could confirm the perception of many physicians, that patients started delaying and postponing their presentation at their respective physician. This did not only affect regular check-ups or chronic treatment, but patients also tried to avoid health care facilities when they developed new symptoms. Even with symptoms, cases of further delay due to worry of additional infection with SARS-CoV2 have been observed (8). When the patients presented at both, resident doctor or hospital, the time delay often was noticeable due to a worsened presentation of the patient (31–34).

In contrast to our results, several researchers like Lawrence *et al,* McGlacken-Byrne *et al* and Dżygało *et al* were able to confirm our suspicion in their studies and could show significant changes in severity of presentations with DKA during COVID-19 pandemic (35–37). In these studies, which successfully proved our hypothesis, the number of included annual cases was higher than in our research. Additionally, they only took into account children with newly diagnosed T1DM, while we included patients independent of the duration of their disease.

When we compared the severity of 49 cases in group A with 12 cases in group B, we could not find a significant change. This also could be seen in the female patients when dividing the groups according to gender before comparing the groups. The only statistically significant worsening we could observe was the severity of DKA according to the S3 guideline, when only taking into account the male presentations. It should be kept in mind, that our male population in group B only consisted of five cases in total, three presenting with severe ketoacidosis and two with moderate ketoacidosis.

Following the comparison of severity, we analyzed the laboratory values used for the classification, pH and bicarbonates, where we hypothesized that worse parameters could be seen. We could not confirm this. Therefore, we performed a subgroup analysis with respect of gender. However, subgroup analysis again did not reveal significant differences reduction in pH or bicarbonates focused on sex.

Literature gives average blood glucose values around 500 mg/dl upon appearance of DKA (24). As a major impact factor on the patients dehydration and wellbeing we compared the glucose levels upon arrival in the emergency room. There was no difference between group A

and group B. The gender-divided analysis also was unable to show a significant increase in blood glucose.

For long term glycemic control, we took the HbA1c value into account as well, here we were unable to prove a difference between the pre-pandemic and pandemic groups. Also subdividing the groups according to gender did not show higher glycation levels in group B compared to group A. In fact, for the general groups A and B the Median value actually was lower in group B. So were the values for both gender specific subgroups.

A study from Portugal examined the adherence to glycemic control in T1DM and was able to show worsened metabolic parameters in teenagers compared to their values before pandemic restrictions (38).

What was conspicuous is, that in the eight years we observed for the pre-pandemic group A, we had nine cases out of 76 presentations which met our exclusion criterium with more than one DKA within one year. This is a 11.8% exclusion rate for that reason. In only two years observation for group B we had to exclude six cases out of 26 presentations for that same reason, meaning a 23.1% dropout rate. We could notice, without having analyzed the data, that in group B the patients age with more than one episode appeared to be focused on the teenage age 14-16, starting with the youngest, aged 12. This seems to contrast the observation, that during the pre-pandemic period the age for those with more than one episode seemed to include all age groups. Not being part of our research, we think these observations should be further investigated in a possible future study, focusing on the readmission rates during the pandemic.

It was noticeable in many files in group B, apparently most predominantly female teenagers, that the treating physician noted incompliance with the treatment at home, which was not noticed to that extend in group A. Again, this is a pure observation which has not been investigated, but provides ground for a further study. It could be investigated whether the COVID-19 pandemic has increased incompliance and if these patients had to be treated for ketoacidotic complications more often, in more severe state, and if the HbA1c values of incompliant patients differs from the pre-pandemic incompliant cases. Since it was observed in some studies that adherence to diabetic medication had worsened due to the pandemic, we suspect, this might be potentiated in those being incompliant already before the outbreak (39).

Due to our exclusion criteria, we also missed the chance to compare the parameters and behavior of those patients, who were both, incompliant before and during the pandemic.

Our study is very limited due to our small sample size in group B. Regarding our exclusion criterion of a diagnosed eating disorder, our insight into the patients medical history is limited, since we only could access the REGIOMED database. Patients with an eating disorder, who were not diagnosed in a REGIOMED hospital and did not provide this information on their own, would not be listed as such. Additionally, our study does not take the patients age and the age distribution in the two groups into account, which might have an influence on the severity. In infants who are not yet able to adequately express themselves and rely on their parents to suspect a disease, it might lead to more severe cases in this age group. We also have no information about the family history of the patients regarding T1DM in their close relatives. Other affected family members and more extensive experience with DM could possibly lead to a sensitizing of parents and patients alike, detecting signs of diabetic ketoacidosis earlier and in a milder state.

6. CONCLUSION

1. Diabetic ketoacidosis, categorized according to the S3 guideline, in children during the pandemic was not more severe compared to the pre-pandemic period.
2. The presentation of male cases, categorized according to the S3 guideline, was in a significantly more severe state, in the pandemic, than the pre-pandemic period.
3. Laboratory values for pH and bicarbonates did not show a significant change between group A and group B, or when group A and group B were compared according to gender.
4. Children with diabetic ketoacidosis during the pandemic did not show higher blood glucose levels compared to the pre-pandemic period.
5. Long term glucose homeostasis, represented by HbA1c, seems not to be negatively affected by the pandemic.

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8. SUMMARY

Objectives: With this study we tried to find an impact of the COVID-19 pandemic on the pediatric patients presenting at the pediatric emergency department with a diabetic ketoacidosis. For this we compared the patients presenting at the ED from the 11th of March 2020 until the 11th of March 2022, after the WHO declared a pandemic situation with those who presented between January 1st 2012 and December 31st 2019.

Materials and Methods: This retrospective observational study was conducted with the available data from the pediatric ward in the REGIOMED hospital Coburg. The categorization for severity of diabetic ketoacidosis was done according to the current S3 guideline for the therapy of Diabetes Mellitus, valid in Germany at the time of the study. We compared the severity from 49 cases in group A and 12 cases in group B, after all necessary exclusions were performed. Apart from the severity we compared laboratory values for pH, bicarbonates, blood glucose and glycated hemoglobin A1c (HbA1c). The comparisons were performed for the whole groups, and between groups A and B divided for gender.

Results: There was no statistically significant difference in severity of diabetic ketoacidosis between group A and group B (P=0.435). When comparing the severity between groups A and B according to gender, no difference could be found in the female subgroup (P=0.957), but a statistically significant change in the male subgroup (P=0.031) could be seen. There was no difference in the pH values (P=0.227), also not when divided according to gender (male P=0.146 and female P=0.521). This was again seen in the analysis of bicarbonate concentrations, no difference could be found (P=0.218), the male subgroup had a P-value of 0.082 and the female subgroup a P-value of 0.617. The blood glucose at admission in both groups was in the expected range with a mean value of 512.6 mg/dl in group A and 544.3 mg/dl in group B. With P=0.276 no difference could be found, this was also true after division into female (P=0.543) and male (P=0.150). Median HbA1c values were actually higher in group A (11.3%) than in group B (10.65%). We therefore failed to prove worse results (P=0.767). Looking only at the male patients we also had a mean reduction of HbA1c from 11.1% to 10.6% and had no worse outcome in group B (P=0.789). The female patients also had better HbA1c results, their median improving from 11.3% to 10.4%, therefore no worsened long term glycemic control was obvious (P=0.671).

Conclusion: We could not prove a worse patient presentation with diabetic ketoacidosis during the COVID-19 pandemic in general. The only significant worse outcome was the severity in male patients.

9. CROATIAN SUMMARY

Naslov: Ozbiljnost pedijatrijske ketoacidoze prije i tijekom pandemije COVID-19
Ciljevi: Ovom smo studijom pokušali utvrditi utjecaj pandemije COVID-19 na pedijatrijske pacijente koji se javljaju na hitnu pedijatriju s dijabetičkom ketoacidozom. U tu svrhu usporedili smo pacijente koji su im se javili u razdoblju od 11. ožujka 2020 do 11. ožujka 2022, odnosno nakon što je WHO proglasio pandemijsku situaciju, s onima koji su se javili između 1. siječnja 2012 i 31. prosinca 2019.
Materijali i metode: Ova retrospektivna opservacijska studija provedena je uz pomoć dostupnih podataka s pedijatrijskog odjela u bolnici REGIOMED Coburg. Kategorizacija prema ozbiljnosti dijabetičke ketoacidoze učinjena je prema trenutnim S3 smjernicama za terapiju dijabetes melitusa, a koje su bile na snazi u Njemačkoj i u vrijeme istraživanja. Usporedili smo tako težinu iz 49 slučajeva u skupini A i 12 slučajeva u skupini B, nakon što su izvršena sva potrebna isključenja. Osim težine, usporedili smo i laboratorijske vrijednosti za pH, bikarbonate, glukozu u krvi i glikirani hemoglobin A1c (HbA1c). Usporedbe su obavljene za cijele skupine te između skupina A i B podijeljenih prema spolu.
Rezultati: Nije bilo statistički značajne razlike u težini dijabetičke ketoacidoze između skupine A i skupine B (P=0.435). Uspoređujući težinu između skupina A i B prema spolu, ustanovili smo da nije bilo razlike u ženskoj podskupini (P=0.957), ali se mogla vidjeti statistički značajna promjena u muškoj podskupini (P=0.031). Isto tako, nije bilo razlike ni u pH vrijednostima (P=0.227), čak ni onda kada bismo gledali s obzirom na spol (muški P=0.146 i ženski P=0.521). Nadalje, analizom koncentracija bikarbonata, opet smo utvrdili to da se nije mogla pronaći veća razlika (P=0.218), muška podskupina imala je P-vrijednost 0.082, a ženska podskupina P-vrijednost 0.617. Glukoza u krvi pri prijemu u obje skupine bila je u očekivanom rasponu sa srednjom vrijednošću od 512.6 mg/dl u skupini A i 544.3 mg/dl u skupini B. S P=0.276 nije se također mogla pronaći razlika, a isto to je vrijedilo i nakon podjele na žene (P=0.543) i muškarci (P=0.150). Srednje vrijednosti HbA1c bile su zapravo više u skupini A (11.3%) nego u skupini B (10.65%). Stoga nismo uspjeli dokazati lošije rezultate (P=0.767). Uzmemo li u obzir samo muške pacijente, isto smo imali prosječno smanjenje HbA1c s 11.1% na 10.6% te lošiji ishod nije bio zabilježen ni u skupini B (P=0.789). Pacijentice su također imale bolje rezultate HbA1c. Njihov medijan poboljšao se s 11.3% na 10.4%, stoga u vezi dugotrajne glikemijske kontrole nisu bila zabilježena značajnija pogoršanja (P=0.671).
Zaključak: Općenito govoreći, nismo mogli dokazati lošiju prezentaciju pacijenata s dijabetičkom ketoacidozom tijekom pandemije COVID-19. Jedini značajno lošiji ishod bila je težina kod muških pacijenata.

10. CURRICULUM VITAE