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Insulin resistance relates to DKA severity and affects insulin requirement in children with type 1 diabetes at onset

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Abstract

Background: Fluid and insulin treatments are the cornerstones of DKA management and indications on dosages are available. However, according to possible confounding factors, relevant data are still required to explain the different insulin dosages adopted at diabetes onset, particularly based upon insulin sensitivity.

Objective: We aimed to explore whether DKA severity is related to different insulin sensitivity states, thus resulting in different insulin requirement at diabetes onset.

Methods: Retrospective data from hospital records of 62 newly diagnosed children with type 1 diabetes with DKA were analyzed. The population was divided into three groups: severe, moderate, and mild DKA. Anthropometric, laboratory test, insulin, and glucose administration data were analyzed. The Glucose Infusion Rate (GIR), Insulin Infusion Rate (IIR), and GIR/IIR were calculated and used as indexes of insulin sensitivity. The area under the curve (AUC) for insulin and glucose infusion was calculated.

Results: Moving among the three groups, IIR decreased while GIR and GIR/IIR increased from severe to mild DKA group (all $p < 0.01$). A similar trend was documented for AUC-insulin and AUC-glucose as well as AUC-glucose/AUC-insulin ratio. The Spearman correlation showed a negative correlation between pH and both IIR and AUC-Insulin as well as a positive correlation between pH and both GIR/IIR and AUC-glucose/AUC-insulin ratio.

Conclusions: Subjects with severe DKA have a higher insulin requirement compared to those with less severe DKA. Significant differences in terms of insulin sensitivity might be documented according to the severity of DKA, which might result in tailored insulin pH requirement in children with new onset type 1 diabetes.

KEYWORDS
children, DKA, insulin administration, insulin resistance, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes is one of the most common chronic autoimmune diseases during childhood accounting for about 5%–10% of all diabetes forms.[1] In the last decades, the incidence of the disease has increased in many countries with estimated overall annual increase at around 3% with its geographic differences.[2] Among complications related to diabetes, DKA is a life-threatening complication in pediatric type

1 diabetes,[3] with a mortality rate ranging from 3% in developed countries to up to 13% in developing countries.[4] It is caused by relative or absolute insulin deficiency. There is wide geographic variation in the frequency of DKA at onset of diabetes with an inverse correlation between rates and regional incidence of type 1 diabetes. In addition, DKA at diagnosis is more common in younger children (<2 years of age), in ethnic minority groups, and in children without access to medical care for social or economic reasons. The diagnosis of DKA is made in presence of hyperglycemia (blood glucose>11 mmol/L [≈200 mg/dl]), venous pH <7.3 or serum bicarbonate<15 mmol/L, ketonemia (blood ß-hydroxybutyrate≥3 mmol/L) or moderate or large ketonuria. The DKA is categorized according to severity into three groups, namely mild (pH <7.3 or bicarbonate<15 mmol/L), moderate (pH <7.2, bicarbonate<10 mmol/L) and severe (pH <7.1, bicarbonate<5 mmol/L).[5]

Fluid and insulin are the cornerstones of DKA management. The objectives of therapy are to restore circulating volume by correcting dehydration, acidosis, and reversing ketosis. If properly adopted, it may reduce the risk of related complications. After initial fluid resuscitation, insulin therapy is essential to normalize blood glucose concentration, to correct acidosis by suppression of the lipolysis and ketogenesis, to generate bicarbonate from ketoacid metabolism, and to restore the normal cellular metabolism. According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines the insulin infusion should be started at least 1 h after starting fluid replacement therapy at dosage ranging from 0.05 to 0.1 unit/kg/h; low dose intravenous insulin administration is safe and effective.[6] Peculiar and relevant indications on different dosages are needed at diabetes onset. However, this information has not been completely investigated yet. Notably, distinct approaches related to different scenarios according to major confounding factors, such as insulin sensitivity states, should be evaluated. Therefore, in children with new onset type 1 diabetes, studies evaluating the effects of insulin sensitivity on insulin requirement are needed. These results might offer unique data for producing guidelines for different insulin dosages related to insulin sensitivity. Therefore, we aimed to explore whether different degrees of DKA are related to different insulin sensitivity thus requiring pH tailored insulin administration in children with new onset type 1 diabetes.

2 | METHODS

2.1 | Subjects

We retrospectively analyzed data from all children admitted for DKA who receive newly type 1 diabetes diagnosis aged from 18 months to 18 years, who had been admitted to the Department of Pediatrics of "SS. Annunziata Hospital" in Chieti, Italy, from 2015 to 2021. Data were collected from medical records of each patient, retrospectively, and included age, sex, weight, height, body mass index (BMI), date of diabetes onset, main medical history, and laboratory analysis and insulin and glucose administration during the first 18 h. The University Hospital of Chieti is a regional reference center for pediatric diabetes at onset. Therefore, all newly diagnosed children with type 1 diabetes, patients admitted to the emergency rooms of peripheral hospitals, as well as subjects evaluated by general pediatricians with a suspected diagnosis of diabetes are sent to the hospital for immediate treatment of acute metabolic disarrangement and subsequently trained in daily management of the disease.

According to the ISPAD guidelines, only subjects with DKA at diabetes onset were included in the study. DKA was defined as: a venous pH <7.30 and/or bicarbonate<15 mmol/L along with ketonemia or ketonuria and hyperglycemia (blood glucose>11 mmol/L [≈200 mg/dl]).[6]

Thus, the study population included 62 children that were further divided into three groups according to DKA severity as suggested by ISPAD guidelines: *severe DKA*, pH <7.1, bicarbonate<5 mmol/L; *moderate DKA* pH <7.2, bicarbonate<10 mmol/L, *mild DKA* pH <7.3 or bicarbonate<15 mmol/L.[5] The average age was 7.8 ± 3.3, 8.8 ± 5.0, and 8.8 ± 5.4 in three groups, respectively. Diabetes diagnosis was made according to the American Diabetes Association Criteria based on a random plasma glucose≥200 mg/dl (11.1 mmol/L) in presence of symptoms of hyperglycaemia or hyperglycaemic crisis.[1] The autoimmune etiology was confirmed by the presence of two or more autoantibodies. Furthermore, patients with pre-diabetes, non-type 1 diabetes or admitted for impaired metabolic control in previously diagnosed diabetes or with diabetes diagnosed in another medical center were not eligible. The paper is exempt from ethical committee approval since (i) it was confined to anonymized and unidentifiable data routinely collected at the S.S. Annunziata Hospital (Chieti); and (ii) the data analyzed for the study are part of routine for patients with diabetes onset admitted to our hospital; and (iii) the study findings would not affect patient care.

2.2 | Measurements

2.2.1 | Anthropometric measurements

Height was measured to the nearest 0.1 cm with Harpenden stadiometer.[7] Body weight was measured to the nearest 0.1 kg with a calibrated scale. BMI, used as index of adiposity, was calculated as the weight in kilograms divided by the square of the height in meters. Height, weight, and BMI z-scores (SDS) were calculated based on the age and sex reference values for the Italian population.[8] In all patients, the pubertal stage was defined based on Tanner's criteria, assessing breast development in girls and genital development in boys.[9] The onset of puberty was defined by a testicular volume ≥4 ml in boys (G2) and the presence of a breast stage 2 (B2) in girls.[10] Prepubertal children are defined as Tanner Stage 1; pubertal subjects are defined as Tanner Stage from 2 to 4; post-pubertal children are defined as Tanner Stage 5.

2.2.2 | Biochemical analysis

Routine basal tests

In our clinical practice in the emergency room, before the first insulin injection, blood samples are obtained from each patient to assess:

plasma glucose, electrolytes, renal function, blood gas analysis with measurement of pH, bicarbonate (HCO3−), B.E. (base excess).

Additional exams

During hospitalization soon after glycemic control has been established, blood samples are collected to assess glucose metabolism: C-peptide, Hemoglobin A1c (HbA1c), and panel of islet antibodies (autoantibodies to glutamic acid decarboxylase [GAD65], islet cell autoantibodies [ICA], the tyrosine phosphatases [IA-2]).[11] Celiac disease screening is also performed for the determination of tissue transglutaminase antibodies IgA and IgG (tTGA-IgA, tTGA-IgG), and Anty-Endomysial antibodies (EMA-IgA) in the serum. Thyroid function screening including Thyrotropin (TSH), free T4 (fT4), Thyroglobulin antibodies (Tg-Abs), Thyroid peroxidase antibodies (TPO-Abs) is achieved. TPO-Ab levels higher than 10.1 UI/ml and Tg-Ab levels higher than 28.7 UI/ml are considered positive.[12,13] Finally, the lipid profile measuring total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides is carried out using an enzymatic calorimetric test.

2.2.3 | Routine DKA management

The established primary infusion solution was 0.9% normal saline to correct dehydration, with the infusion rate set to 10 ml/kg/h for the first hour and it was successively adapted. According to ISPAD guidelines[6] all children admitted with diagnosis of DKA started insulin infusion at least 1 h after starting fluid replacement therapy; that is, after the patient has received initial volume expansion. In addition, correction of insulin deficiency was achieved by an initial intravenous dose of 0.05 to 0.1 units/kg/h after dilution of 50 units regular insulin in 50 ml normal saline (1 unit = 1 ml). The insulin dosage was adjusted based on the blood glucose level. In addition, in order to prevent an unduly rapid decrease in plasma glucose concentration, 5% or 10% glucose infusion, was added to the IV fluid according to guidelines in order to maintain a blood glucose level above 200 mg/dl. In all subjects the insulin and glucose administration were recorded in order to calculate the total amount of insulin used during the first 18 h.

2.2.4 | Indexes of insulin sensitivity

Insulin sensitivity was expressed by the following indexes:

- GIR = Mean of grams of Glucose Infused after starting glucose infusion therapy during the first 18 h;
- IIR = Mean of U/kg/h of Insulin Infusion after starting insulin infusion therapy during the first 18 h;
- GIR/IIR = Ratio between GIR and IIR during the first 18 h;
- AUC insulin (AUC-I) = Area Under the Curve (AUC) of insulin over the first 18 h using the trapezoidal rule[14];
- AUC glucose (AUC-G) = Area Under the Curve of glucose infusion over the first 18 h using the trapezoidal rule;
- AUC-G and AUC-I ratio.

2.3 | Statistical analysis

All data were expressed as means ± *SD*. Differences in categorical variables across the three groups were assessed by the χ^2 test. Differences in term of anthropometric parameters and laboratory measurements across the three DKA severity Groups were analyzed by Kruskal Wallis test using then U-Mann Whitney for post hoc analysis. In addition, in order to finally explore the relationship between pH values and different variables of interest in the entire study population a Spearman correlation was performed. At last, a linear backward regression analysis was performed in order to confirm the significant correlation between pH values and main clinical and laboratory parameters in the entire study population. *P* values ≤ 0.05 were considered statistically significant. Statistical analysis was performed using SPSS Program (Statistical Package for Social Science), version 21.0 software for Windows (SPSS, Chicago, IL, USA).

3 | RESULTS

3.1 | Clinical and anthropometric characteristics of all subjects with DKA divided into three groups

The clinical and anthropometric characteristics of the study population are reported in Table 1. The population was divided into three groups: *severe DKA* included 21 children (male/female: 8/13) aged of 7.8 ± 3.3 years; *moderate* DKA consisted of 16 subjects (male/female: 8/8) aged 8.8 ± 5.0 years; *mild* DKA included 25 children (male/female: 16/9) aged 8.8 ± 5.4 years. No differences for age, sex, weight, height, BMI and their respectively SDS values were found across the three groups (all $p > 0.05$).

As expected according to the classification, a significant difference between the three groups was documented for pH, bicarbonate, and base-excess, reflecting the different class of severity described above (all $p < 0.001$). In addition, a significant difference was documented for blood glucose ($p = 0.01$). Instead, no significant differences were documented for HbA1c and C-peptide.

The presence of thyroiditis was assessed by the presence of autoantibodies positivity. The number of subjects with thyroid autoantibodies positivity was similar among the three groups. However, among these patients, none had hypothyroidism or thyrotoxicosis thus not requiring additional treatment. The celiac disease was defined according to ESPGHAN guidelines[15] and no significant differences between the three groups was documented. Total, LDL and HDL cholesterol were similar between the three groups. In contrast, triglycerides were higher in groups of severe DKA with a significant difference across the three groups ($p = 0.02$). No patients have developed DKA-related complications such as hypoglycemia and other main complications.

3.2 | Insulin sensitivity of all subjects with DKA divided into three groups

The indexes of insulin sensitivity of the three groups are shown in Table 1. The GIR was significantly different between the three groups.

TABLE 1 Main anthropometric and metabolic parameters of children divided according to DKA severity at diabetes onset

	Severe DKA	Moderate DKA	Mild DKA	*p*
Anthropometric parameters				
Number	21	16	25	
Gender (male/female)	8/13	8/8	16/9	0.21
Age (years)	7.8 ± 3.3	8.8 ± 5.0	8.8 ± 5.4	0.60
Pubertal stage (pre−/pubertal/post-)	15/6/0	10/3/3	14/5/6	0.22
Weight (Kg)	28.5 ± 14.7	33.5 ± 17.0	32.9 ± 18.5	0.66
Weight-SDS	−0.52 ± 1.38	−0.41 ± 1.24	−0.39 ± 1.19	0.86
Height (cm)	124.2 ± 22.5	133.2 ± 31.7	128.3 ± 32.5	0.50
Height SDS	−0.4 ± 1.1	0.2 ± 1.4	−0.2 ± 1.5	0.25
BMI (Kg/m^2)	17.5 ± 5.3	17.3 ± 3.0	18.2 ± 4.6	0.59
BMI-SDS	−0.50 ± 1.62	−0.46 ± 1.05	−0.47 ± 1.71	0.84
Blood Gas analysis data				
pH	7.00 ± 0.07	7.14 ± 0.02	7.25 ± 0.03	**<0.001**†‡§
HCO3 (mmol/L)	7.02 ± 2.89	9.80 ± 2.87	14.80 ± 3.33	**<0.001**†‡§
Base Excess (mmol/L)	−23.7 ± 4.0	−19.9 ± 2.3	−12.5 ± 4.2	**<0.001**†‡§
Laboratory parameters				
Blood Glucose (mg/dl)	509 ± 105	423 ± 90	436 ± 128	**0.01**
HbA1c (%)	12.1 ± 1.8	12.4 ± 1.7	12.3 ± 1.5	0.66
HbA1c (mmol/mol)	108.7 ± 19.5	113.1 ± 19.3	112.0 ± 16.3	0.63
C-peptide (ng/ml)	0.38 ± 0.29	0.30 ± 0.31	0.32 ± 0.24	0.54
Total Cholesterol (mg/dl)	166 ± 29	162 ± 31	152 ± 40	0.67
HDL- Cholesterol (mg/dl)	39 ± 9	43 ± 12	43 ± 14	0.67
LDL-Cholesterol (mg/dl)	100 ± 26	92 ± 36	92 ± 40	0.87
Triglycerides (mg/dl)	139 ± 65	128 ± 74	97 ± 64	**0.02**
Autoimmune diseases				
Thyroiditis (yes/no)	1/20	2/20	4/21	0.48
Celiac Disease (yes/no)	3/18	1/15	3/22	0.74
Indexes of insulin sensitivity				
GIR (g/h)	5.25 ± 1.32	6.71 ± 1.99	6.31 ± 1.35	**0.01**†‡
AUC-I (U/kg/h)	4.42 ± 1.36	4.25 ± 2.00	2.82 ± 0.93	**<0.001**‡§
AUC-G (g/kg/h)	299 ± 76	387 ± 113	347 ± 90	**0.03**†‡
AUC-G/AUC-I	72 ± 24	112 ± 58	138 ± 65	**<0.001**†‡

Note: Significant values for post hoc analysis: † Severe DKA versus moderate DKA; ‡ severe DKA versus Mild DKA; § moderate DKA versus mild DKA.

In detail, children with severe DKA received a lower glucose infusion rate compared with moderate and mild DKA groups ($p = 0.02$ and $p = 0.01$, respectively); while no significant difference was documented between moderate and mild DKA groups ($p = 0.34$). A significant difference across the three groups was also documented for IIR values. As shown in Figure 1A, in the group of severe DKA, IIR values were significantly higher compared with the moderate and mild DKA groups ($p < 0.001$). In addition, as shown in Figure 2A, although a higher mean IIR value was reported in groups with moderate DKA compared to mild DKA it did not reach significant values ($p = 0.06$). As a consequence, a significant difference of the GIR/IIR ratio was documented across the three groups, having the severe DKA group a lower GIR/IIR ratio compared with moderate and mild groups ($p = 0.002$ and $p < 0.001$, respectively) as shown in Figure 1B. In addition, as shown in Figure 2B, although a lower mean GIR/IIR ratio value was reported in group with moderate DKA compared to mild DKA it did not reach significant values ($p = 0.13$). As shown in Figure 1 the three DKA severity groups exhibit a stepwise and progressive variation of IIR (Figure 1A) and GIR/IIR (Figure 1B) showing the group of severe DKA higher insulin requirement and lower GIR/IIR compared to the moderate and mild ones. These differences were better described by AUC values. Particularly, a significant difference was documented for AUC-I values across the three groups. In detail, both children with severe and moderate DKA showed a higher AUC-I compared with the mild DKA group (all $p = 0.01$). In addition, AUC-I values were higher in the severe group compared to the moderate

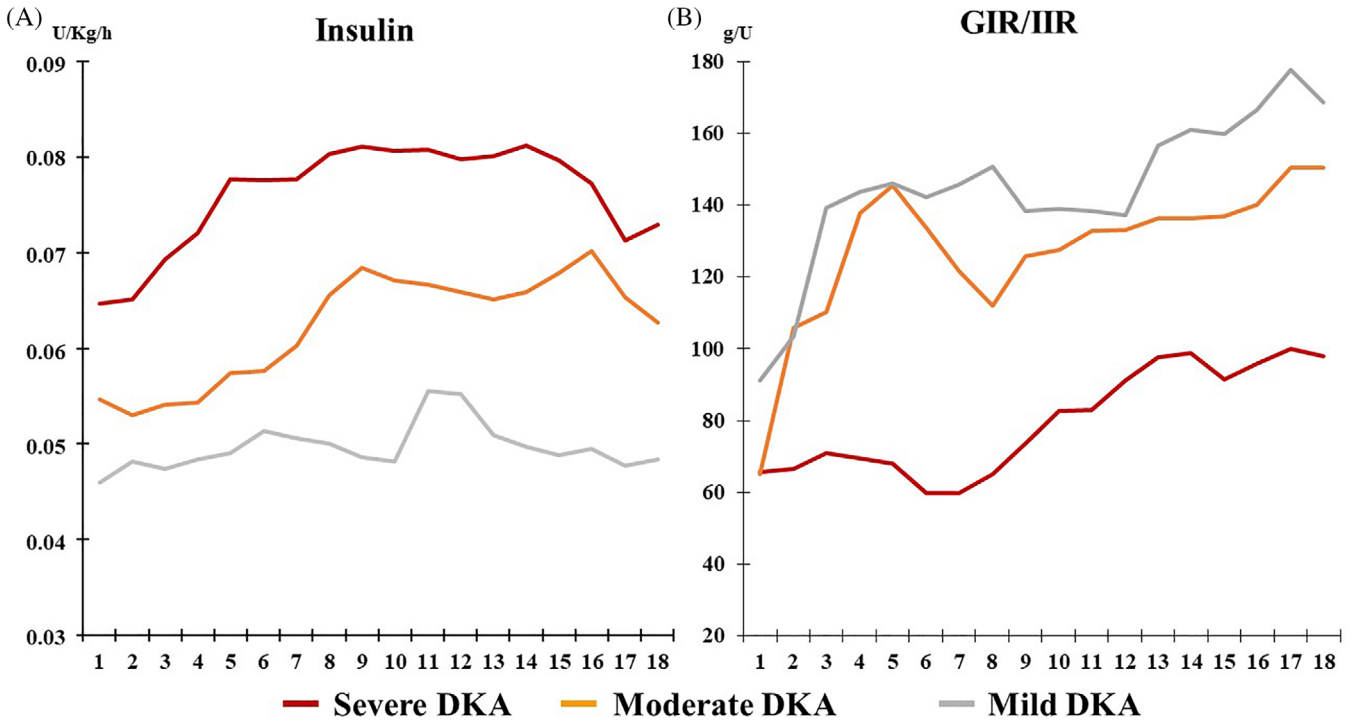

FIGURE 1 (A, B). Differences of insulin infusion rate (A) and GIR/IIR (B) in the three groups divided according to DKA severity at type 1 diabetes onset.

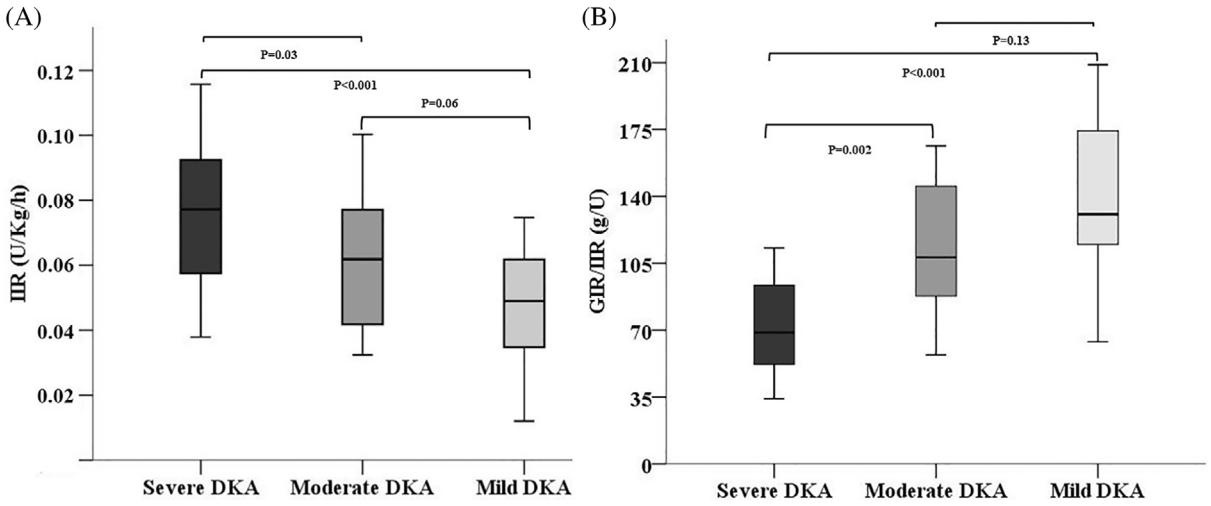

FIGURE 2 (A, B). Difference of the mean IIR (A) and GIR/IIR (B) across the three groups divided according to DKA severity at type 1 diabetes onset.

group, although they did not reach significant differences ($p = 0.42$). Similarly, AUC-G values across the three groups were statistically different. Indeed, children with severe DKA showed a lower AUC-G compared with moderate and mild DKA groups ($p = 0.01$ and $p = 0.03$, respectively). No significant difference was documented between moderate and mild DKA groups ($p = 0.22$). Consequently, a significant difference of the AUC-G/AUC-I ratio was documented ($p < 0.001$), giving the severe DKA group a lower AUC-G/AUC-I ratio compared with the other two groups ($p = 0.02$ and $p < 0.001$, respectively). No significant difference was documented between moderate and mild DKA groups ($p = 0.40$), although higher levels were documented in the former one.

3.3 | Correlation analysis between pH values and the main clinical and metabolic parameters

The main data evaluating correlations between pH values and the main clinical and metabolic parameters in the entire population are reported in Table 2. As shown, no significant correlation was found

TABLE 2 Main correlation between pH values and main clinical and metabolic parameters at diabetes onset

	Spearman Correlation		Linear Regression							
	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p
Age	0.66	0.61	−0.02	0.85	0.13	0.22	−0.02	0.85	−0.02	0.85
Gender	−0.24	0.06	−0.08	0.45	−0.12	0.29	−0.08	0.45	−0.08	0.45
Weight	0.10	0.40								
Weight-SDS	0.06	0.62								
Height	0.04	0.73								
Height-SDS	0.10	0.42								
BMI	0.07	0.58								
BMI-SDS	0.01	0.94	−0.04	0.6	0.01	0.87	−0.04	0.65	−0.04	0.65
Blood glucose	−0.39	**<0.001**								
IIR	−0.53	**<0.001**	−0.23	0.14	−0.49	<0.001			−0.23	0.14
GIR	0.21	0.09								
GIR/IIR	0.63	**<0.001**	0.53	**<0.001**			0.53	<0.001	0.53	<0.001
AUC-I	−0.51	**<0.001**								
AUC-G	0.10	0.40								
AUC-G/AUC-I	0.49	**<0.001**	0.12	0.46						

Abbreviations: AUC-G, area under the curve of glucose; AUC-I, area under the curve of insulin; GIR, glucose infusion rate; IIR, insulin infusion rate; SDS, standard deviation score.

for age, gender, weight and weight-SDS, height and height SDS, BMI and BMI SDS. A significant correlation was reported for glycemia in the entire population. Furthermore, pH values were significantly related with indexes of insulin sensitivity showing a significant correlation with IIR and GIR/IIR ratio (all $p < 0.001$) but not with GIR ($p = 0.09$). In addition, pH values were negatively correlated with AUC-I ($p < 0.001$) and positively with AUC-G/AUC-I ratio ($p < 0.001$). No significant correlation was found for AUC-G ($p = 0.40$). Moreover, a significant correlation was documented between pH values and triglycerides ($p = 0.006$). No significant correlation was found for total cholesterol ($p = 0.44$), HDL-cholesterol ($p = 0.80$) and LDL-cholesterol ($p = 0.69$). After performing a linear regression analysis, even after adjustment for age, gender and BMI-SDS a significant correlation between pH values and both IIR and GIR/IIR ratio was confirmed when introducing the variables at time (Table 2). If the two variables are added in the analysis simultaneously only the GIR/IIR ratio persisted significant.

4 | DISCUSSION

In this study, we have demonstrated that children with different severity of DKA at diabetes onset need a different insulin requirement, which seems to be mainly related to a different insulin sensitivity status. In fact, across classes of DKA severity a stepwise and progressive increase of insulin expressed in units/kg/h is clearly documented as shown by differences in terms of IIR, GIR, and GIR/IIR. Therefore, in those children with a more severe form of DKA, a higher insulin requirement needs to be adopted compared to the moderate and mild ones, as well as in those with a moderate form compared to mild ones. In addition, we documented a negative correlation between pH and both the insulin infusion rate and AUC of insulin infused/hour. Furthermore, a positive correlation between pH and both glucose infusion rate and AUC of glucose infused/hour was documented. Interestingly, in our population, no patients have developed hypoglycemia or other complications, independently of the group analyzed. Therefore, even in those subjects with a higher insulin requirement no risk of complications was documented.

Guidelines might clear suggest the insulin administration during the first hours of DKA at admission so far, and a different insulin dosage related to different age-dependent insulin sensitivity.[16,17] However, no evidence on potentially different insulin requirements according to the severity of DKA reflecting different insulin sensitivity have been yet reported.[18] One of the most relevant studies exploring the relationship between DKA and insulin resistance was performed by Barret and colleagues; this study showed that the time course of plasma glucose after insulin administration differed strikingly between the subjects with DKA and the control, in whom the mean rate of fall of plasma glucose great exceeded demonstrating thus severe resistance to the glucose-lowering action of insulin of patients with DKA.[19] The insulin therapy has evolved during 4 decades to identify a perfect dose that will not only correct ketoacidosis but also prevent complications.[20] In the past, the insulin infusion at 0.1 U/kg/h became standard in the management of DKA but it does not have strong clinical evidence of its superiority in contrast to the lower doses,[21] particularly in relation to DKA severity.[20] A study of Noyes and colleagues has demonstrated that insulin doses of 0.03 and 0.05 U/kg/h could adequately normalize ketosis in DKA.[22] Similar results obtained by Puttha et al. have suggested that a dose of

0.05 U/kg/h was as effective as the standard dose in correcting acidosis[23] and in preventing rapid decrease of blood glucose.[24] Noteworthy, our results suggest a possible systematic approach to be adopted in the definition of insulin dose requirements in children with new onset type 1 diabetes and DKA. In fact, in those children with a more severe DKA, a higher insulin (U/kg/h) dosage seems to be effective and safe in controlling glucose homeostasis, while in those with less severe forms a progressive lower insulin might be adopted. In our study a mean insulin infusion of 0.08, 0.06, and 0.04 U/kg/h was initially started in children with severe, moderate and mild DKA, respectively, which was thereafter adjusted with dextrose infusion according to blood glucose levels and ketosis in order to properly approach DKA at onset. Such an approach, and particularly a step increase of insulin dosage adopted according to the severity of DKA, might test the ability of normalizing ketonemia and acidosis without modifying the risk of its related complications.

Furthermore, in our study, by evaluating not only the differences in terms of insulin administration but also of glucose infused and glucose/insulin infusion rate ratio, we tried to characterize different insulin sensitivity across the three groups. Particularly, a stepwise and progressive decrease of glucose infusion as well as Glucose/Insulin infusion rate ratio was documented ranging from mild to severe form of DKA at onset. In addition, by using AUC of insulin and glucose as insulin sensitivity markers, we have also demonstrated that subjects with severe DKA showed an increased AUC of insulin for hours and decreased AUC of glucose for hours demonstrating that the severe DKA group had a worse insulin sensitivity than mild and moderate classes. Taken together, these results suggest a progressive worsening of insulin sensitivity state ranging from mild to severe DKA state. It is well known that insulin levels during a fasting state and after an oral glucose load differs significantly according to insulin sensitivity, having subjects with insulin resistance (e.g., obese children or subject with lipodystrophies) significantly higher values.[17,25] Similarly, it is well known that values of glucose/insulin ratio in a fasting state significantly and inversely reflects insulin sensitivity.[26] Although a strong correlation is documented between pH values and IIR, GIR and GIR/IIR ratio suggesting a strong relationship between insulin sensitivity state and severity of DKA, these indexes represent surrogate markers of insulin sensitivity thus further multicenter studies are needed to confirm our results.

One of the major limits of this study is that it is not a population-based study; consequently, the data do not reflect the general population but only a small part affected by the disease. Therefore, the small sample size is due to the fact that data were obtained in a single center. The availability of new multicenter studies might further confirm our data particularly characterizing some age specific limitation and application. In addition, a bigger population might allow to adjust results for important confounding factors such as puberty, obesity, concomitant infection, etc. One of the major strengths is that this study correlates the severity of DKA to the different insulin dosage administration and the complete characterization of insulin and glucose requirement evaluating per kg/h, therefore giving a comprehensive picture of the glucose homeostasis.

5 | CONCLUSIONS

In conclusion, we demonstrated that subjects with severe DKA at diabetes onset might receive a higher insulin infusion rate compared with moderate and mild DKA groups. In addition, differences in insulin infusion might be related to differences in terms of insulin sensitivity at diabetes onset. Thus, it is important to establish a personalized treatment of patients according to insulin sensitivity at diabetes onset thus reducing the risk of severe complications related to therapy itself.

AUTHOR CONTRIBUTIONS

Concetta Mastromauro collected and analyzed data and wrote the manuscript. Nella Polidori, Annalisa Blasetti, Laura Comegna collected the data. Angelika Mohn and Francesco Chiarelli reviewed the manuscript. All authors provided final approval to submit. Cosimo Giannini wrote and reviewed the manuscript. Cosimo Giannini is the guarantor of this work and, as such, had full access to all the data in the study.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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