Hypertriglyceridemia in Type 1 Diabetes Children During Diabetic Ketoacidosis; Relation to DKA Severity and Glycemic Control

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Abstract

Background: Diabetic ketoacidosis (DKA) is a common, life-threatening complication of type 1 diabetes (T1D). Insulin deficiency impairs lipoprotein lipase (LPL) resulting in elevated serum triglycerides (TG) that usually normalize after establishing IV insulin.

Objectives: To study the prevalence of hypertriglyceridemia during DKA in T1D patients and assess its relation to DKA severity and glycemic control after 3 months.

Methodology: This cohort study included 84 children with T1D presenting with DKA at the Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), Cairo University. Patients were evaluated for serum TG on admission and 48 h after initiating insulin therapy. HbA1c was assessed 3 months later.

Results: In our cohort, 74 patients (88.1%) had hypertriglyceridemia at onset of DKA that resolved in 41 of them after 48 h, while 33 patients still had hypertriglyceridemia. There was significant improvement in TG after 48 h of DKA management (p<0.001). When basal serum TG was correlated with other study parameters, a significant positive correlation was found with BG (p=0.005) and duration of ICU stay (p< 0.001), while a significant negative correlation was found with serum bicarbonate and GCS (i.e. Conscious level) with a p value of 0.012 & 0.022 respectively. No significant correlation was found between TG (basal & after 48 h) and glycemic control or insulin requirements after 3 months.

Conclusion: Hypertriglyceridemia was detected in most patients of T1D during DKA that significantly improved with insulin therapy. TG correlated with the DKA severity and BG levels. However, it did not affect glycemic control or insulin dose later.

Keywords: Hypertriglyceridemia; Diabetic ketoacidosis; Insulin; Glycemic control; Insulin therapy; Lipid metabolism; Circulation; Pancreatic capillaries; Acute pancreatitis; Cerebral edema; Plasmapheresis; Heparin

Abbreviations: DKA: Diabetic Ketoacidosis; T1D: Type 1 Diabetes; LPL: Lipoprotein Lipase; TG: Triglycerides; DEMPU: Diabetes, Endocrine and Metabolism Pediatric Unit; FFA: Free Fatty Acids; TC: Total Cholesterol; TINIA: Turbidimetric Inhibition Immunoassay; DCCT: Diabetes Control and Complications Trial; SPSS: Statistical Program for Social Science; SD: Standard Deviation

Introduction

Regulation of lipid metabolism is greatly influenced by insulin through inhibiting the hormone-sensitive lipase in adipose tissue [1]. The anti-lipolytic action of insulin promotes excessive storage of triglycerides (TG) in the adipocytes with reduction of free fatty acids (FFA) release into the circulation [2]. Diabetic ketoacidosis (DKA) is by far a serious and potentially life-threatening complication of T1D [3]. During an episode of DKA, an increase in TG (in 30-50% of cases) and total cholesterol levels (TC) was reported that probably results from temporary impairment of lipoprotein lipase (LPL) activity [4]. This increase

in serum TG is also associated with increase in chylomicron level leading to milky blood serum [5]. In DKA, insulin deficiency activates lipolysis in adipose tissue releasing FFA accelerating the formation of VLDL in the liver. Reduced activity of LPL in peripheral tissue decreases the removal of VLDL from the plasma as well, causing hypertriglyceridemia [6]. The incidence of acute pancreatitis and cerebral edema is increased in patients with DKA and hypertriglyceridemia [7]. Severe hypertriglyceridemia can increase risk of acute pancreatitis, especially with TG levels higher than 1,000–1,772 mg/dl [8,9].

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This can be attributed to the fact that TG and chylomicrons are hydrolyzed by lipase in the pancreatic capillaries and the released FFA activate the trypsinogen, triggering the capillary damage by free radicals [10,11]. On the other hand, DKA may mask coexisting acute pancreatitis occurring in 10–15% of cases. Ranson's prognostic criteria can overestimate the severity of acute pancreatitis during DKA, so it's not beneficial to use it for assessment of severity. Severity index based on CT findings can be used instead with better prognostic value. Elevation of serum lipase and amylase occurs in DKA. However, elevation in lipase levels appears to be less specific than amylase [12]. Insulin is considered to be the drug of choice in severe hyperlipidemia-induced pancreatitis with concomitant hyperglycemia, while plasmapheresis and heparin can also be used during emergency [13]. The aim of our study was to evaluate the prevalence of hypertriglyceridemia at onset of DKA in T1D patients and assess its relation to DKA severity and glycemic control after 3 months (Figure 1).
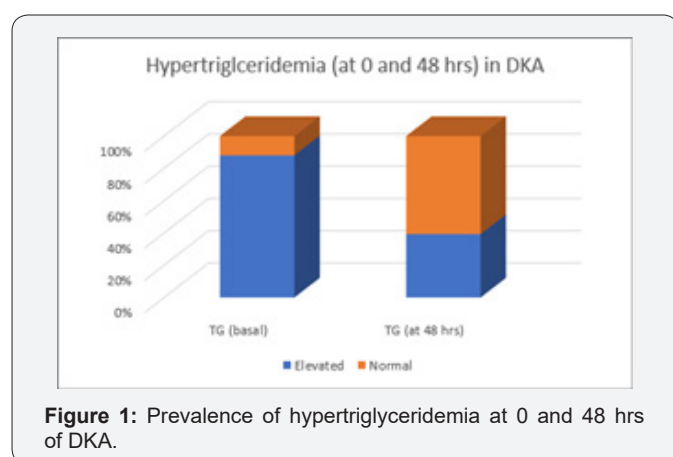

Figure 1: Prevalence of hypertriglyceridemia at 0 and 48 hrs of DKA.

Methodology

This cross-sectional observational study was conducted on random cohort of 84 children with T1D presenting with DKA episode at the Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), Children hospital, Cairo University during the period from January to August 2016. This study was approved by the Research Ethics Committee of Cairo University. The diagnosis of DKA was established according to the ISPAD Clinical Practice Consensus Guidelines 2014 (BG > 200mg/dl, Venous pH < 7.3 or bicarbonate <15 mmol/L, ketonemia and ketonuria) [14]. Children with T2D, with diabetes secondary to post-surgical pancreatectomy, cystic fibrosis, or steroid therapy, or those using thyroxin therapy or any lipid lowering medications as well as those who had family history of dyslipidemia were excluded from the study.

All patients included in the study (after taking informed consents from their legal guardians) were evaluated clinically for conscious level assessment (using Glasgow coma scale) as well as biochemical analysis for BG, ABG, serum electrolytes (Na, K) kidney functions (urea, creatinine). Serum TG were measured initially during DKA presentation then at 48 h of

DKA management (insulin therapy). 2ml blood was drawn into vacutainer tube containing no anticoagulant then incubated in an upright position at room temperature for 20-30 min to allow clotting. Centrifugation for 10 minutes was done. Serum was aspirated (using a clean pipette for each tube) and TG levels (mg/dl) were measured by glycerol phosphate oxidase/peroxidase method by fully automated chemistry analyzer Beckman coulter Inc, USA [15].

A TG level below 150 mg/dl was considered normal. HbA1c (%) levels were measured 3 months later. The HbA1c% measurement is based on a turbidimetric inhibition immunoassay (TINIA) principle, and the measurement of total hemoglobin is based on a modification of the alkaline hematin reaction. Using the values obtained for each of these two analytes in (g/dl), the percentage of the total hemoglobin that is glycated is calculated and reported as %HbA1c. The final HbA1c% result has been standardized to the results obtained in the Diabetes Control and Complications Trial (DCCT).

Data was analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data was expressed as frequency and percentage. Mann Whitney U test was used for two-group comparisons in non-parametric data. Spearman's rank correlation coefficient was used to assess the degree of association between two sets of variables. Linear regression was used to test and estimate the dependence of a quantitative variable based on its relationship to one or more independent variables. P-value <0.05 was considered significant and <0.001 was considered highly significant.

Results

Among the study group (84 cases),43 (51.19%) were males and 41 (48.81%) were females with mean age of 7.1±2.65 years (ranging between 2.5 and 13 years). Sixty-eight (80.95%) were newly diagnosed and 16 (19.05%) were known to be diabetic. Mean BG level at presentation was 490.86±278.74 mg/dl and median TG was 237.75 mg/dl (Table 1). There was a significant difference in prevalence of hypertriglyceridemia at onset of DKA and after 48 h of management (p<0.001). In our cohort, 74 patients (88.1%) had hypertriglyceridemia at onset of DKA ranging from 75.8-10500 mg/dl with significant improvement in TG after 48 h of DKA management (p<0.001). Hypertriglyceridemia completely resolved in 41 of them after 48 h, while 33 patients still had hypertriglyceridemia. One of our patients had high TG level reaching 10500 mg/dl (with milky serum), but acute pancreatitis was ruled out by serum lipase, amylase and CT abdomen, his TG level improved after 48 h of DKA management reaching a level of 1860 mg/dl and resolved completely after 14 days (140 md/dl). When basal serum TG were correlated with other study parameters in our cohort, a significant positive correlation was found with BG level (r= 0.703, p=0.005) and duration of ICU stay (r=0.37, p<0.001), while a significant negative correlation was found with serum bicarbonate and GCS (i.e. conscious level) with a p value of

0.012 & 0.022 respectively. On the other hand, correlating TG after 48 h with different study parameters showed a significant positive correlation with BG level (r= 0.704, p=0.005) and a significant negative correlation with pH, serum bicarbonate and GCS (p=0.01, 0.004 & 0.013 respectively) (Table 2). When insulin requirements and HbA1c were assessed 3 months later in the study group, no significant correlation was found between triglycerides (either basal or after 48 h of DKA) and glycemic control or insulin requirements. When we compared between different study parameters in relation to the onset of DKA (newly diagnosed with first attack of DKA & those known to be diabetic presenting with DKA), we found a significant difference between both groups in mean difference in TG at 0 and at 48 h (p=0.049) (Table 3).

Table 1: Metabolic and biochemical study parameters

	Range	Mean±SD	Median (IQR)
Wt SDS	-3.08-2.33	-0.39±1.06	-0.24 (1.27)
RBG (mg/dl)	249-1170	490.86±278.74	419.5 (178)
pH	6.9-7.34	7.16±0.12	7.1 (0.24)
HCo3 (mEq/l)	1.9-14	8.51±3.01	7.55 (4.25)
GCS	12-15	14.52±0.86	15 (1.25)
TG1 (mg/dl)	75.8-10500	393.53±1126.30	237.75 (128.85)
TG2 (mg/dl)	65.8-1850	160.96±197.17	115.5 (133.93)
HbA1c after 3 mo (%)	6.8-11	8.47±1.03	8.5 (1.075)
TDD of insulin after 3 mo (IU/kg/d)	0.66-1.8	1.18±0.26	1.185 (0.315)

Wt SDS: Weight; RBG: Random Blood Glucose; GSC: Glasgow Coma Scale; TG1: Initial Triglycerides; TG2: Triglycerides after 48 hrs; TDD: Total Daily Dose

Table 2: Correlation between TG1 (basal) & TG2 (after 48 h) and other study parameters

	TG1		TG2	
	r	p-value	r	p-value
Age (years)	-0.166	0.13	-0.142	0.201
RBG (mg/dl)	0.703	0.005	0.704	0.005
pH	-0.187	0.089	-0.283	0.010
HCo3 (mEq/l)	-0.274	0.012	-0.314	0.004
GCS	-0.250	0.022	-0.27	0.013
HbA1c after 3mo (%)	0.056	0.611	0.055	0.624
TDD of insulin after 3mo (IU/kg/d)	-0.005	0.965	0.049	0.657
Duration of total hospital stay (h)	0.528	< 0.001		
Duration of ICU stay (h)	0.37	< 0.001		

RBG: Random Blood Glucose; GSC: Glasgow Coma Scale; TG1: Initial Triglycerides; TG2: Triglycerides after 48 hrs; TDD: Total Daily Dose

Table 3: Comparison between new onset and known T1D regarding study parameters

		Onset of T1D		p-value
		New	Known	
Sex	Male	33 (48.5%)	10 (62.5%)	0.314
	Female	35 (51.5%)	6 (37.5%)	
Age (yrs)		6.860±2.570	8.125±2.831	0.086
RBS (mg/dl)		508.750±298.302	383.500±65.761	0.577
pH		7.160±0.109	7.147±0.142	0.681
HCo3 (mEq/L)		8.238±3.083	9.656±2.453	0.09
GCS		14.500±0.889	14.625±0.719	0.603
TG1 (mg/dl) *		224.9 (141)	297 (249)	0.565
TG2 (mg/dl) *		119 (98)	104 (117)	0.869
HbA1C (%)		8.528±1.047	8.244±0.956	0.324
Insulin TDD after 3 mo (IU/kg/d)		1.177±0.262	1.204±0.243	0.703
TG mean difference (mg/dl)		255.209±1041.397	146.438±124.669	0.049

RBG: Random Blood Glucose; GSC: Glasgow Coma Scale; TG1: Initial Triglycerides; TG2: Triglycerides after 48 hrs; TDD: Total Daily Dose
*Regarding TG, median values were used in comparison instead of mean due to outliers.

Discussion

Moderate hypertriglyceridemia is common during episodes of DKA [16]. However, severe hypertriglyceridemia, which is defined as a TG level >2,000 mg/dl is rare. In severe hypertriglyceridemia, there is an increased risk of developing acute pancreatitis [11].

In our cohort, 74 patients (88.1%) had hypertriglyceridemia at onset of DKA that significantly improved after 48 hrs of DKA management. Our results were similar to Weidman et al. [17] who studied 13 patients with DKA (15-60 yrs) and found that before insulin treatment, plasma TG levels ranged from 63-2800 mg/dl and that 12 patients out of 13 demonstrated dramatic decreases in plasma TG levels after 24 h of insulin therapy. Similarly, Fulop & Eder [16] measured plasma TG and cholesterol concentrations in 50 episodes in 46 adults hospitalized on a Municipal hospital medical service and reported that 32 patients (64%) had TG levels above the 95th percentile (adjusted for age and sex), and 18 patients (36%) had cholesterol levels above the 95th percentile. Severe hypertriglyceridemia (levels above 5.65 mmol/L) was found in 14 patients (28%) and that treatment of the ketoacidosis was associated with a rapid decrease in plasma lipid levels.

Fulop & Eder [6] concluded that 12 of the 15 patients with DKA and hypertriglyceridemia did not have an underlying genetic hyperlipidemia contributing to their original severe hypertriglyceridemia during DKA episode. However, Karagianni et al. [18] analysed the lipoprotein lipase coding gene sequence in a 10-year-old girl with new-onset T1D, ketoacidosis and severe hypertriglyceridemia (TG > 112.9 mmol/l) and revealed that the patient was a compound heterozygote for two mutations, D9N in exon 2 and S447X in exon 9. Although these two mutations usually did not considerably impair lipolytic enzyme activity, the combination of both in that patient may have played a role in the development of severe hypertriglyceridemia. Similar findings were reported also by Rodríguez Santana et al. [19].

In our cohort, despite high TG that reached 10500 mg/dl in one patient, none of our patients developed acute pancreatitis. Similarly, a case report in Brazil had TG level during DKA episode of 11578 mg/dl, yet she did not develop acute pancreatitis and the levels of TG decreased significantly with hydration and intravenous insulin [20]. Many case reports showed the association of DKA with severe hypertriglyceridemia and acute pancreatitis [21-28]. Nair et al. [12] studied 100 patients with DKA and hypertriglyceridemia and confirmed that the prevalence of acute pancreatitis was 11%.

When basal serum TG were correlated with other study parameters, a significant positive correlation was found with BG level and duration of ICU stay, while a significant negative correlation was found with serum HCO3 (i.e, severity of DKA) and GCS (i.e. conscious level). This could be attributed to the fact that the insulin deficiency is the cause of hypertriglyceridemia and that the more severe the insulin deficiency, the higher the BG level and the more severe the DKA (more acidosis) and the higher the TG will be and the longer the duration of ICU stay (need for IV insulin therapy for correction of acidosis and dehydration). When we compared between different study parameters in relation to the onset of DKA (newly diagnosed with first episode of DKA & those known to be diabetic presenting with DKA), we found a significant mean difference in TG (p=0.049). This also can be attributed to the degree of insulin deficiency as those with first episode of DKA are supposed to be more insulin deficient that those who are known to be diabetic on insulin therapy but developed DKA due to relative insulin deficiency.

When insulin requirements and HbA1c were assessed 3 months later in the study group, no significant correlation was found between triglycerides (either basal or after 48 hrs of DKA) and glycemic control or insulin requirements (TDD). This could be explained by the fact that the severity of DKA (and insulin deficiency) that affected serum TG during DKA episodes was not persistent after establishing insulin therapy, hence not affecting glycemic control after 3 months.

Conclusion

Hypertriglyceridemia was detected in most patients of T1D during episodes of DKA (reaching values as high as 10500 mg/dl without developing acute pancreatitis) that significantly declined with insulin therapy. Serum TG correlated with the DKA severity and BG levels. However, it did not affect glycemic control or insulin dose later on.

Acknowledgement

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of Cairo University and National Research Center and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed Consent

Informed consent was obtained from every individual participant included in the study.

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