

Assessment of Metabolic Derangements in Diabetes and Associated Hyperglycemic Emergencies

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ABSTRACT

Objective: To assess and compare the plasma insulin level and Pre-treatment metabolic and acid base status findings in patients with uncontrolled T1DM, uncontrolled T2DM, DKA and HHS with healthy non-diabetic subjects.

Study Design: A retrospective analytical study.

Place and Duration of Study: This study was conducted at the Army Medical College, Rawalpindi during the period from 2004 to 2006.

Materials and Methods: This study was conducted on T1DM, T2DM, DKA and HHS patients and monitored insulin level, plasma osmolality, serum electrolytes and arterial blood gases levels revealed that the clinical records and data confirmed and described each event and its likely causes.

Results: Ketoacidosis was frequently seen among persons with type 1 diabetes with marked hypoinsulinemia, hyperkalemia and acidosis. Hyperinsulinemia, acidosis and hyperosmolality were the significant finding in HHS.

Conclusion: The observed association between insulin level and pretreatment metabolic and acid base derangements were statistically highly significant.

Key Words: diabetic ketoacidosis (DKA), Hyperosmolar hyperglycemic state (HHS), Oxygen saturation, plasma osmolality, Hypokalemia.

INTRODUCTION

A dwarfish thief today, diabetes, is a menace that haunts the society, thriving every single moment. The onset of T2DM is mostly seen in middle-aged adults; whereas, T1DM is usually seen at a younger age group¹. Uncontrolled and persistent hyperglycemia in diabetes can lead to the development of serious life-threatening medical emergencies i.e. diabetic ketoacidosis (DKA) and Hyperosmolar hyperglycemic state (HHS)². HHS, first reported by Sament and Schwartz in 1957³, is characterized by significant hyperglycemia, hyperosmolality and dehydration without marked ketoacidosis. It is mostly a consequence of T2DM. Its diagnosis was established by the American Diabetic Association according to which diagnostic features are plasma glucose level ≥ 600 mg/dl, serum osmolality ≥ 320 mOsm/kg, severe dehydration, blood pH >7.30 , Bicarbonate conc. > 15 mEq/L and altered sensorium⁴.

Diabetic Ketoacidosis, usually a consequence of T1DM, is typically characterized by hyperglycemia (blood glucose ≥ 300 mg/dl), low plasma bicarbonate level (< 15 mEq/L), and acidemia (blood pH ≤ 7.30) associated with ketonemia, ketonuria and altered sensorium. Absolute insulin deficiency, in T1DM, impairs uptake and utilization of glucose by the cells leading to hyperglycemia and ketoacidosis. HHS is less common than DKA and differs in the degree of dehydration, ketosis, and acidosis⁴.

Serum Osmolality: Hyperglycemia and associated dehydration raises plasma osmolality due to increase in

the number of osmotically active glucose particles. It is a diagnostic feature of HHS⁵.

Plasma Electrolytes: Electrolyte balance is vital for normal functioning of cells and various systems of our body. Significant electrolyte abnormalities are seen in DKA and HHS. Osmotic Diuresis leads to significant loss of salts, mainly potassium and sodium, into the urine leading to Hypokalemia and hyponatremia respectively. In DKA, Ketoacids are excreted in urine as salts of potassium and sodium. Hence, Hypokalemia is a potentially lethal complication of DKA. However, due to hypoinsulinemia and raised plasma osmolality, intracellular potassium moves into the extracellular fluid. Hence, clinically initial laboratory tests may show hyperkalemia. Correction of acidosis and insulin administration will force the Extracellular potassium to move back into the cells resulting in lethal Hypokalemia⁶.

Acid Base balance: In both hyperglycemic states of DM, ketoacids (i.e. β -hydroxybutyrate and acetoacetate) and lactic acid overproduction seriously alters the blood pH and develops acidosis. The bicarbonate ions act as a buffer to maintain the normal blood pH. Hence, Bicarbonate levels are measured to assess the acid base status of body fluids (normal 22-30 mmol/L). As severity of hypoinsulinemia increases, more ketoacidosis results in fall of blood pH and metabolic acidosis is induced⁷.

MATERIALS AND METHODS

The present retrospective, analytical case control study was conducted during the period of 2004 -2006. Non-

probability convenient sampling technique was used. The sample size was 72. The patients were selected from Military hospital (MH), Combined Military hospital (CMH) Rawalpindi. Patients were divided into five groups:

Control Group (n = 25) Non diabetic healthy subjects, having a fasting blood glucose level ≤ 6 mmol/L.

Patients with Uncontrolled T2DM (n = 20). Already diagnosed cases of T2DM and treated with oral hypoglycemic, were included in this group.

Patients with Uncontrolled T1DM (n = 14). Already diagnosed type 1 diabetics, who were on insulin therapy, were included in this group.

Patients with Diabetic ketoacidosis (DKA) (n = 9) This group comprised of comatose or semi-comatose patients having findings of acetone breath, ketonuria, random blood glucose level > 10 mmol/L, serum osmolality < 350 mOsm/L and Arterial blood pH < 7.35 .

Diabetic Patients with Hyperosmolar hyperglycemic state (HHS). (n = 4)

Patients having findings of HHS like absence of acetone breath and ketonuria, Random blood glucose levels > 30 mmol/L and Serum Osmolality > 350 mOsm/L.

Laboratory investigations: Venous blood was analyzed for plasma glucose, Osmolality and serum

electrolytes. Arterial Blood samples were analyzed for arterial blood gases and degree of acidosis.

Plasma glucose was estimated by an enzymatic colorimetric method (glucose Oxidase enzyme), Plasma insulin level was estimated by enzyme — linked immunosorbent assay (ELISA) technique (8), Plasma osmolality was determined by Freezing point depression method, Plasma electrolytes, blood gases and pH was estimated by Ion selective electrode method, conc. of HCO_3^- ions was calculated by using the measured parameters in the Henderson — Hasselbalch equation⁹.

RESULTS

Results are summarized and shown in tables 1 – 2. Table 1 shows the distribution of sex, age, plasma glucose, plasma Insulin, serum sodium and serum potassium levels among various study groups as compared with controls. Mean age of patients with Diabetic ketoacidosis was significantly lower ($p < 0.05$) whereas significantly higher in patients with type 2 DM ($p < 0.05$) and HHS ($p < 0.001$). Mean plasma glucose level in patients of all four groups was significantly higher ($p < 0.001$) as compared with control subjects. Mean plasma insulin level in the patients of uncontrolled T2DM was significantly higher ($p < 0.05$) and significantly lower in patients with T1DM ($p < 0.05$) and DKA ($p < 0.01$) as compared with control subjects. The mean plasma sodium level was significantly lower in patients with Uncontrolled T1DM ($p < 0.001$), DKA ($p < 0.05$) and HHS ($p < 0.001$). The mean plasma potassium level was significantly higher in patients with Uncontrolled T1DM and DKA ($p < 0.001$), T2DM ($p < 0.05$) and HHS ($p < 0.01$).

Table No. 1: Comparison of gender, age, plasma glucose, plasma Insulin, serum sodium and potassium levels of various study groups (values= mean $\pm$ s.e.m).

Sex		Control(25)	T2DM (20)	T1DM (14)	DKA (09)	HHNK (04)
	Males	50 %	56 %	58 %	65 %	59 %
	Females	50%	44 %	42 %	35 %	41 %
Age (years)		38.5 $\pm$ 1.3	49.2 $\pm$ 3.1*	32.0 $\pm$ 2.5	29 $\pm$ 5.8*	63.45 $\pm$ 5.8***
Plasma glucose(mmol/L)		5.35 $\pm$ 0.1	18.7 $\pm$ 1.23***	17.9 $\pm$ 0.82***	28.6 $\pm$ 0.4***	39.7 $\pm$ 0.38***
Plasma insulin (ng / 100 ml)		56.5 $\pm$ 10.8	83.0 $\pm$ 0.25*	31.5 $\pm$ 1.36*	17.5 $\pm$ 1.43**	44 $\pm$ 1.02
Serum sodium (mmol/L)		137 $\pm$ 0.5	137.5 $\pm$ 0.7	130.6 $\pm$ 1.28***	136.8 $\pm$ 0.3*	134 $\pm$ 0.4***
Serum potassium (mmo1/L)		3.7 $\pm$ 0.20	4.02 $\pm$ 1.2*	4.8 $\pm$ 0.8***	4.53 $\pm$ 0.23***	4.4 $\pm$ 0.2**

Table 2 shows the comparison of plasma osmolality, blood pH, PCO_2 , PO_2 Plasma HCO_3^- , Base excess and Oxygen saturation of various study groups with the control group. Mean plasma osmolality was significantly higher in the patients with uncontrolled T2DM ($p < 0.01$), uncontrolled T1DM ($p < 0.05$), DKA

and HHNK ($p < 0.001$) as compared with control subjects. Blood pH was significantly lower in the patients with T1DM ($p < 0.01$), DKA ($p < 0.001$) and HHS ($p < 0.05$). Plasma HCO_3^- was also significantly lower in the patients with HHS ($p < 0.05$) and DKA ($p < 0.001$). PCO_2 was significantly lower ($p < 0.05$) in

DKA. Highly Significant base deficit ($p < 0.001$) was observed in patients with DKA as compared with the control group. Oxygen saturation was found to be

significantly lower ($p < 0.001$) in the patients with T1DM, DKA and HHS.

Table No.2: Comparison of plasma osmolality, blood pH, PCO₂, PO₂, Plasma HCO₃, Base excess and Oxygen saturation of study groups.

	Control (25)	T2DM (20)	T1DM (14)	DKA (09)	HHNK (04)
Plasma osmolality (mOsmol/Kg of water)	280 ± 0.6	299 ± 1.9**	290 ± 1.4*	325.9 ± 3.1***	367 ± 2.2***
pH	7.43 ± 0.02	7.42 ± 0.04	7.36 ± 0.13**	7.33 ± 0.07***	7.37 ± 0.33*
Plasma HCO₃ (mmol/L)	23.7 ± 0.2	25.0 ± 0.4	26.0 ± 2.2	14.4 ± 2.5***	19.0 ± 0.3*
PCO₂ (mm Hg)	38.0 ± 0.9	38.25 ± 2.5	37.44 ± 1.786	26.75 ± 3.25*	30.12 ± 0.24
PO₂ (mm Hg)	85.2 ± 2.7	87.21 ± 1.37	79.5 ± 3.21	86.5 ± 10.2	84.9 ± 2.10
Base excess/Deficit	2.6 ± 0.2	3.0 ± 0.4	3.2 ± 1.4	0.3 ± 2.0***	3.8 ± 1.7*
Oxygen saturation (%)	96.2 ± 0.2	96.4 ± 0.3	90.6 ± 1.6***	79.2 ± 7.0***	81.0 ± 2.1***

As compared with normal control subjects * $p < 0.05$ (significant).
** $p < 0.01$ (very significant). *** $p < 0.001$ (highly significant).

DISCUSSION

This study focused primarily on assessment and comparison of the plasma insulin level and pre-treatment metabolic findings in patients with uncontrolled T1DM, uncontrolled T2DM, DKA and HHS with healthy non-diabetic subjects.

Age & Sex Distribution: It was noted that various types of diabetes and associated hyperglycemic emergencies were more common in males. T1DM and DKA were mostly seen in younger age group. This finding was in accordance with previous studies¹⁰.

Plasma Insulin & Hyperglycemia: Significant insulin excess was observed in uncontrolled T2DM due to insulin resistance mainly affecting adipose tissues, liver, and muscle cells. Marked hyperglycemia induces more insulin production. The decreased number of insulin receptors also contributes in hyperinsulinemia in T2DM¹¹. This also shows the inability of cells to properly oxidize glucose resulting in hyperglycemia⁵.

Hypoinsulinemia observed in T1DM and DKA, determines the intensity of osmotic and ketotic excess. If plasma insulin and glucose levels are monitored regularly, metabolic disturbances can be minimized i.e. more careful management of T1DM can make DKA preventable¹².

Most of the patients belonged to lower socioeconomic status. In our study negligence in treatment, poor dietary habits and lack of exercise were also found among the major causes of uncontrolled hyperglycemia¹³.

Plasma Osmolality was significantly raised in DKA and HHNK. As the magnitude of hyperglycemia and dehydration is more marked in HHS, hence the degree of hyperosmolality was also more marked¹⁴.

Electrolyte disturbances: An inverse relationship between the serum concentration of sodium and

potassium was observed in diabetic patients. Serum sodium level was significantly decreased in patients with uncontrolled T1DM, DKA and HHS. Osmotic diuresis leading to electrolytes loss, older age, severe dehydration and impaired fluid intake in HHS accounts for higher mortality¹⁵.

The ketoacids fully dissociate at physiological pH. So ketonuria leads to excretion of positively charged cations (i.e. Na⁺, K⁺, NH₄⁺). The hydrogen ions are titrated by plasma bicarbonate, resulting in metabolic acidosis and retention of anions leads to increase in the plasma anion gap¹⁶.

During DKA and HHS, hyperglycemia and increased plasma Osmolality results in intracellular dehydration which is associated with a shift of potassium out of cells into the extracellular space leading to hyperkalemia. This is further enhanced by acidosis and the breakdown of intracellular protein secondary to insulin deficiency. Moreover, insulin deficiency prevents re-entry of K⁺ into the cells. Hence it is a false hyperkalemic state. Osmotic diuresis and ketonuria leads to increase K⁺ loss in urine. Hypokalemia can be prevented by better intake of food, salt and fluid prior to diabetic emergencies. Whereas, diabetic patients with poor history of food, salt and fluid intake develop acute metabolic decompositions, dehydration, hyperosmolality and impaired renal function leading to an increased anion gap and altered sensorium¹⁷.

Arterial Blood Gases: Analysis of the blood Ph, PCO₂ and PO₂ is essential to evaluate the severity of disease. Acidemia was observed in T1DM, DKA and HHS. In DKA, ketoacids dissociate and get neutralized by the bicarbonate ions; hence, serum bicarbonate level is decreased¹⁸. This leads to the increased anion gap, a characteristic feature of DKA. Metabolic acidosis leads to hyperventilation resulting in decreased PCO₂¹⁹.

In HHS, hyperglycemia is usually accompanied with lactic acidosis. This can also be aggravated by oral hypoglycemic drugs²⁰.

Oxygen saturation represents the amount of oxygen carried by erythrocyte hemoglobin and helps to assess the extent of hypoxia and acidosis. It was markedly reduced in T1DM, DKA and HHS due to tissue hypoxia. These findings are in accordance with the previous studies²¹.

CONCLUSION

With increase in severity of insulin deficiency, drastic outcomes of DM in the form of DKA and HHS result with serious metabolic and acid base disturbances. Improvement in glycaemic control can decrease the severity of the symptoms. Moreover patients should be educated about the importance of low calorie diet, regular exercise and glycaemic control to avoid fatal complications of DM.

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