Evaluation of Diabetic Coma in Ondokuz Mayıs University Medical Faculty, Department of Internal Medicine:A retrospective study of 12 years

Dr. Hakkı KAHRAMAN, Dr. Fulya TANYERİ, Dr. Birol ÖZER,
Dr. Nadir KAYA, Dr. Nihat TEKDEN
Ondokuz Mayıs Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı SAMSUN

✔ Diabetic ketoacidosis (DKA) and nonketotic hyperglycemic hyperosmolar coma (NHHC) are the two most common acute complications of diabetes mellitus and make up a significant percentage of the nonsurgical emergencies seen in any general hospital. These syndromes have devastating outcomes if not treated promptly. The aim of this study was to evaluate clinical and biochemical characteristics of our patients with diabetic coma.
In this study, patients with diabetic coma admitted to the clinics of internal medicine from 1984 to 1996 were evaluated retrospectively. Fifty eight patients (mean age 52.47±17.92 years), 36 female, 22 male, were hospitalised because of diabetic coma. Seventeen patients had type I diabetes mellitus, 41 patients had type II diabetes mellitus. DKA was diagnosed in 28 patients and 30 patients had NHHC. The factors that precipitated coma were detected in 29 patients (50%), 4 patients (6.9%) had ceased insulin therapy by themselves. After the patients were admitted to the hospital, miniinsulin regimen was started in addition to fluid and electrolyte therapy. Ketonuria, blood glucose, plasma osmolality and pH, blood urea nitrogen (BUN), creatinin, sodium, potanssium levels were determined before the treatment and after 24 hours of miniinsulin therapy. Ketonuria was still present in 12 patients with DKA within 24th hours of miniinsulin therapy. Hypopotassemia (27.5%) was the most common complication of the therapy. Fatality was 14.2% in patients with DKA and 36.6% in patients NHHC. There was no correlation between hypopotassemia and mortality rates. Mortality rate in patients with NHHC was higher than patients with DKA, but this difference was not statistically significant.

Key Words: Diabetes mellitus, diabetic ketoacidosis, nonketotic hyperglicemic hiperosmolar coma

✔ Diyabetik ketoasidoz ve nonketotik hiperglisemik hiperozmolar koma diyabetes mellitus'un, en ciddi ve tedavi edilmedikleri zaman ölümle sonlanabilen akut komplikasyonlarındandır. Cerrahi dışı acil vakaların önemli bir kısmını oluştururlar. Bu retrospektif çalışmada, diyabetik komalı (DKA ve NHHK) hastalarımızın klinik ve biyokimyasal özellikleri ile birlikte tedavi sonuçlarının değerlendirilmesi amaçlandı.
1984–1996 yılları arasında iç hastalıkları servisine alınan, ortalama yaşı 52 olan, 36'sı kadın, 22'si erkek olmak üzere toplam 58 diyabetik komalı hasta retrospektif olarak incelendi. Onyedi hastada tip I, 41 pastada tip II diyabetes mellitus mevcuttu. Yirmi sekiz hastaya DKA, 30 hastaya da NHHK tanısı konuldu. Yirmi dokuz (%50) hastada komayı presipite eden neden belirlendi, 4(%6.9) hasta insülin tedavisini kendiliğinden terketmişti. Hastaneye yatırıldıktan sonra her hastaya düşük doz insülin tedavi protokolü uygulandı. Tedavi öncesi ve tedavinin 24. saatinde, ketonüri ve plazma ozmolalitesine, serum glukoz, BUN, kreatinin, sodyum ve potasyum düzeylerine bakıldı. Koma tedavisi süresince ortaya çıkan komplikasyonlar tespit edildi. En sık rastlanan komplikasyon hipopotasemiydi ve hastaların %27.5'inde görüldü. Mortalite hızı DKA için %14.5, NHHK için %36.6 olarak hesaplandı. NHHK'nın mortalite oranı DKA'ya göre daha yüksekti, ancak bu fark istatiktiksel olarak anlamlı değildi.

Anahtar Kelimeler: Diyabetes mellitus, diyabetik ketoasidoz, nonketotik hyperglisemik hiperosmolar koma

Diabetic ketoacidosis (DKA) and nonketotic hyperglycemic hyperosmolar coma (NHHC) are two of the most common acute complications of diabetes that have devas-

tating outcomes if not treated promptly. Because diabetes is a common illness in the general population, the syndromes of diabetic coma (DKA and NHHC) make up a significant percentage of the nonsurgical emergencies seen in any general hospital[1]. These complications can be the first presentations of diabetes mellitus or can occur secondary to inappropriate therapy. In both situations, intercurrent stress or illness can precipitate the coma.

DKA is a common illness in patients with diabetes. True prevalance is unknown, but the rate was established to be 13.4 episodes per 1000 patient-years in young persons with insulin dependent diabetes mellitus[2]. Annual rate is 14 per 100.000 of total population[3]. Diagnostic criteria for DKA are as follows: serum glucose >250 mg/dl, serum bicarbonate <15 mEq/L, blood pH<7.3, ketonemia and ketonuria[4].

Good epidemiologic studies on the incidence of NHHC are sparse. Recent data suggest an incidence of 10 cases per 100.000 of the general population[3]. It usually occurs in elderly diabetic patients, but this syndrome can also develop in childhood (even in infants) and adult insulin dependent diabetics, and ketosis-prone diabetes mellitus [5,6,7]. NHHC is defined as those individuals with the following biochemical profile: serum osmolality >330 mOsmol/kg, serum glucose >600 mEq/L, mental obtundation, no ketonuria and no ketonemia[8].

The aim of this retrospective study was to investigate clinical and biochemical characteristics of our patients with diabetic coma, results with the low dose insulin therapy, comlications of therapy, and mortality rates of DKA and NHHC.

PATIENTS and METHODS

Fifty eight patients, 36 (62.1%) female, 22 (37.9%) male, who were hospitalized because of diabetic coma in Ondokuz Mayıs University Medical Faculty Department of Internal Medicine between 1984-1996 years were evaluated retrospectively. Their mean age were 52.47±17.92 years (range 17 to 85). Duratian of the disease, type and chronic complications of diabetes, illness or stress provoked coma were determined. Admitting laboratory data including, ketonuria, blood glucose, plasma osmolality and pH, serum creatinin, BUN, sodium and potassium were recorded before the treatment. The diagnosis of DKA and NHHC were made according to previously published criteria[4,8]. All patients received low dose insulin regimen in addition to fluid and electrolyte therapy. Biochemical study had been repeated every six hours, but only laboratory data of the 24th hour were used for statistical analysis. Complications or events seen during therapy, and fatality rates were recorded. The statistical analysis of the data were performed using student's t-test, paired t-test Mann-Whitney U test, yates corrected chi-squared test and Fisher exact test. Unless otherwise specified, results were expressed as the mean±SD for all 58 patients.

RESULTS

Fifty eight patients (22 male, 36 female) with diabetic coma were evaluated. The diagnosis was type I diabetes mellitus in 17 (29.3%), type II diabetes mellitus in 41 (70.7%) patients. Mean age of type I diabetic was 30.31±8.04, mean age of type II diabetics was 60.90±12.58 years. Type II diabetics were older than type I diabetics ($p<0.001$). Precipitating factors for the development of coma were established in 33 (56.9%) patients (Table-1). On admission, DKA was diagnosed in 28 (48.3%) patients, NHHC was diagnosed in 30 (51.7%) patients. Chronic complications of diabetes that could be determined are shown in Table-2. In some

Tablo-1: Possible acute precipitating factors for development of DKA and NHHC

	Number	Percent
Urinary tract infection	8	13.8
Upper airway infection	7	12.1
Abscess	5	8.6
Gastroenteritis	4	6.9
Omission or inadequate insulin	4	6.9
Pneumonia	3	5.2
Trauma	2	3.4
Unknown/micellaneous	25	43.1

Tablo-2: Chronic diabetic complications determined in patients with diabetic coma

	Number	Percent
Neuropathy	19	32.7
Retinopathy	17	29.3
Nephropathy (late phase)	13	22.4
Macroangiopathy	7	12.0

patients, there were multiple complications. All clinical and biochemical data of the patients are summarised in Table-3. Low dose insulin regimen was preferred in all patients after admission. The laboratory findings of patients with DKA and NHHC, at the beginning and 24 hours after the therapy, are summarised in Table-4,5. Ketonuria was still present in 12 (42.9%) patients with DKA at the end of 24th hour of therapy. Hypopotassemia was the most common complication during treatment of diabetic coma (Table 6).

Fifteen patients died, in this series, the overall mortality rate for diabetic coma was 25.9%, and females had a higher mortality (eleven of 36, 30.6%) than males (four of 22, 18.2%). Duration of diabetes was significantly longer in the patients who died, compared with the patients who survived

Tablo-3: Clinical and laboratory findings of patients with DKA and NHHC

	DKA (n=28)	NHHC (n=30)	p value
Age (years)	43.53±15.99	60.80±15.62	<0.001
Duration of diabetes (months)	79.38±81.96	90.80±81.71	>0.05
Laboratory results (on admission)			
• Plasma Na (mEq/L)	137.35±5.56	143.46±10.78	<0.01
• Plasma K (mEq/L)	4.84±1.07	4.97±1.32	<0.05
• Plasma glucose (mg/dl)	484.50±148.35	707.80±180.16	<0.001
• Plasma BUN (mg/dl)	33.57±26.13	61.93±39.28	<0.01
• Plasma creatinine (mg/dl)	1.36±0.54	2.94±1.69	<0.001
• Plasma osmolality (mOsmol/kg)	318.57±14.87	353.60±27.74	<0.001

Tablo-4: Laboratory features of patients with DKA

	On admission	24 hours after treatment	p value
Na (mEq/L)	137.35±5.67	139.15±4.88	>0.05
K (mEq/L)	4.84±1.07	3.82±0.61	<0.001
Glucose (mg/dl)	484.50±148.35	221.42±98.74	<0.001
BUN (mg/dl)	33.57±26.13	23.75±15.25	<0.05
Creatinine (mg/dl)	1.36±0.54	1.12±0.67	>0.05
Osmolality (mOsmol/kg)	318.57±14.87	297.50±42.68	<0.01

($p<0.01$). Mean age and initial laboratory results did not differ significantly between two groups. There was no correlation between hypopotassemia and mortality rate. Four (14.2%) patients with DKA and eleven (36.6%) patients with NHHC were died. Mor-

Tablo-5: Laboratory features of patients with NHHC

	On admission	24 hours after treatment	p value
Na (mEq/L)	143.46±10.78	143.04±8.90	>0.05
K (mEq/L)	4.97±1.32	4.13±0.76	<0.01
Glucose (mg/dl)	707.80±180.16	267.11±116.40	<0.001
BUN (mg/dl)	61.93±39.28	43.60±32.80	<0.01
Creatinine (mg/dl)	2.94±1.69	2.33±1.71	>0.05
Osmolality (mOsmol/kg)	353.60±27.74	319.56±16.57	<0.001

Tablo-6: Complications that developed in the course of treatment for diabetic coma

	Number	Percent
Hypopotassemia (K <3.4 mEq/L)	16	27.5
Heart failure	7	12.0
Arrhythmias	6	10.3
Brain edema	4	6.9
Hypoglycemia	3	5.2
Infection	2	3.4
Intracranial hemorrhage	1	1.7

tality rate of patients with NHHC was higher than the patients with DKA, but this difference was not statistically significant.

DISCUSSION

Patients with diabetes mellitus are vulnerable to acute complications such as diabetic coma that is fatal if not treated appropriately. In diabetic patients, these complications are frequently encountered problems and major causes of death. In USA, diabetic coma (DKA and NHHC) accounts for 67.400 hospitalizations and result in 3600 deaths each year[9]. Decompensation of the disease can occur secondary to intercurrent events or illness, or appear spontaneously

in the absence of obvious precipitating factors. If pathophysiological mechanisms of diabetic coma are well understood and precipitating illness are known, and if diabetic coma could be diagnosed early and rapidly appropriate treatment could be judiciously applied, most patients would recover[10].

In spite of advances over the past several decades in the understanding and treatment of insulin dependent diabetes mellitus, the incidence of diabetic ketoacidosis has not decreased[11]. Also, overall incidence of NHHC did not decrease. Patients with insulin dependent diabetes are usually prone to DKA, but NHHC can occur in childhood and adult insulin dependent diabetes mellitus[6,7]. If a type I diabetic patient takes enough insulin to prevent ketoacidosis (by limiting free fatty acid mobilization), but not eough to control hyperglycemia, NHHC may develop(10). In our series, NHHC developed in 2 (11.7%) patients with type I diabetes mellitus. Since type II diabetes is more frequent among adults, 70.7% of patient with diabetic coma who were hospitalized in our clinic belonged to this type. For the same reason, type II diabetes was olsa more frequent (46.4%) among our patients with DKA. In other words, 13 of 41 type Ii diabetic patients (31.7%) had DKA. İt was generally reported that DKA is rarely seen in the type II diabetics(12,13). But there are several studies in contrast with this opinion. Yudkin et al[14] have found DKA in 34% of their patients with diabetic coma over 70 years of age. Similarly, the frequency of DKA was reported to be high in elderly patients[15,16]. Furthermore, Johnson had declared that 58% of his patients with DKA had adult type diabetes[2].

In many instances acute illness is the precipitating factor for development of DKA and NHHC. Infection, such as pneumonia septicemia, gastroenteritis, abscess or urosepsis were reported as the most frequent precipitating causes, that were noted in occurance of 35 to 60%[17,18,19]. In 45 percent of our patients, precipitating factor was infection, this rate is not different from literature. Second most common precipitating cause is the omission or inadequate usage of insulin. In diabetic patients, this factor contributes to the DKA in 28 percent of the cases[3]. In our series 14.2 percent of cases with DKA stopped their insulin therapy themselves.

At the begining of this century, DKA accounted for more than 60 percent of deaths in diabetic patients. With the use of insulin therapy, this figure decreased to 1.5% in the 1950s[20]. Since then no major strides have been made in improving the survival of patient with diabetes mellitus. The mainstay of therapy in diabetic coma is insulin, replacement of fluid and electrolytes. But there has been much discussion during the last few years on the amount of insulin that should be used in the treatment of DKA.

There may be some advantage of larger doses, since presumably at higher concentrations, binding of insulin to the insulin–like growth factor–I (IGF–I) receptor would occur, providing additive metabolic effect after the insulin receptor is saturated[21] It has been shown that diabetic ketoacidosis can be reversed by IGF–I infusion, in a patient with severe insulin resistance(22). In contrast, most authorities continued to advocate the use of low dose insulin for DKA therapy. In a previus study, 48 patients with moderate to severe DKA were randomly assigned to receive either conventional high–dose insulin therapy or low–dose insulin therapy. The time required for the plasma glucose level to reach 250 mg/dl or lower was not significantly different in the high-

dose and low-dose groups. Other biochemical and clinical features in both groups were similar except for the development of hypoglycemia in 25% of patients in the high-dose group and the absence of hypoglycemia in the lower-dose group. Furthermore, hypopotassemia (potassium <3.4 mEq/L) was observed during treatment of seven patients (29.2%) in hing-dose groupbut in a few patients (4.2-7 %) in low-dose group[19,23]. Only low-dose insuline regimen is preferred in our clinic. Hypoglycemia developed in 5.2% of our patients with diabetic coma.

Although all patients received low-dose insulin regimen in our series, hypopotassemie (potassium <3.4 mEq/L) developed in 16 (27.5%) of our patients with DKA, which was higher than reported in the literature.

Infection, pancreatitis, urinary infection, shock, vascular thrombosis, myocardial infarction, pneumonia can be either precipitating factors or complications of diabetic coma[4,24,25]. Urinary tract infections may occur because of poor urine flow, and pneumonia may be due to dehydration or to aspiraiton. In this study, most infections are evaluated as a precipitating factor (Table-1). Other complications of diabetic coma are shock and vascular thrombosis [25]. We did not diagnose any vascular thrombosis but six (10,3%) of our patients developed shock. In diabetic coma, vascular collapse (shock) is due to combination of profound volume depletion and acidosis. If the response to appropriate treatment is not prompt, gram-negative sepsis or silent myocardial infarction may be present[10]. The mechanism of vascular thrombosis is multifactorial. Dehydration and contracted intravascular volume, low cardiac output, increased blood viscosity, underlying atherosclerosis and certain hemostatic changes prodispose a patient with diabetic coma to thrombosis[25,26,27].

There are a number of complications that accompany or follow a successfully DKA and NHHC treatment. When death occurs in patients with diabetic coma, it may be result of the disease itself or a result of the complications of the therapy. Metabolic derangements are of greatest concern in patients with diabetic coma because they can result in early death. Many of the therapeutic complications can be prevented by knowledgeable, continuous and systemic approach to treatment. Hypoglycemia, cerebral edema, pulmonary edema, hyperchloremic acidosis, paradoxical central nervous system acidosis, phosphorus depletion, hypopotassemia are the most frequent complications of therapy[4,11,24,28,29]. Hypoglycemia is the most common complication (25% of patients) in high dose insulin infusion protocols[23]. This complication can be decreased by the utilization of low dose insulin protocols[8]. Hypoglycemia was developed in 5.2% of our patients. This rate was low in this series, because low dose insulin regimen had been used in all of our cases.

Brain edema is relatively common in DKA, but can also be seen in NHHC[30,31]. Thus, careful monitoring of the patient's clinical status is important throughout therapy. The true incidence of this complication is unknown but appears to be low. Although CT imaging has demonstrated subclinical brain edema in all of children scanned during DKA, clinically apparent brain edema occurs in only 0.7 percent of children with DKA[11,29]. In adult patients with DKA, it has been shown that subclinical brain edema may be a common phenomenon during treatment[32,33]. Clinically apparent brain edema developed in 4 (6.9%) of our patients with diabetic coma. One of these patients had DKA, the others had NHHC. Patient with DKA who developed brain edema recovered with appropriate

therapy; but 3 patients with NHHC died. The pathogenesis of brain edema in these patients has not been established, and there is no consesus on treatment. Some authors speculate that less rapid correction of hypertonicity may decrease the frequency of this rare complication[32,34]. Even though rare, the outcome of patients with brain edema is poor, or associated with serious neurologic sequelae[8,28]. Intracranial hemorrhage developed in one of our patient during the course of the treatment. The exact mechanism of this complication is unknown.

Prior to the discovery of insulin, the mortality rate associated with episodes of DKA was almost %100, and NHHC was also very high(3). In most reports after 1960s, mortality rates are 1 to 15 percent for DKA, and 36 to 70 percent for NHHC[3,8,31,35-38]. However, in one series, Gerich et al[5] reported even better results for NHHC with a mortality of 20 percent. In children with NHHC, mortality is lower than older patients[31]. There is almost unanimous agreement among reviewers on the subject that the mortality rate is far greater for NHHC than DKA. Our results were not different from most reports, in this series, mormality rate was 14.2% for DKA and 36.6% for NHHC. Many factors such as prompt therapy, continuous observation, patient's age, appropiriate therapy of the precipitating illness, appropriate use of insulin fluid may affect mortality rate in diabetic coma.

In conclusion, despite many advances in then verall treatment of diabetes mellitus during the last few years, no major advances has been made in decreasing the mortality rates of DKA and NHHC. A major concern in both of these disease states is the development of some complications. The principles of therapy in both disease states are rehydration, electrolyte replacement, insulin therapy, and treatment of any underlying illnesses. Our findings clearly show that one of the most important factors in the management of patient with these disorders is the frequent monitoring of the patient's clinical and metabolic condition.

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