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Research Article

INFLUENCE OF DIABETES MELLITUS ON OUTCOME OF PATIENTS IN THE MEDICAL INTENSIVE CARE UNIT

***Badurudeen Mahmood Buhary[1], Abdul Muthalib Hussain[2], Mohammed Zikrullah Tamanna[3]**
[1]Specialized Diabetes & Endocrine Center, King Fahad Medical City (KFMC), Riyadh, Saudi Arabia
[2]Department of Pulmonary and Critical Care Medicine, KFMC, Riyadh, Saudi Arabia
[3]Department of Emergency Medicine, KFMC, Riyadh, Saudi Arabia
**Author for correspondence: badrudeenmahmood@hotmail.com*

ABSTRACT
Electrolyte imbalance and disturbances of acid-base equilibrium occur in a variety of clinical conditions mostly encountered in the Intensive Care Unit (ICU). Diabetes mellitus is the most common metabolic disorder in the community. Disturbances of the acid-base balance are common in diabetics. The aim of this study is to analyze the effect of diabetes on electrolyte and acid base disturbances in relation to morbidity and mortality of a medical ICU. This retrospective, single centre study included 100 patients with various acid-base and electrolyte imbalances, who were admitted in the medical ICU in Sri Ramachandra Medical Centre, a Harvard associated Tertiary, University hospital in Chennai, India, for a period of six months. From medical records ABG, venous blood results were analyzed and outcome of patients were noted (patient discharged, dies or seeks discharge against medical advice). This study show that diabetes is one of the contributing factors toward complications observed in acid base and electrolyte imbalance and it leads to significantly higher mortality and influences patient outcomes. Diabetics had increased mortality compared to those without Diabetes Mellitus (DM) (43.06% vs. 14.28%, p=0.0090). There were statistically significant differences between the groups having DM to the group without DM in terms of mean potassium, bicarbonate and PCO_2 (p= 0.0042, 0.0014 and 0.014 respectively). This study provided data to show that diabetic subjects in the medical ICU have a high prevalence of having metabolic acidosis and electrolytes imbalance characterized with depletion in potassium and bicarbonate ions accompanied with lowered PCO_2 levels compared with their non-diabetic counterparts. Mortality is 4.4 times more likely in patients with diabetics than non-diabetics (OR 4.4 [95% CI 1.24-17.044], p=0.015).

Key Words: *Acid base disorder, Anion gap, Diabetes mellitus, Electrolyte imbalance, ICU*

Abbreviations
ABG: Arterial Blood Gas
CI: Confidence Interval
DAMA: Discharge against Medical Advice
DM: Diabetes Mellitus
HCO_3: Bicarbonate
ICU: Intensive Care Unit
OR: Odds Ratio
PCO_2: Partial Pressure of Carbon Dioxide

INTRODUCTION
Electrolytes play an important role in many body processes, such as controlling fluid levels, acid-base balance (pH), nerve conduction, blood clotting and muscle contraction. Disorders of acid-base and electrolytes are commonly seen in critically ill patients and in diabetics. Acid base disturbances cause blood pH to shift away from normal range when renal or respiratory function is abnormal or when an acid/base load overwhelms excretory capacity. This evokes compensatory responses by the body that

returns pH toward near normal to maintain the PCO_2/ [HCO_3^-] ratio (Haber 1991, Jeffrey 2007, Ishihara 1998). A drop or rise in PCO_2 will result in a drop or rise in Hydrogen respectively. The HCO_3/ PCO_2 relationship in extra-cellular fluids is useful in classifying disorders of acid base balance (Horacio 1998, Ishihara 1998) namely *acidosis* (Horacio 1998, Ishihara 1998) due to gain of acid or loss of alkali, i.e. fall in HCO_3/ PCO_2 ratio and *alkalosis* (Horacio 1998) due to gain of base or loss of acid, i.e. rise in HCO_3/ PCO_2 ratio.

Electrolyte imbalance resulting from kidney failure, dehydration, fever and vomiting has been suggested as one of the contributing factors toward complications observed in DM and other endocrine disorders (Rao 1992). Diabetes Mellitus is increasingly prevalent and associated with significant end organ damage, which increased mortality in critically ill patients. Patients of diabetes mellitus (DM) are prone to have acid-base and electrolytes disorders caused by the disease itself and the medications (diuretics and calcium channel blockers) they receive that influence the electrolyte balance (Zawada 1989, Patel 1997).

Acid base and electrolyte disturbances were found in many ICU patients mostly with DM. These disturbances need to be immediately analyzed to provide information about changes in respiratory function, electrolyte imbalance and underlying disease and, also to find out the combination of disorders they have.

The primary objective of this study is to analyze the outcome effect of patients with DM in medical intensive care unit compared to those individuals without DM. Secondary outcome was to analyze the pattern of electrolyte and acid base imbalances commonly seen in the ICU.

MATERIALS AND METHODS

This retrospective study included 100 patients from 276 patients, who met the inclusion criteria during a study period of 6 months in Sri Ramachandra Medical Centre, India after approval of Institutional ethical committee clearance. Patients admitted to the medical ICU with electrolyte and acid base abnormality were included. Patients without any acid base disturbance on arrival to the ICU were excluded from the study.

The following variables were recorded from patients' medical record, patient demographic data [Table 1], diabetic history and days in hospital and the possible outcomes were recorded (discharge from the ICU (improved), or patient discharges against medical advice due to personal reasons (DAMA) or patient dies (death)). Results of Blood Urea Nitrogen (BUN), Creatinine, Sodium, Potassium, and bicarbonate were recorded. Arterial Blood Gas (ABG) results (from Siemens 238 Blood Gas Analyzer System) were recorded for analysis of electrolyte disturbances and acid base imbalance.

Sample analysis was done; values falling outside normal ranges for Sodium, Potassium and Bicarbonate are described as abnormally high or low. Each patient's ABG result was analyzed to identify the single or mixed acid-base disorder (Fulop 1998) and the anion gap was calculated.

Patients were categorized based on their diabetic status and this factor was studied to find out the effect on morbidity and mortality. They were also compared by categorizing them into 3 groups, those that improved, died or went DAMA.

Statistical Analysis

Data was presented as percentage (%) for frequencies and mean and, standard deviation for continuous variables. Independent Student's T-test and analysis of variance (ANOVA) were done for comparison of continuous variables, and Chi-square test for frequencies. Odds ratio and 95% confidence intervals were calculated using logistic regression. A p-value ≤ 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

A total of 100 patients were included in this study (88 male and 32 female), with an age range from 13 to 81 years. The study consisted of patients with metabolic acidosis (n=67), metabolic alkalosis (n=8), respiratory acidosis (n=18), respiratory alkalosis (n=12), and mixed acid base disorders (n=5). Since 5 patients had mixed acid base disorder total count is coming to 110 (Figure 1). In terms of electrolyte imbalance, the study included patients with normal sodium (n=58%), hyponatremia (n=33%), hypernatremia (n=9%) and patients with normal potassium (n=48%), hypokalemia (n=13%), and hyperkalemia (n=39%). There were 72 patients with DM and 28 patients without DM. Patients were compared by various baseline characteristics (table 1).

High mortality was noticed in patients with DM (43.06% vs. 14.28%, p=0.0090) (Table 1). However there is no significant difference in values obtained for gender. Patients with DM had poor prognosis, there were 31 deaths (mean anion gap of 18.4 mmol/l) compared with four deaths in the group of patients without DM (mean anion gap of 20 mmol/l). Mortality was 4.4 times more likely in patients with DM than in the non-diabetic group (OR 4.4 [95% CI 1.24-17.044], p=0.015).

Comparison between the patients on basis of diabetic status was statistically significant (table 2). There were no differences in age, mean sodium, chloride, anion gap, BUN, creatinine, pH and duration of days in the hospital between both groups. There was significant reduction in the concentrations of mean potassium and bicarbonate (p= 0.0042, 0.0014 respectively) in the serum of diabetic individuals compared with the non-diabetics. PCO_2 was significantly lower (P=0.014) in diabetics.

Metabolic acidosis was the most prevalent disorder (n=43) among the diabetic patients. Mortality was also significantly higher in the DM group with metabolic acidosis (p= 0.034) compared to the patients with no DM and metabolic acidosis. Among the DM patients there were patients with metabolic acidosis (n=43), metabolic alkalosis (n=7), respiratory acidosis (n=16), respiratory alkalosis (n=10), and mixed acid base disorders (n=3). In terms of electrolyte imbalance, the study included diabetic patients with normal sodium (n=15), hyponatremia (n=19), hypernatremia (n=9) and patients with normal potassium (n=10), hypokalemia (n=12), and hyperkalemia (n=21). The most common electrolyte disorder among DM patients is hyperkalemia. Another common disorder found among all the patients was the combined disorder of metabolic acidosis, hyperkalemia and hyponatremia (14.9%).

Acid base disorders often seen in patients in the ICU are the primary contribution to morbidity and mortality (Fulop 1998) in the ICU. There are few studies (Tsuboi 1197, Sotirakopoulos 2012, Yoshimi 1992), which have looked into the effect of DM with co-existing electrolyte disturbances on morbidity and mortality in acid base disorder, thus the objective of this study. This study shows that DM is a factor that complicates patient outcomes in acid base and electrolyte disorders. Even though mean anion gap was lower (17.335) in the patients with DM there were still significantly higher mortality in that group compared to those without DM. All the patients that died when anion gap increased had DM.

DM complicates acid base disorders (Elisaf 1996, Levere 1983, Gamblin 1986). In the present study the patients with DM had poor prognosis. The results showed patients with DM had 43% mortality, while 14.3% mortality was seen in non- diabetics (p value = 0.0090).

Metabolic acidosis (ketoacidosis, lactic acidosis, hyperchloremic acidosis or renal tubular acidosis) is one of the serious acid base disorders complicated by DM and it is associated with an increased anion gap caused by the presence of organic anion (beta-hydroxybutyrate, acetoacetate, and lactate) (Yoshimi 1992) this was observed in this present study where metabolic acidosis was observed in 60% of the patients with DM (43/72).

Potassium and bicarbonate significantly decreased in the diabetic patients (p= 0.0042, 0.0014 respectively). The observed reduction in serum potassium in diabetic patients might be a result of electrolyte loss which arises due to dehydration or a result of kidney dysfunction caused by DM (Rao 1992). As the body tries to flush out excess glucose due to hyperglycemia, water is also flushed out continuously through the kidney. This water loss is accompanied by rapid loss of sodium and potassium loss. Such loss if continued could soon bring about depletion of base in the body sufficient to cause dehydration of the tissues which may result in death (Leonard 1989). Sodium and potassium depletion is a common feature of essential hypertension and type II DM (Van Style 1928). Though we did not find statistically significant reduction in Sodium, it was comparatively lower in the diabetic patients (Table 2).

Another cause for reduced potassium is the fact that total potassium of the body in insulin-dependent patients and in non-insulin-dependent patients is reduced during periods of poor control of DM and increases when the blood glucose levels are normal (Walsh 1976) The levels of potassium can also be reduced by use of diuretics (Zawada 1989) as well as due to diabetic ketoacidosis (increased loss in urine).

Diabetic ketoacidosis is an important cause for elevation of serum chloride and reduction in bicarbonate in diabetic subjects (Cowie 1995). The low serum insulin levels in diabetics signal the body to produce more glucose via gluconeogenesis, glycogenolysis and ketogenesis which results in excess production of ketone bodies. When the ketone bodies are elevated in the blood, serum bicarbonate may fall to near zero, resulting in severe acidosis (Haffner 1997). The reduction in blood pH caused by the ketoacidosis might result in acid base imbalance which leads to elevation of chloride by the system in order to compensate for the anion loss (Leonard 1989). This electrolytes imbalance might also occur due to inhibition of the rennin-angiotensin-aldosterone system, which plays a key role in the regulation of fluid and electrolyte balance. This enzyme system has been reported to be affected in many endocrine and cardiovascular diseases particularly DM (Van Style 1928). This relates to the results of this study where we saw an increase in chloride and a significant reduction in bicarbonate in the patients with DM. In our study the mean pH in the DM patients was not very low because of the coexisting metabolic alkalosis and respiratory alkalosis in 24% of the patients. Metabolic alkalosis which was observed in about 10% of the diabetic patients may occur due to the use of diuretics and other medications that reduce the total sodium of the body.

The academia suggests that in acid-base disorders in diabetic patients when pH falls below 7.1-7.2 it reduces myocardial contractility, predisposes patients to cardiac arrhythmias, causes vascular constriction and may reduce peripheral vascular resistance, blood pressure, hepatic blood flow and tissue oxygen release. These changes contribute to increased mortality and morbidity (Kraut 2001).

Table 1: Characteristics of the study population.

	Total	IMPROVED	DEATH	DAMA	P value$^{\infty}$
		Number of Patients (%)			
TOTAL	100	58	35	7	
Age (47.24 ± 17.63)					
<40	34	22 (64.71%)	12(35.29%)		0.135†
≥ 40	66	36 (54.55%)	23(34.85%)	7(10.6%)	
Sex					
Male	68	40 (60%)	23(33.3%)	5 (6.7%)	0.9291†
Female	32	18 (63.6%)	12(31.8%)	2 (9.1%)	
Diabetes Mellitus					
Non- Diabetic	28	21 (75%)	4 (14.28%)	3 (10.72%)	0.0090*
Diabetic	72	37 (51.39%)	31(43.06%)	4 (5.55%)	

DAMA: Discharge Against Medical Advice; AG: Anion Gap
**: Significant finding*
† *: Non Significant finding*
$^{\infty}$ *p value between groups improved and death*
There were significantly higher mortality in patients with diabetes (p=0.0090)

Diabetics usually take medication that influences the electrolyte balance. Thus, loop diuretics and thiazides may cause hyponatremia, hypokalemia and deficiency of magnesium, disturbances in calcium handling (increased renal loss with loop diuretics and reabsorption by thiazides) and hyperglycemia. Potassium-sparing diuretics may cause hyperkalemia and calcium channel blockers may disturb the metabolism of carbohydrates in diabetics (Zawada 1989).

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The positive outcome of this study shows that there is an association between DM and increase in the severity of illness. Having DM with acid base disorders and electrolyte imbalance leads to poor prognosis compared to patients not having DM. Mortality is 4 times more likely in patients with DM than non-diabetics (OR 4.4 [95% CI 1.24-17.044], p=0.015). Mortality was also significantly higher in the DM group with metabolic acidosis (p= 0.034) compared to the patients with no DM and metabolic acidosis.
The strengths of this study are that the population was a homogenous one representing the general medical ICU population in a tertiary care hospital, Chennai.

Table 2. Characteristics of the study participants based on their diabetic status

	Non-Diabetic (n=28)	**Diabetic (n=72)**	**p value**
	Mean ± SD		
Age (years)	51.79 ± 14.39	45.47 ± 18.52	0.1081†
S.Sodium (136-145 mmol/L)	135.95± 12.859	131.39± 11.868	0.1071†
S.Potassium (3.5-5 mmol/L)	5.49± 1.61	4.49± 1.5	0.0042*
S.Chloride (98-106 mmol/L)	99.36 ± 12.51	100.65 ±12.06	0.6342†
S.Bicarbonate (24-30 mmol/L)	17.911± 5.99	13.52 ± 6.01	0.0014*
Anion Gap (8-14.9 mmol/L)	18.518 ± 8.75	17.335± 9.766	0.5772†
BUN (10-20 mg/dl)	38.26 ± 31.54	49.61 ± 33.22	0.1146†
Creatinine (<1.5 mg/dl)	3.139± 4.34	3.529 ± 3.301	0.6691†
pH (7.38-7.44)	7.298 ± 0.189	7.286 ± 0.192	0.7722†
PCO_2 (35-45 mm/Hg)	37.287±22.28	25.99 ±13.67	0.014*
PO_2 (80-100 mm/Hg)	86.986 ± 33.39	98.35 ± 57.59	0.3294†
Days in hospital	15.5± 23.71	13.1 ± 11.88	0.5027†

S: Serum; AG: Anion Gap; BUN: Blood Urea Nitrogen; *PCO_2: Partial Pressure of Carbon Dioxide; PO_2: Partial Pressure of Oxygen; Normal value ranges are represented in the brackets;*
**: Significant finding*
† : Non Significant finding
There were statistically significant differences between the diabetes and those without diabetes in terms of mean potassium, bicarbonate, and PCO_2.

Table 3. Characteristics of the study participants with metabolic acidosis

Metabolic Acidosis	**Total**	**IMPROVED**	**DEATH**	**DAMA**
		Number of Patients (%)		
Total	67	40 (59.7%)	22(32.84%)	5 (7.46%)
Sex				
Male	45 (67.2%)	27 (60%)	15(33.3%)	3 (6.7%)
Female	22 (32.8%)	13(59.1%)	7(31.8%)	2 (9.1%)
Diabetes Mellitus				
Non- Diabetic	24	18 (75%)	4 (16.67%)	2 (8.33%)
Diabetic	43	22 (51.16%)	18 (41.86%)	3 (6.97%)

DAMA: Discharge Against Medical Advice; There were significantly higher mortality in patients with diabetes (p=0.034)

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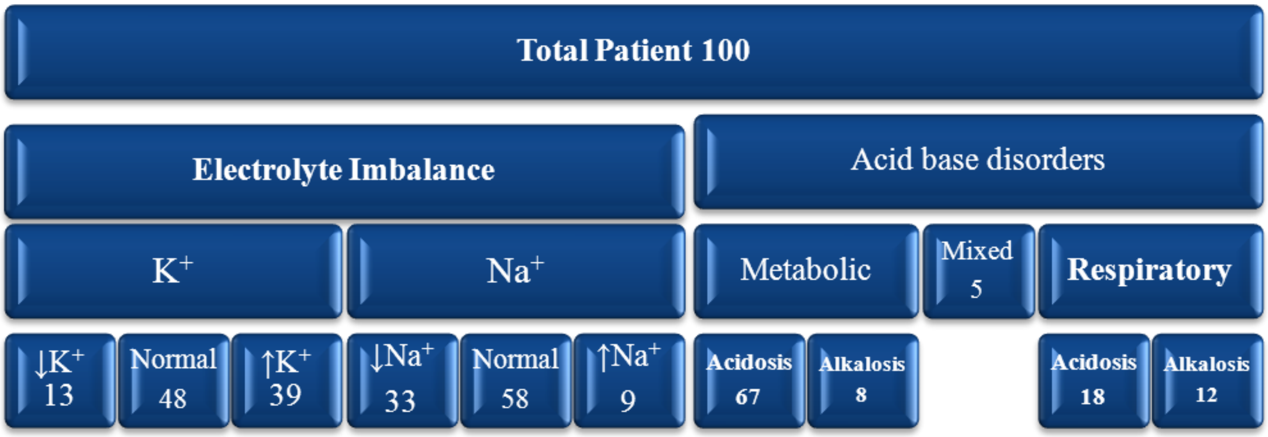

Figure 1: Acid base and electrolyte imbalance distribution among patients. Na^{+}: Sodium, K^{+}: Potassium; ↓: decreased; ↑: increased

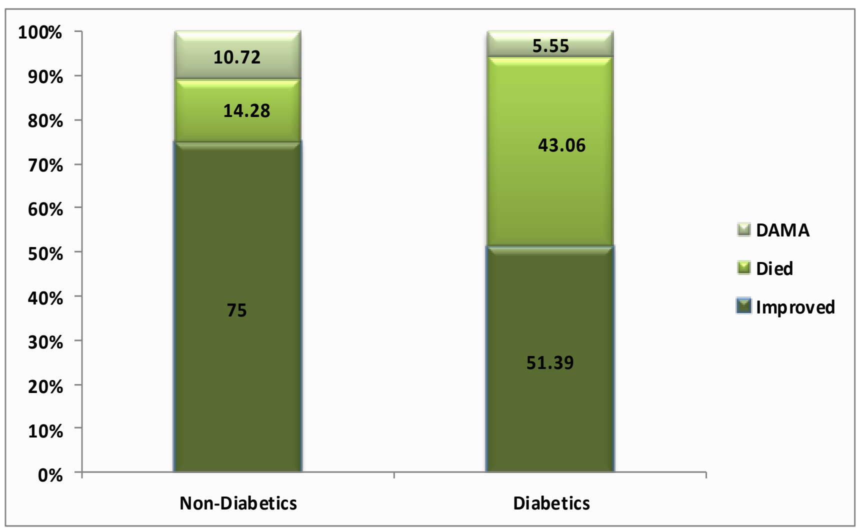

Figure 2: Effect of having diabetes with acid base and electrolyte imbalance on patient outcomes. There were significantly higher mortality in patients with diabetes (p=0.0090)

Conclusions

This study show that DM is one of the contributing factors toward complications observed in acid base and electrolyte imbalance and it leads to significantly higher mortality. This study shows that diabetic subjects in the medical ICU have a high prevalence of having metabolic acidosis and electrolytes imbalance characterized with depletion in potassium and bicarbonate ions accompanied with lowered PCO_2 levels compared with their non-diabetic counterparts. Mortality is 4.4 times more likely in patients with DM than non-diabetics (OR 4.4 [95% CI 1.24-17.044], p=0.015).

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REFERENCES

Cowie CC, Harris MI (1995). Physical and metabolic characteristics of persons with diabetes. Diabetes in America. 2nd ed. National Institutes of Health 117-164.

Elisaf MS Tsatsoulis AA, Katopodis KP, Siamopoulos KC (1996). Acid-base and electrolyte disturbances in patients with diabetic ketoacidosis, Diabetes Research and Clinical Practice Sep **34** (1) 23-7.

Fulop M (1998). Flow diagrams for the diagnosis of acid base disorders, Journal of emergency medicine Jan-Feb **16**(1) 97-109.

Gamblin GT, Ashburn RW, Kemp DG, Beuttel SC (1986). Diabetic ketoacidosis presenting with a normal Anion Gap. The American Journal of Medicine April **80** 758-760.

Haber RJ (1991). A Practical Approach to Acid-Base Disorders, Western Journal of Medicine August **155**(2) 146–151.

Haffner SM, Miettinen H (1997). Insulin resistance implications for type II diabetes mellitus and coronary heart disease. American Journal of Medicine **103** 152-162.

Horacio J, Adrogué, Nicolaos E Madias (1998). Management of Life-Threatening Acid–Base Disorders, New England Journal of Medicine **338** 26-34.

Ishihara K, Szerlip HM (1998). Anion Gap acidosis, Seminar Nephrology Jan **18**(1) 83-97.

Jeffrey A Kraut, Nicolaos E Madias (2007). Serum Anion Gap: Its Uses and Limitations in Clinical Medicine. Clinical Journal American Society of Nephrology January vol. **2** (no 1)162-174

Kraut JA, Kurtz I (2001). Use of base in the treatment of severe acidemic states. American Journal of Kidney Diseases **38**(4) 703-27

Leonard IK, John M (1989). Physiology and pathophysiology of body water and electrolytes. In: Kaplan and Pesce (Eds.), Clinical Chemistry: Theory, analysis and correlation. The C.V. Mosby Co. St Louis 313-331.

Levere, Jaspan JB (1983). Sodium bicarbonate therapy in severe Diabetic ketoacidosis presenting with a normal anion gap. The American Journal of Medicine. Aug **75** 263-268.

Patel KP, Zhang PL, Zeigler DW, Kauker ML (1997). Renal response to volume expansion in streptozotocin-induced diabetic rats: influence of calcium channel blockade. Diabetes Research and Clinical Practice **35**(2-3) 69-74.

Rao GM (1992). Serum electrolytes and osmolality in diabetes mellitus. Indian Journal of Medical Sciences 1992; **46** (10):301-303.

So**tirakopoulos N, Kalogiannidou I, Tersi M, Armentzioiou K, Sivridis D, Mavromatidis K (2012).** Acid-base and electrolyte disorders in patients with diabetes mellitus. Saudi Journal of Kidney Diseases and Transplantation **23** 58-62.

Tsuboi Y, Saito T (1997). Water and electrolyte disorders and acid-base imbalance in diabetic patients. Nippon Rinsho Oct **55** supplement 648-53.

Van Style DD, Serdroy J (1928). Studies on diabetes and electrolyte equilibrium in blood. Journal of Biological Chemistry **18** 20-26.

Walsh CH, Soler NG, James H (1976). Studies in whole body potassium and whole body nitrogen in newly diagnosed diabetics. Oxford Journal of Medicine **45** (178) 295-301.

Yoshimi T (1992). Acid-base balance disorder in various diseases-diabetes mellitus. Nippon Rinsho **50** (9) 2206-12

Zawada ET Jr. (1998). Metabolic considerations in the approach to diabetic hypertensive patients. American Journal of Medicine **87**(6A):S34-8