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RESEARCH ARTICLE

KIDNEY PROFILE EVALUATION IN THE HYPOGLYCEMIC TYPE II DIABETIC SUBJECTS

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a group of metabolic diseases which if not controlled can cause serious complications.
Aim: Kidney Profile Evaluation In The Hypoglycemic Type II Diabetic Subjects.
Methodology: Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), serum urea, creatinine, sodium (Na+), potassium (K+) and microalbuminuria levels were evaluated. Total sample size was 60, which was divided into 30 study group with type II DM having hypoglycemia (blood glucose level <70 mg/dl) who attended the Medicine OPD of AVBRH Hospital and 30 age, sex matched healthy controls included in the study.
Results: Results of serum urea and creatinine levels were higher in cases as compared to the controls ($p<0.0001$). Urinary Microalbumin level were 70.71±5.57 which was higher in the cases as compared to controls ($p<0.0001$). Serum Sodium level in the cases were 128.26 ± 2.46 which was significantly lower in the cases as compared to controls ($p<0.0001$). Level of serum Potassium level in the cases were 6.09 ± 0.23 which was significantly higher in the cases as compared to controls ($p<0.0001$). HbA1c has significant negative correlation with Creatinine ($p<0.01$).
Conclusion: Early detection of Kidney Profile abnormalities can minimize the risk for development of Nephrotic complications in the hypoglycemic type II diabetic subjects.

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Diagnosis and Classification of Diabetes Mellitus, 2009). Type II DM is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretary response. This form of DM, accounts for approximately 90 - 95%. According to the International Diabetic Foundation, currently the disease affects >62 million Indians, which is >7.1% of India's adult population. According to Wild *et al*. (2004) the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030, with maximum increase in India. Due to the alarming increase in the incidence and prevalence of diabetics in India, WHO has declared India as the — Diabetic Capital of the World (Gupta, 2002). Chronic hyperglycemia is associated with significant long-term complications like damage to the nerves, heart, blood vessels, eyes and kidneys (Yki-Yarvinen, 1998). Hypoglycemia, also called low blood glucose or low blood sugar, occurs when the level of glucose in the blood drops below normal. According to National Institute of Diabetes and Digestive and Kidney Diseases for diabetics hypoglycemia means blood glucose level is 70 mg/dL or less. Hypoglycemia is a medical emergency, where there is reduction in plasma glucose concentration causing signs and symptoms of altered mental status, sympathetic nervous system stimulation due to abnormalities in the mechanisms of glucose homeostasis (Stedman, Thomas Lathrop (December 2005)). Incidence of hypoglycemia with diabetes varies in compared to people without diabetes (Turnbull *et al*., 2009). Hypoglycemia is the commonest side effect of treatment of diabetes and is associated with adverse health outcomes like dementia, falls, fall-related fractures, cardiovascular events, poor quality of life, and increased mortality. According to the American Diabetes Association (ADA) HbA1c level of <7% is the goal of optimal blood glucose control (American Diabetes Association. (2003)) and the American Association of Clinical Endocrinologist has further recommended HbA1c level of <6.5% is the target goal (The American Association of Clinical

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Endocrinologists medical guidelines for the management of diabetes mellitus 2002). The glycated hemoglobin (HbA1c) provides an index of average blood glucose level during the past 2–3 months and considered to be the most reliable measure of long-term metabolic control of blood glucose level in type II diabetes mellitus (Nathan, 1984). HbA1c is formed by the condensation of glucose with the N-terminal Valine residue of each β-chain of HbA to form an unstable Schiff-base, which is the most widely used as the long-term glycemic control. (Selvin *et al*., 2005) American Diabetes Association (ADA) proposed the use of HbA1c in the definition of diabetes and the category of increased diabetes risk (which also includes impaired fasting glucose and impaired glucose tolerance) in 2010 (American Diabetes Association Diabetes Care, 2010). Lower HbA1c values, has been shown to delay the onset and slow the progression of diabetic complications like- retinopathy, nephropathy, and neuropathy in Diabetes (Kadiyala *et al*., 2010). People with type II diabetes develop severe renal complications early, especially those with high urinary albumin excretion (Michel Marre *et al*., 2004). Nelson *et al*. (1993) identified multiple factors contributing to the initiation and progression of diabetic nephropathy including proteinuria, hyperglycemia, hypertension, genetic susceptibility, ethnicity, high protein intake and familial predisposition to renal disease. Longer the duration of diabetes, higher the frequency of diabetic nephropathy. Microalbuminuria is a term to describe a moderate increase in the level of urine albumin. It occurs when the kidney leaks small amounts of albumin into the urine, in other words, when there is an abnormally high permeability for albumin in the glomerulus of the kidney. Microalbuminuria can be diagnosed from a 24-hour urine collection (between 30–300 mg/24 hours) or, more commonly, from elevated concentration in a spot sample (20 to 200 mg/L). Measurement of the plasma urea and creatinine is widely regarded as a test of renal function. Diabetic patients frequently develop electrolyte disorders. These disturbances are particularly common in decompensated diabetics, especially in- diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar syndrome. These patients have markedly potassium-, depleted. Diabetes mellitus (DM) is linked to both hypo- and hyper-natremia and have the coexisting mechanism of hyperglycemia. The most important causal factor of chronic hyperkalemia in diabetic individuals is the syndrome of hypoaldosteronism. Other factors are impaired renal function, potassium sparing drugs and insulin deficiency also involved in the development of hyperkalemia.

Even though Diabetes is prevalent in India, studies are lacking to find out the risk of developing diabetic nephropathy with HbA1c, Kidney Profile and microalbumin levels in the hypoglycemic type II Diabetics. Our study is a rural hospital based study and it will provide the necessary insight into the situation. Our aim is to evaluate the Kidney Profile in the Hypoglycemic Type II Diabetic Subjects. We hypothesize with hypoglycemia in type II Diabetics may lead to the Nephrotic complications. The study was carried out in the Department of Biochemistry in association with Department of Medicine, Jawaharlal Nehru Medical College and Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha, Maharashtra, India.

MATERIALS AND METHODS

A comparative and cross-sectional study was conducted. Institutional Ethical Committee approved the study. The study was done from June 2016 to January 2017, total sample size 60 including males and females and divided into two groups. Informed written consent was taken for the study purpose. 30 study group with type II DM with hypoglycemia (blood glucose level <70 mg/dl) who attended the outpatient clinic of the Medicine Department of AVBRH Hospital, Sawangi (Meghe), Wardha, India and 30 age, sex matched healthy controls. All patients with known history of type II DM within the age group of 35-70 years included in the study. Information about subject's age, sex, lifestyle, family history of diabetes and other chronic diseases/disorders were written in pre-design format. HbA1c assay was done by immunoassay method, fasting blood glucose by GOD/POD method (Maughan, 1982), Urea by kinetic method, Creatinine by JAFFE (Enzymatic) method, Sodium by Sodium Calib. Set Barcode Levels, Potassium by Potassium Calib. Set Barcode Levels and Microalbumin by Immunoturbidimetric method - all measured by Randox auto-analyzer on the same day of collection.

Sample Collection

3mL blood sample was collected from each subject. Fasting blood sample in sterile fluoride bulb for FBS, plain bulb for urea, creatinine, sodium, potassium and in EDTA bulb for HbA1c under all the aseptic conditions with consent of the patient. Spot morning urine sample – collected for urinary micro albuminuria in the urine pot. Blood Sample was allowed to stand for clotting for 25 to 30 minutes. Serum was separated by centrifuging blood at 3000rpm for 10 mins.

Inclusion Criteria

All patient with known history of type II DM, age group between 35-70 years blood glucose level <70 mg/dl and diabetic patients, those who gave the consent for the study were included in the study.

Exclusion Criteria

Patient with major illness like liver disease, renal failure, cardiovascular disease, which can directly or indirectly affect the result, previous or current treatment with drugs known to interfere with glucose and lipid metabolism were excluded from the study.

Statistical Analysis

Statistical analysis was done by using descriptive and inferential statistics using Student's unpaired t test and Pearson's Correlation Coefficient and software used in the analysis were SPSS 17.0 version and EPI-INFO 6.0 version and $p<0.05$ is considered as level of significance.

RESULTS

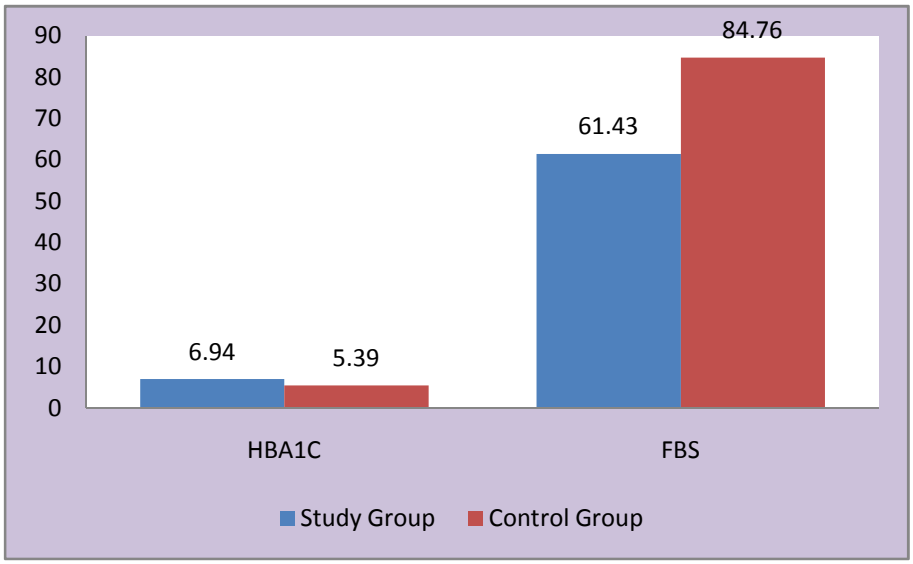
Table 1 shows mean value for HbA1c in the study group was 6.94± 0.47, which was significantly higher in the cases as compared to the controls ($p<0.0001$) and the mean value for FBS in the study group was 61.43 ± 2.84, which was significantly lower in the cases as compared to the controls ($p<0.0001$). Mean value for urea, creatinine and Microalbumin levels in the study group were 51.43 ± 5.31, 2.80 ± 0.48, 70.71 ± 5.57 respectively, which were significantly higher in the cases as compared to the controls ($p<0.0001$).

Table 1. Comparison of biochemical parameters in two groups

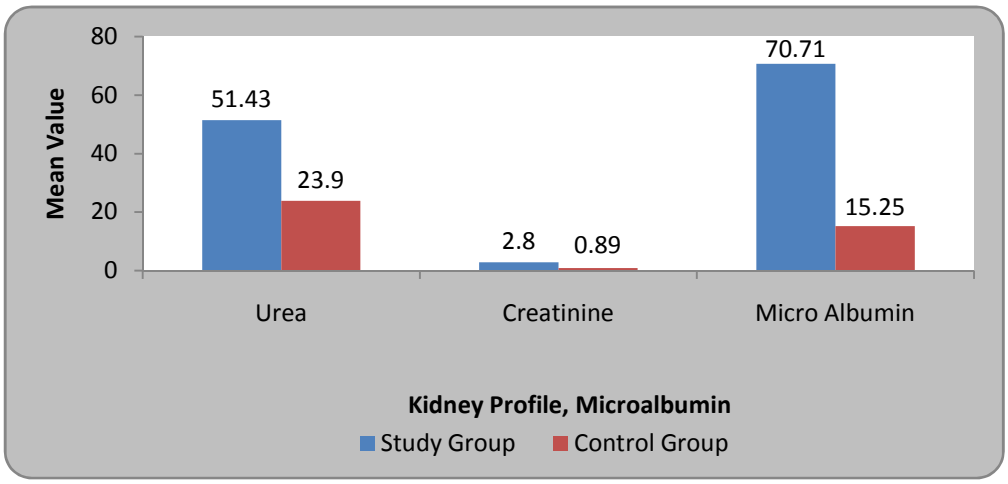
	Group	N	Mean	Std. Deviation	Std. Error Mean	t-value	p-value
HbA1c	Study	30	6.94	0.47	0.08	16.26	0.0001,S
	Control	30	5.39	0.23	0.04		
FBS	Study	30	61.43	2.84	0.52	29.43	0.0001,S
	Control	30	84.76	36.27	0.59		
Urea	Study	30	51.43	5.31	0.97	21.58	0.0001,S
	Control	30	23.90	4.53	0.82		
Creatinine	Study	30	2.80	0.48	0.08	19.73	0.0001,S
	Control	30	0.89	0.20	0.03		
Microalbumin	Study	30	70.71	5.57	1.01	48.34	0.0001,S
	Control	30	15.25	2.89	0.52		
Na+	Study	30	128.26	2.46	0.44	13.73	0.0001,S
	Control	30	138.30	3.15	0.57		
K+	Study	30	6.09	0.23	0.04	24.22	0.0001,S
	Control	30	4.03	0.40	0.07		

Table 2. Correlation of HbA1c with other parameters in study group

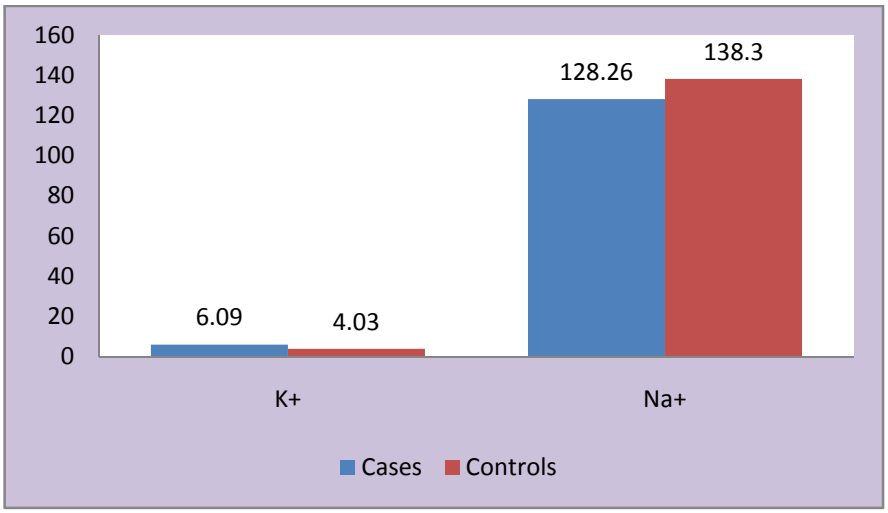
	Mean	Std. Deviation	N	Correlation 'r'	p-value
HbA1c	6.94	0.47	30	-	-
FBS	228.50	30.751	30	0.08	0.65,NS
Urea	152.10	40.98	30	0.16	0.39,NS
Creatinine	40.73	6.58	30	-0.45	0.012,S
Na+	153.13	27.74	30	0.14	0.44,NS
K+	33.33	9.93	30	0.10	0.59,NS
Micro Albumin	70.71	5.57	30	0.12	0.51,NS



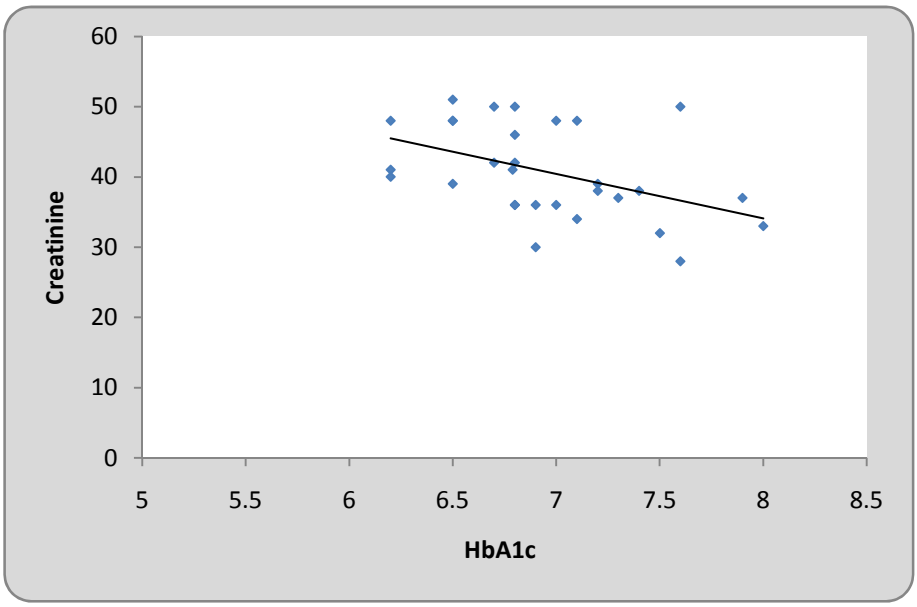
Graph 1. Comparison of HbA1c and FBS in two groups



Graph 2. Comparison of Kidney Profile and Microalbuin levels in two groups



Graph 3. Comparison of Na+, K+ in two groups



Graph 4. Correlation of HbA1c with Creatinine in study group

Serum Sodium level in the cases were 128.26 ± 2.46 which was significantly lower in the cases as compared to controls ($p<0.0001$). Level of serum Potassium level in the cases were 6.09 ± 0.23 which was significantly higher in the cases as compared to controls ($p<0.0001$). Table 2 shows HbA1c has significant negative correlation with Creatinine ($p<0.01$).

DISCUSSION

In the present study, we have evaluated the Risk Factors of Hypoglycemia in Type II Diabetic Subjects. The present study was carried out at AVBRH and JNMC, Sawangi (Meghe), Wardha, India. The findings are as follows-In our study, HbA1c in the study group was significantly higher in the cases as compared to the controls ($p<0.0001$). Diabetic patients with elevated HbA1c considered as a very high risk group for severe complications. Improving glycaemic control can reduce the risk of various complications in diabetic subjects. (Selvin *et al*., 2006) According to the Diabetes Complications and Control Trial (DCCT) HbA1c is the gold standard of glycaemic control and the level of HbA1c value ≤7.0% is the level of significance for reducing diabetic complications. (Rohlfing *et al*., 2002) It has also been showed in previous study conducted by Khaw *et al* that by reducing the level of glycated hemoglobin (HbA1c) by 0.2% could lower the mortality rate by 10%. (Khaw *et al*., 2001) HbA1c reflects average blood glucose concentration over the course of the RBC lifespan in normal individuals. HbA1c is the most widely used biomarker for long-term glycemic status. (Selvin *et al*., 2005) Rudberg *et al*. (1997), in a study of adolescents with a mean duration of disease of 10.9 years, found that the duration of disease was an important factor in the overall severity of glomerulopathy. Diabetic nephropathy is a clinical hall mark of microangiopathy and is the most important single disorder leading to renal failure in adults (Ramachandran *et al*., 1997). The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels of albumin in the urine. In addition to its being the earliest manifestation of nephropathy, albuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with type II diabetes. Thus, the finding of microalbuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all renal and cardiovascular risk factors.

In our study serum Urea and Creatinine concentration was found significantly higher in the cases as compared to the controls ($p<0.0001$). A research conducted by Anjaneyulu *et al*

2004 had found that increase urea & serum creatinine in diabetic rats indicate progressive renal damage (Anjaneyulu and Muragundla, 2004). Serum Urea and Creatinine are the established marker of Glomerular Filtration Rate (GFR). Serum Creatinine is although a more sensitive index of kidney function compared to the Urea. Its because it fulfills the requirements of a perfect filtration marker according to Perrone *et al*. (1992) In the study, HbA1c shows significant negative correlation with creatinine ($p<0.01$). In our study there is significant increase in urinary Microalbumin levels in the cases as compared to the controls ($p<0.0001$). The causal risk factors for microalbuminuria are raised blood pressure and poor glycaemic control. Some studies have revealed duration of diabetes, male sex, and pre-existing retinopathy as major risk factors for microalbuminuria. (Klein *et al*., 1993) In our study, multiple logistic regression analysis revealed age, duration of diabetes, HbA1c, and fasting plasma glucose as the risk factors for microalbuminuria. Gupta *et al*. reported HbA1c to be associated with microalbuminuria. (Gupta *et al*., 1991) The association of glycaemic control with microalbuminuria has been well established by various studies. (Klein *et al*., 1993; Gupta *et al*., 1991) In our study there is significant lower sodium values are seen in the cases ($p<0.0001$). This is due to Hyperglycemia increases serum osmolality, resulting in movement of water out of the cells and subsequently in a reduction of serum sodium levels (Na+) by dilution. Moreover, in diabetic ketoacidosis ketone bodies (b-hydroxybutyrate and acetoacetate) obligate urinary electrolyte losses and aggravate the renal sodium wasting. (Liamis *et al*., 2011; Chiasson *et al*., 2003) Drug-induced hyponatremia due to hypoglycemic agents (chlorpropamide, tolbutamide, insulin) or other medications (*e.g.*, diuretics, amitriptyline for the treatment of diabetic neuropathy) should be considered in every diabetic patient with low (Na+). (Liamis *et al*., 2008; Beukhof *et al*., 2007) In our study there is also significantly higher potassium levels are also seen ($p<0.0001$). Causes of Hyperkalemia may be due to redistribution of potassium from the intracellular to the extracellular compartment (shift hyperkalemia), reduced glomerular filtration of K+ (due to acute kidney injury and chronic kidney disease), many drugs that interfere with K+ excretion are associated with hyperkalemia. In the typical healthy diabetic diet is often rich in K+ and low in sodium contributing to the occurrence of hyperkalemia in susceptible individuals (Palmer, 2004; Uribarri and Carroll, 1990) and the most common cause of chronic hyperkalemia in diabetics is the reduced tubular secretion of K+ due to the syndrome of hyporeninemic hypoaldosteronism. (DeFronzo, 1980)

Conclusion

The prevalence of Type II diabetes mellitus is increasing day by day and is associated with a very high mortality rate, reduced quality of life and high costs of treatment, despite intensive insulin treatment. HbA1c can be use as a early detector of diabetic complications and hypoglycemia in addition to glycemic control. Screening for microalbuminuria will allow the identification of patients with nephropathy at very early course of the disease. Risk factor modification, HbA1c levels and renal function monitoring and combined therapies are the current integrated approaches to manage the diabetic nephropathy in patients with type II diabetes.

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REFERENCES

American Diabetes Association. 2003. Implications of the United Kingdom Prospective Diabetes study. Diabetes Care, 26, 28-32.

American Diabetes Association. 2010. Diagnosis and classification of Diabetes Mellitus. *Diabetes Care*, 33: s6 2-s69.

Anjaneyulu, Muragundla ; Chopra, Kanwaljitquercetin, an anti-oxidant bioflavonoids, attenuates diabetic nephropathy in rats. Clinical & Experimental Pharmacology & Physiology 2004; 31: 244-8.

Beukhof CM, Hoorn EJ, Lindemans J, Zietse R. 2007. Novel risk factors for hospital-acquired hyponatraemia: a matched casecontrol study. Clin Endocrinol (Oxf), 66: 367-372 (PMID: 17302870 DOI: 10.1111/j.1365-2265.2007. 02741.x)

Chiasson JL, Aris-Jilwan N, Bélanger R, Bertrand S, Beauregard H, Ekoé JM, Fournier H, Havrankova J. 2003. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ*, 168: 859-866 (PMID: 12668546)

DeFronzo RA. 1980. Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int*., 17: 118-134 (PMID: 699 0088)

Diabetes Care 2009 Jan; 32(Supplement 1): S62-S67, http://dx. doi.org/10.2337/dc09-S062

Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association

Gupta DK, Verma LK, Khosla PK, *et al.* 1991. The prevalence of microalbuminuria in diabetes: a study from north India. *Diabetes Res Clin Pract.,* 12:125–128.

Gupta, V. 2002. Diabetes in Elderly Patients. JK Practitioner, 91(4): 258-259.

Haffner SM, Morales PA, Gruber MK, *et al.* 1993. Cardiovascular risk factors in non-insulin dependent diabetic subjects with microalbuminuria. *Arterioscler Thromb*., 13:205–210.

Kadiyala R, Peter R, Okosieme OE. 2010. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. *Int J Clin Pract*., 64(8):1130-1139

Khaw KT, Wareham N, Luben R, *et al*. 2001. Glycated hemoglobin, diabetes and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC Norfolk). *BMJ*, 322(7277):15- 18.

Klein R, Klein BEK, Moss SE 1993. Prevalence of micro albuminuria in older-onset-diabetes. *Diabetes Care,* 16: 1325–1329.

Liamis G, Milionis H, Elisaf M. 2008. A review of drug-induced hyponatremia. *Am J Kidney Dis*., 52: 144-153 (PMID:18468754 DOI: 10.1053/j.ajkd.2008.03.004)

Liamis G, Milionis HJ, Elisaf M. 2011. Hyponatremia in patients with infectious diseases. *J Infect*, 63: 327-335 (PMID:21835196 DOI: 10.1016/j.jinf.2011.07.013)

Maughan RJ. 1982. A simple, rapid method for the determination of glucose, lactate, pyruvate, alanine, 3-hydroxybutyrate and acetoacetate on a single 20-mul blood sample. *Clinica Chim Acta*., 122(2):231-240.

Michel Marre, Michel Lievre, Gilles Chattellier. 2004. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin randomized, double blind, placebo control trial (theDIABHYCAAR study) *BMJ*, 328: 495.

Nathan, D.M., Singer, D.E., Hurxthal, K., and Goodson, J.D. 1984. The clinical information value of the Glycosylated hemoglobin assay. *N. Engl. J. Med*., 310:341–346.

Nelson RG, Knowler WC, Mc Cane DR, Sievers ML, Pettitt DJ. 1993. Determinants of ESRD in Pima Indians with type 2 DM & proteinuria. *Diabetologia*, Oct.36 (10): 1087-93

Palmer BF. 2004. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med.,* 351: 585-592 (PMID: 15295051 DOI: 10.1056/NEJ Mra035279)

Perrone, R.D., N.E. Madias and A.S. levey, 1992. Serum Creatinine as index of renal function, *Clin. Chem*., 38: 1933-1953.

Ramachandran A, Snehalatha C, Latha E *et al*. 1997. Rising prevalence of NIDDM in an urban population in India. *Diabetologia*, 40: 232-237.

Rohlfing CL, Wiedmeyer HM, Little RR, *et al*. 2002. Defining the relationship between plasma glucose and HbA1c: analysis of glucose profiles and HbA1c in the diabetes control and complications trial. *Diabetes Care*, 25(2):275-278.

Rudberg S, Qsterby R, Dahlquist G, Nyberg G, Persson B. 1997. Predictors of renal morphological changes in the early stage of microalbuminuria in adolescents with IDDM. *Diabetes Care*, 20: 265

Selvin E, Coresh J, Shahar E *et al* 2005. Glycaemia (HbA1c) and incident of ischemic stroke: the Atherosclerosis Risk in Communties (ARIC) Study. *Lancet Neurol*., 4:821-826.

Selvin E, Coresh J, Shahar E *et al*. 2005. Glycaemia (hemoglobin A1c) and incident of ischemic stroke: the Atherosclerosis Risk in Communties (ARIC) Study. *Lancet Neurol.,* 4:821-826.

Selvin E, Wattanakit K, Steffes MW, *et al*. 2006. HbA1c and peripheral arterial disease in diabetes: the atherosclerosis risk in communities study. *Diabetes Care*, 29(4):877-882.

Stedman, Thomas Lathrop (December 2005) (1911). "Stedman's Medical Dictionary" (28th ed.).Baltimore: Lippincott Williams & Wilkins. p. 2100.

The American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus 2002. The AACE system of intensive diabetes self-management-2002 update. Endocrine Pracice, 8, 40-82.

Turnbull FM, Abraira C, Anderson RJ, *et al*. 2009. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. Aug 5.

Uribarri J, Oh MS, Carroll HJ. 1990. Hyperkalemia in diabetes mellitus. *J Diabet Complications*, 4: 3-7 (PMID: 2141843)

Wild S, Roglic G, Green A, Sicree R, King H. 2004. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27(3):1047–53. (PubMed)

Yki-Yarvinen, H. 1998. Toxicity of hyperglycaemia in type 2 diabetes. *Diabetes Metab Rev*., 14(Suppl 1): S45-S50.

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