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OPTIMUM RANGE OF HBA1C FOR PREVENTION OF DIABETIC NEPHROPATHY IN TYPE I AND TYPE II DIABETES MELLITUS

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Abstract- Background and Aim:Diabetic nephropathy is one of the most common complications of diabetes mellitus. 30 to 40 % of all type 1 and type 2 diabetic patients develop diabetic nephropathy [(1)].Various studies have been done to find out relation between glycemic control and development of diabetic nephropathy. Recent studies indicate that an interplay between genetic predisposition and other factors such as hyperglycemia, blood pressure, age, gender, smoking, and ethnicity predispose to nephropathy both in type 1 and type 2 diabetes mellitus. It has also become clear that trace albuminuria (microalbuminuria) provides a unique opportunity to recognize incipient renal involvement early on, particularly in type 1 and less specifically in type 2 diabetes. Increasing evidence indicates that early intervention delays progression of nephropathy. The most important strategies to combat the medical catastrophe of increasing numbers of diabetic patients with end-stage renal failure include (i) prevention of diabetes, (ii) glycemic control to prevent onset of renal involvement and (iii) meticulous antihypertensive treatment to avoid progression of nephropathy.

Methods: Literatures published from 1978 to 2015 was identified by searching in the following databases: MEDLINE, MEDLINE ALERT, SCI SEARCH, SOCIAL SCI SEARCH, AMED, EMBASE EMBASE Alert, Elsevier Bio base, Biotechnobase. HbA1c was taken as the sole indicator for glycemic control. References were taken from both the internet and textbooks.

Result: Of the 43 literary articles that were reviewed, all the large scale population based studies unanimously favoured keeping the HbA1c levels between 7-8%.

Conclusion: It can be safely concluded that keeping the glycemic levels in check brings favourable output for prevention of all the complication of diabetes including Diabetic Nephropathy. Meticulous calculations of population based studies hint that HbA1c levels below 7% is optimum for prevention of Diabetic Nephropathy.

Keywords –: Diabetes, Diabetic Nephropathy, Hyperglycemia, Blood sugar, End Stage Renal Disease (ESRD), Renal Failure, HbA1c, Hypertension.

I. INTRODUCTION

1. Definition :

=>Proteinuria: Urinary protein >0.5 g/24 hours
=>Albumin/creatinine ratio (ACR) >30 mg/mmol.
=>Albuminuria: Urinary albumin excretion rate >300 mg/day or >200 µg/min.
=>Microalbuminuria: Urinary albumin excretion rate 30–300 mg/day or 20–200 µg/min. ACR ≥3.0 mg/mmol
Diabetic nephropathy is typically defined as micro albuminuria i.e. a urinary albumin excretion > 300 mg in a 24 hour collection, OR micro albuminuria and abnormal renal function as represented by an abnormality in serum creatinine, calculated by creatinine clearance or GFR. Clinically, Diabetic nephropathy is characterized by progressive increase in proteinuria and decline in GFR, hypertension and a high risk of cardiovascular morbidity and mortality [(2).]

2. Epidemiology:

International Diabetes Federation released new figures showing that the number of people living with diabetes worldwide is expected to rise from 366 million in 2011 to 552 million by 2030. This equates to approximately three new cases every 10 seconds, and one adult in 10 have diabetes by 2030 [(3)].There is 12 fold increased incidence of End Stage Renal Disease (ESRD) in diabetics compared to non-diabetics [(4)]. Diabetes nephropathy is the leading cause of ESRD, and it affects 30% of patients with type 1 diabetes mellitus and 20% of patients with type 2 diabetes mellitus [(5)]. Diabetes is the most common cause of ESRD to the point requiring dialysis or kidney transplantation accounting for 45% of all patients enrolling into ESRD program [(6)]. 8% of Chinese patients with Type 2 diabetes mellitus may have co existing diabetes nephropathy and non-diabetes renal disease [(7)].

3. Classification of diabetic nephropathy:

The Joint Committee on Diabetic Nephropathy has revised its Classification of Diabetic Nephropathy (Classification of Diabetic Nephropathy 2014) in line with the widespread use of key concepts, such as the estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD). Major revisions to the classification are summarized as follows: (i) eGFR is substituted for GFR in the classification; (ii) The subdivisions A and B in stage 3 (overt nephropathy) have been reintegrated; (iii) Stage 4 (renal failure) has been redefined as a GFR <30 mL/min/1.73 m2, regardless of the extent of albuminuria; and (iv) stress has been placed on the differential diagnosis of diabetic nephropathy versus non-diabetic kidney disease as being crucial in all stages of diabetic nephropathy [(8)].

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Classification of Diabetic Nephropathy 2014

Stage	Urinary albumin (mg/g Cr) or Urinary protein (g/g Cr)	GFR (eGFR)
Stage 1 Prenephropathy	Normoalbuminuria (<30)	≥30
Stage2 Incipient nephropathy	Microalbuminuria (30–299)	≥30
Stage3 Overt nephropathy	Macroalbuminuria (≥300) or persistent proteinuria (≥0.5)	≥30
Stage 4 Renal failure	Any albuminuria/proteinuria status	<30
Stage 5 Dialysis therapy	Any status on continued dialysis therapy	<30

As published on Journal of Diabetes Investigation on March 2015- A new Clasification of Diabetic Nephropathy 2014: A report from joint committee on Diabetic Nephropathy. [8]

1. Natural history of Diabetic Nephropathy:

An understanding of the natural history of renal disease complicating diabetes is required to assess the impact of therapeutic intervention. In the early stages of type 1 diabetes, glomerular filtration rate is (GFR) is increased reflecting underlying glomerular hyperfiltration and hyperperfusion. Following stabilization of diabetes with therapy, GFR returns to normal, usually for a prolonged period. During this time, however, histological changes including thickening of the glomerular basement membrane (GBM), mesangial expansion and glomerular hypertrophy and tubular changes occur. This leads over a period of years to the development of microalbuminuria, defined as a urinary albumin excretion rate (AER) of 20–200 mcg/min (30–300 umol/24h). In patients with type 1 diabetes, microalbuminuria predicts the subsequent development of overt proteinuria, an event associated with worsening of hypertension. In patients with type 2 diabetes the link between microalbuminuria and the development of nephropathy is less clear. It was noted that in both type 1 and type 2 diabetes, the development of microalbuminiria is the strong predictor of the development cardiovascular disease (CVD) [9].

2. Pathophysiology:

It is important to understand the pathophysiology of diabetic nephropathy to know the present and future therapeutic interventions. The consequences of hemodynamic and metabolic processes within the glomerulus which are independent, leads to renal injury in diabetes[9]. The hemodynamic abnormalities are common to diabetic and nondiabetic renal disease, and comprise arterial hypertension and increased intraglomerular pressure. Epidemiological evidence supports a role for sustained elevation of plasma glucose which may produce glomerulosclerosis through a variety of mechanisms [9].

The first is the production of advanced glycosylation end products (AGE) [10]. Inhibition of AGE products by aminoguanidine slows the development of microalbuminuria and (glomerular changes) [11]. Activation of the polyol pathway and protein kinase C may also contribute to glucose mediated renal injury [12-14].

The onset of diabetic nephropathy is determined by both genetic and non-genetic factors [15]. Several genes have been implicated as determinants of the risk of nephropathy, but so far no genetic test has been sufficiently sensitive and specific to gain acceptance by clinicians [15]. However, one important argument for strong genetic determination is the observation of familial clustering of nephropathy in type 1 [16] and type 2[17] diabetics. Recent studies also suggest that Apolipoprotein (apo) E gene polymorphism may be important in development of diabetic nephropathy [18, 19]. Although results are still conflicting, a study in Taiwanese patients by Hsieh MC, Lin SR, Yang YC et al. demonstrated that the frequency of apo E2 allele was significantly higher in patients with diabetic nephropathy than in normal controls and diabetics without nephropathy [20]. These findings imply that apo E polymorphism is apparently related to the development of diabetic nephropathy in type 2 diabetes in Taiwan [21]. The risk factors for diabetic nephropathy include genetic predisposition, poor glycemic control, older age, male sex, duration of diabetes, hypertension, and smoking [22]. Renal complications tend to occur after 5 years of duration of disease, reach a peak after 5 to 10 year and thereafter rarely occur in same patient [23]. In microalbuminiric type 2 diabetics, only 20% develop overt nephropathy in a 10 year period [24], and by 20 years after the onset of overt nephropathy, only 20% will have progressed to ESRD.

Diabetic Kidney disease is characterized pathophysiologically by increased permeability of the glomerular capillary wall to protein leading to proteinuria [5]. In its early appearance, the first morphological alteration is hypertrophy of glomerular and tubular elements. Subsequently, a thickening of glomerular and tubular basement is evident, with enhanced glomerular permeability to albumin. This leads to progressive accumulation of extracellular matrix (ECM) in glomerular mesangium and in tubulointerstitial structure [25]. Histopathologically, 4 types are described: Glomerular Class Ⅰ, glomerular basement membrane thickening; Class Ⅱ, mesangial expansion, mild (Ⅱa) or severe (Ⅱb); Class Ⅲ, nodular sclerosis (Kimmelstiel-Wilson lesions); and class Ⅳ, advanced diabetic glomerulosclerosis [22].

II. MATERIALS AND METHODS:

Patient selection: Patients with type 1 and type 2 Diabetes Mellitus.

Following factors were not considered; Age, Sex, Body Mass Index (BMI), Preexisting renal diseases, Family history of renal disease without diabetes mellitus, time duration between onset of diabetes mellitus and commencement of treatment, and comorbidities including hypertension and dyslipidemia.

Life style factors like: exercise, diet, Smoking were not taken into account.

Several studies suggest that the incidence and progression of diabetic nephropathy is consistently reduced in diabetic patients with tight glycemic control (glycated hemoglobin [HbA1c] <7% or lower). Action in Diabetes and Vascular disease: PreterAx and Diamicrov NMR Controlled Evaluation (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Veterans Affairs Diabetes Trial (VADT) have shown a significant reduction in new or worsening nephropathy, and progression to macroalbuminuria in high-risk patients with type 2 diabetes assigned to an intensive glucose-control strategy [(26)]. Shurraw et al[(27)] determined whether HbA1c level is independently associated with important clinical outcomes, such as all-cause mortality, cardiovascular events, hospitalizations and kidney failure, in people with diabetes mellitus and stage 3–4 CKD. They reported that a higher HbA1c (>9%) in diabetic CKD patients was associated with markedly worse clinical outcomes, and lower HbA1c (<6.5%) was associated with excess mortality. They emphasized the importance of a high HbA1c level as a risk factor for renal outcomes and that prudent practice was required for moderately intensive risk factor management while minimizing the potential for serious adverse effects of the treatment regimens. In conclusion, they suggested that appropriate and timely control of fasting and postprandial glucose, and HbA1c level in people with diabetes mellitus and CKD might be more important than previously realized. Oh et al. retrospectively assessed the appropriate HbA1c level for diabetics to minimize the incidence of ESRD. They reported that HbA1c <6.5% was associated with reduced development of ESRD in all patients and later stages of CKD compared with HbA1c >6.5%, regardless of glomerular filtration rate. However, HbA1c <6.5% showed no benefit on ESRD development in patients older than 80 years and in patients with diabetic duration of more than 10 years [(28)]. In the UKPDS (UK Prospective Diabetes Study, 1998a, 1998b), 18% of the patients had micro and/or macroalbuminuria (UK Prospective Diabetes Study, 1998b). During the study, 33% of the patients developed albuminuria of more than 50 mg/l and 6.6% of more than 300 mg/l, while 2.0% developed renal failure. However, the number of patients was too small to show any effect of improved metabolic control or tight blood pressure control (UK Prospective Diabetes Study, 1998a, 1998b). During a 10-year period, the cumulative risk for renal failure in type 2 diabetic patients with proteinuria has been shown to be at least 11% (Humphrey et al., 1989) [(29)].

Convincing evidence has been reported that renal damage rarely occurs both in patients with type 1 and 2 diabetes when postprandial blood glucose levels are <200 mg/dl and glycated hemoglobin A1c is <7.5 to 8.0% [(30,31)]. More particular, a 37% decrease in the incidence rate of micro-macroalbuminuria and retinal complications was observed in the UK Prospective Diabetes Study Group study for any decrease of HbA1c by 1% [(32)]. This was also the case for decrease of HbA1c <7.0 to 6.5%. Approximately 75% of the patients had a decrease in GFR. These patients had HbA1c values >7.5 to 8.0%. No change in GFR was found in 25% of the patients who conversely had HbA1c values <7.5 to 8.0%. These findings suggest that HbA1c levels >7.5 to 8.0% are closely associated with a rapid decay of renal function in type 2 diabetes. Also, postprandial plasma glucose values were closely linked to a rapid decay of GFR. More particular, all but two of the patients with postprandial plasma glucose >200 mg/dl had a decay of GFR, whereas no or trivial change was observed when postprandial plasma glucose was <200 mg/dl. Also, fasting plasma glucose values were significantly related to the changes in GFR, although less commonly than with the other two parameters. This finding of a closer relationship of postprandial than fasting plasma glucose with the changes of GFR may be explained by the fact that most of the day, during the morning, in the afternoon, and during the first hours of the night, the patients are in postprandial phase [(31)].

During 7.5 years in the Stockholm study, nephropathy (with a glomerular filtration rate below the normal range) developed in six of the patients in the standard treatment group (mean HbA1c, 8.7%) but in none of those in the intensified treatment group (mean HbA1c, 7.2%) (P=0.02). No patient with mean HbA1c of less than 9.0% developed clinical nephropathy (urinary albumin > 300 mg/24 h) in the Stockholm study [(33)]. All who progressed more than 200 mg/24 h in urinary albumin excretion during 8 years in the Oslo study had HbAl>10% (corresponding to HbA1c>8.5%) [(34)]. In the combined follow up of Steno I and II studies (mean 7 years), 12 patients developed clinical nephropathy (urinary albumin > 300 mg/24 h). All of them, except one, had HbAlc of more than 8.5% during these 7 years [(35)].

A longitudinal cohort study was collected from 587 type 2 diabetic patients with microalbuminuria. Cohort members received intensified treatment to meet the following ADA recommended goals:

HbA1c < 7%, systolic blood pressure (SBP) < 130 mmHg, diastolic blood pressure < 80 mmHg, low-density lipoprotein cholesterol < 100 mg/dL), triglyceride < 150 mg/dL), high-density lipoprotein cholesterol > 40 mg/dL) for men and > 50 mg/dL) for women. Remission of microalbuminuria was defined as shift of albumin–creatinine ratio from mircoalbuminuria to normoalbuminuria. During the 4.5-year period, 210(35.8%) patients achieved remission to normoalbuminuria [(36)].

Lewis and colleagues studied 409 patients with type1 diabetes, proteinuria in excess of 0.5 gm/day and serum creatinine less than 2.5 mg/dl [(37)]. Patients were randomized to captopril or placebo (in addition to conventional anti hypertensive therapy) and followed for a median of 3 years. All patients developed diabetes before 30 years of age and more than 7 years before recruitment of the study. The primary end point was doubling of serum creatinine. 43 patients in the placebo group and 25 in the captopril group reached this end point. There were similar levels of blood pressure control in the captopril placebo groups during the study 128-34/77-82(captopril) 120-36/80-84 (placebo). Overall, captopril therapy produced a 48% reduction in risk for doubling serum creatinine (43% when corrected for mean arterial blood pressure) and a 50% (46% corrected) reduction in combined end points of death, dialysis and transplantation. This study firmly demonstrated the potential benefits of good blood pressure control using ACE inhibition in patient with IDDM and established nephropathy.

Long term glycemic control is closely related to the development of diabetic complications [38]. In patients with type 1 diabetes, the strongest evidence on the influence of metabolic control in Diabetic nephropathy comes from the DCCT (Diabetes Control and Complications Trial) and specific analyses on the development of nephropathy [39]. The primary prevention cohort compromised 726 patients, aged 13-39, with type 1 diabetes of 1-5 year duration and who were normotensive (<140/90 mmhg) with normal renal function and who had neither retinopathy nor significant albuminuria (AER < 28 mcg/min). In a secondary cohort, there were 715 patients with a duration of type 1 diabetes of 1-15 years, minimum to moderate retinopathy and AER < 139mcg/min. Seventy-three patient in this group had microalbuminuria (AER >28mcg/min). The mean follow-up was 6.5 years (range 3-9), and intensive therapy achieved a mean reduction of about 2% in HbA1c, maintained throughout the study (7.2 vs.9.1%, p<0.001). Of the primary prevention cohort, 16% of the intensive group developed an AER>28mcg/min at some point during the follow up period, compared with 27.3% of the control group [a 34% reduction; 95% CI 2,56]. Only 6.9 and 2.7%, respectively, however, had a sustained AER>28mcg/min at 9 years [56% reduction] which just failed to achieve significance. In the secondary prevention group, there were significant benefits in terms of reduction in AER, the cumulative incidence of sustained microalbuminuria at 9 years was 18.6 vs. 7.4%; a reduction of 61% [95% CI 36,77]. Overall, 5.2% of the intensive group developed overt proteinuria [AER>300mg/24 h] compared with 11.3% at 9 years in the control groups.

Intensive glucose control, aiming for a target glycated hemoglobin (HbA1c) level of <6.0%, was once considered a treatment goal in patients with type 2 diabetes mellitus (T2DM). However, in 2008, primary results from the ADVANCE1 and ACCORD2 trials, which compared intensive (target HbA1c levels of ≤6.5% and ≤6.0%, respectively) with standard glucose control (as defined by local guidelines or HbA1c 7.0–7.9%, respectively), challenged the benefits of intensive glycemic control in this population. Now, new findings from a 6-year follow-up evaluation of the surviving ADVANCE trial participants (ADVANCE-ON) 3 and a post hoc analysis of the ACCORD data, 4 provide further evidence that intensive glucose control might not be beneficial in patients with T2DM, particularly in those with chronic kidney disease (CKD). Glycemic control in patients with T2DM requires a balance to be found between a low target HbA1c level to retard development and progression of microvascular complications (including CKD), and a high target HbA1c level to avoid excess mortality once nephropathy has ensued [40]. Hyperglycemia has been documented as an extremely important risk factor for the onset of microalbuminuria both in type 1 and type 2 diabetes [41,42]. There is no risk threshold, i.e. the renal risk increases progressively with higher HbA1c values.

III.RESULTS AND DISCUSSIONS

Of the 586 citation titles studied, relevant information from 43 articles were obtained. These included one meta-analysis, one review article and the rest were original research articles. JMCP Supplement and editorials from various journal were also studied. The researches were unanimously in favour of keeping the HbA1c levels in the range of 7-8% to prevent, delay, or halt the progression of Diabetic Nephropathy in both Type I and Type II Diabetes Mellitus.

IV.CONCLUSION

Diabetic Nephropathy continues to account for a large proportion of all cases of CKD and is the most common cause for chronic dialysis among all kidney diseases [43], and their economic burden for management of advanced CKD and ESRD has become a significant problem for individual patients and society. Studies have shown that poor metabolic control is associated with development of high blood pressure with progression of nephropathy. Hence, earlier detection of diabetic nephropathy is essential for prevention of progression to advanced CKD. Several studies have shown that HbA1c level close to 7 is the optimal glycemic control for the prevention of diabetic nephropathy avoiding the risk of hypoglycemia. Although, until now, the optimal glycemic control in patients with CKD had not been determined, the American Diabetes Association and National Kidney Foundation both recommend achieving a HbA1c level of 7% in most patients with diabetes, regardless of the presence of CKD.

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