Study of the Influence of Erythropoietin Treatment on Hemoglobin Alc Levels in diabetic patients with Chronic Renal Failure on Hemodialysis

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Abstract

Monitoring of glycemic control is the cornerstone of management for insulin-dependent diabetes mellitus, HbA1C levels in hemodialysis patients can be influenced by starting or stopping EPO treatment, and HbA1C levels can decrease or increase according to the increase or decrease of hematocrite caused by changing the EPO dosage, respectively.

Our study included 40 patients on regular hemodialysis who are EPO naïve: 30 patients diabetic and 10 patients were not diabetics' controls. HBA1c was measured before and after a 3 month EPO therapy by column chromatography, fasting blood sugar, hemoglobin, electrolytes, albumin and renal functions were measured. HBA1c decreased significantly with negative correlation with hemoglobin, but independent of FBS and other variables .The study concluded that HBA1c was not reliable marker for glycemic control in diabetic hemodialysis patient on EPO therapy.

Keywords:

- **Erythropotien**
- **HBA1c**
- **Diabetes mellitus**
- **CRF**
- **Hemodialysis**

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ACC	The American College of Cardiology
ACE	angiotensin-converting enzyme inhibitors
ADA	American Diabetes Association
AHA	American Heart Association
ARBS	Angiotensin II Receptor Blockers
ASA	Aspirin
BTP	Beta-Trace Protein
BUN	Blood urea nitrogen
CERA	Continuous erythropoietin receptor activator
CHD	Coronary heart disease
CKD	Chronic kidney disease
CRF	Chronic renal failure
CVD	Cardiovascular disease
CysC	Cystatin C
DCCT	the Diabetes Control and Complications Trial
DTPA	labeled diethylenetriamine pentaacetic acid
ECG	Electrocardiogram
EDIC	Diabetes Intervention and Complications
eGFR	Estimated Glomerular filtration rate
EPO	Erythropoietin
ESA	Erythropoietin stimulating agent
ESRD	End stage renal disease
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	US Food and Drug Administration
GFR	Glomerular filtration rate
KDOQI	Kidney Disease: Outcomes Quality Initiative
L- PGDS	lipocalin-type urinary prostaglandin D synthase
MOH	Ministry of health
NKF	National Kidney Foundation
PRCA	pure red cell aplasia
RAAS	Renin-angiotensin-aldosterone system
TSAT	Transferrin saturation
UKPDS	United Kingdom Prospective Diabetes Study
β VEGF	Vascular endothelial cell growth factor.

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Introduction

Monitoring of glycemic control is the cornerstone of management for insulin-dependent diabetes mellitus and is recommended by the American Diabetes Association for the prevention of micro vascular complications associated with hyperglycemia. ***(United Kingdom Prospective Diabetes Study, 1998)***

Two laboratory measures are recommended for assessing glycemic control: blood glucose level, which measures the immediate level of glycemia, and hemoglobin A1C, which reflects long-term glycemia. ***(American Diabetes Association, 2004)***

The HBA1c measures the amount of glycosylated hemoglobin in the blood, a compound formed by the irreversible binding of glucose to hemoglobin. Glycosylated hemoglobin can be differentiated into three distinct fractions A1A, A1B, and A1C; of these, HBA1c is the most abundant**.**

The process of glucose binding to hemoglobin occurs continuously during the life span of a red blood cell, approximately 120 days. Thus, it is commonly accepted that the level of HBA1c reflects the previous 2-3 months of glycemic control and is widely used as a measure of long-term control. ***(Saudek, et al. 2005)***

Considerable literature exists that establishes the relationship of HBA1c to mean plasma glucose level. ***(Rohlfing, et al. 2002)***

However, evidence suggests that HBA1c may not be a true measure of the previous 3 months, but rather weighted to the latter days in the erythrocyte life span. Such weighting has even been quantified into a mathematic formula, which indicates that the mean glycemia during the

preceding 30 days before HBA1c measurement contributes to approximately 50% of the resultant HBA1c level, with 25% from the previous 30-60 days and another 25% during the previous 60-120 days. ***(Saudek, et al. 2005)***

Physiologic factors affecting HBA1c need to be considered when interpreting a laboratory result, the most significant factor being erythrocyte turnover rate. The more extensively an erythrocyte has circulated in the blood stream, the more glycated its hemoglobin may become. **(*Inaba, et al. 2007)***

Conditions that may cause the HBA1c to be falsely elevated include uremia, chronic alcohol intake, splenectomy, chronic renal failure, iron deficiency anemia, and hypertriglyceridemia. ***(Wallach, et al. 2000)***

However, factors shortening the life span of erythrocytes will decrease HBA1c level, as the erythrocytes have a decreased time in circulation to be glycated. The A1C level has been shown to be falsely decreased in patients with conditions that may cause hemolysis, such as sickle cell anemia or thalessemia, and with blood transfusions. ***(Vivian, et al. 2004)***

EPO is recently widely used in the treatment of renal anemia and approximately 75% of the hemodialysis populations are candidates for EPO. Anemia in CKD is marked by an early relative EPO deficiency, but several factors besides Hb may persistently stimulate EPO synthesis. Although EPO deficiency is likely the main determinant of anemia in patients with advanced CKD, the presence of anemia in those with mGFR >30 ml/min per 1.73 m^2 calls for other explanatory factors. **(*Lucile Mercadal , et al. 2011*)**

World Health Organization criteria define anemia as hemoglobin [Hb] <13 g/dl in men and 12 g/dl in women, EPO response to Hb level varied by mGFR level. EPO and Hb levels were negatively correlated (r=−0.22, P=0.04) when mGFR was >30 ml/min per 1.73 m^2, whereas they were not correlated when mGFR was <30 (r=0.09, P=0.3; P for interaction=0.01). ***(Lucile Mercadal , et al. 2011*)**

In patients with anemia, the ratio of observed EPO to the level predicted by the equation for their Hb level decreased from 0.72 (inter quartile range, 0.57–0.95) for mGFR ≥60 ml/min per 1.73 m^2 to 0.36 (inter quartile range, 0.16–0.69) for mGFR <15. Obesity, diabetes with nephropathy other than diabetic glomerulopathy, absolute iron deficiency, and high C-reactive protein concentrations were associated with increased EPO levels, independent of Hb and mGFR. ***(Lucile Mercadal , et al. 2011*)**

Aim of the work

The aim of this thesis is to study the effect of erythropoietin treatment on HBAıC levels in diabetic patients on regular hemodialysis, and to assess the reliability of HbA1c as a marker for glycemic control in such patients.

CHRONIC KIDNEY DISEASE

Introduction

Chronic kidney disease (CKD) is a devastating disease with clinical, economic and ethical dimensions, and is a recognized major public health problem. CKD is defined as kidney damage or glomerular filtration rate (GFR) less than 60 ml/min/l .73m^2 for 3 months or more, regardless of cause. ***(Levey A, et al. 2005)***

The major outcomes of CKD, regardless of cause include progression to ESRD, complications of decreased kidney function, and cardiovascular disease (CVD). Increasing evidence indicates that some of these adverse outcomes can be prevented or delayed by early detection, and treatment. ***(Remuzzi G, et al. 2002)***

CKD is the preferred term because another widely used one, chronic renal failure or insufficiency, is not as easily identifiable by patients as a disorder that affects the kidney. In addition, chronic renal failure (CRF) suggests that the kidneys have lost all of their function, whereas CKD covers the spectrum of clinical problems beginning with abnormalities detectable only by laboratory testing to a late stage, labeled uremia. When the kidney fails to perform most of its function, the clinical state is labeled end-stage renal disease ESRD, and dialysis or transplantation is required to sustain life. **(*Mitch W, 2007)***.

ESRD is defined as either GFR less than 15mL/min per 1.73 $m^{2,}$ which is accompanied in most cases by signs and symptoms of uremia a need to start kidney replacement therapy. (Dialysis or transplantation) ***(Levey A, et al. 2003)***

More than 400,000 people all over the world received some form of renal replacement therapy, and this number is expected to reach 2.2 million by the year 2030. ***(Jaar B, et al. 2008)***

Causes of chronic kidney disease

CKD results from a large number of diseases that either are systemic and damage the kidney or are intrinsic to the kidney (Table 1). CKD has two characteristics. First, there is chronicity because the kidney damage of CKD is rarely repaired and loss of function persists, unlike the course of acute kidney injury (AKI). Second, loss of kidney function generates even more kidney damage so that CKD progressively worsens even if the disorder that caused it becomes inactive. ***(Mitch W, 2007)***

Table 1: Causes of chronic kidney disease

Diabetic Glomerulopathy or nephropathy
Hypertensive nephrosclerosis
Glomerular disease: Glomerulonephritis Amyloidosis, light chain disease Systemic lupus erythematosus, Wegener's granulomatosis[*]
Tubulointerstitial disease: Reflux nephropathy (chronic pyelonephritis) Analgesic nephropathy Obstructive nephropathy (stones, benign prostatic hypertrophy) Myeloma kidney [*]
Vascular disease: Scleroderma [*] Vasculitis[*] Renovascular renal failure (ischemic nephropathy) Atheroembolic renal disease [*]
Cystic diseases: Autosomal dominant polycystic kidney disease Medullary cystic kidney disease

[*] Systemic disease involving the kidney***. (Mitch W, 2007).***

Risk factors for chronic kidney disease

Risk factors for CKD are defined as attributes associated with increased risk for its adverse outcomes. Table 2 shows defining susceptibility and initiation factors are to identify persons at increased risk for developing CKD, while defining progression factors is used to indentify persons at high risk for worsening kidney and subsequent loss of kidney function. Because kidney disease usually begins late in life and progresses slowly, most persons in the stage of decreased GFR die of CVD before they develop ESRD. However, decreased GFR is associated with a wide range of complications, such as hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life, which can be prevented or ameliorated by treatment at earlier stages. Treatment can also slow down the progression to ESRD. Thus measures to prevent, detect, and treat CKD in its earlier stages could reduce its adverse outcomes. ***(Levey A, et al .2003)***

Table 2: Risk factors for chronic kidney disease

Risk Factor	Definition	Examples
Susceptibility factors	Increased susceptibility	Old age, family history, low birth weight
Initiation factors	Directly initiate kidney damage	Diabetes, hypertension &autoimmune disease
Progression factors	Cause worsening kidney damage	Proteinuria, higher blood pressure, smoking
End stage factors	Increase morbidity & mortality in CRF	Low dialysis dose, anemia, low serum albumin, late referral

(Levey A, et al .2003)

Diagnosis of chronic kidney disease

(I) History

A history of nephrotic syndrome suggests previous glomerular disease as a cause of the CKD. Recurrent gross hematuria may accompany IgA nephropathy or membranoproliferative glomerulonephritis. A careful personal and family history for hypertension and diabetes mellitus should be obtained, including information on any family members in whom ESRD developed. Families may have a genetic predisposition not only for essential hypertension and diabetes mellitus but also for the development of renal disease secondary to these systemic diseases. A history of recurrent renal stones or obstructive uropathy, including prostatism, or excessive mixed analgesic intake may suggest primarily tubulointerstitial disease. ***(Luke R, 2003)***

(II) Physical examination

On physical examination, signs of hypertensive (left ventricular hypertrophy and hypertensive retinopathy) or diabetic disease (peripheral neuropathy, diabetic retinopathy) are important. Knobby, bilaterally enlarged kidneys support a diagnosis of polycystic kidney disease, and a palpable bladder or large prostate suggests obstructive uropathy and is an indication for measurement of residual urinary volume after voiding. Gouty tophi and a history of gout may be relevant. Signs and symptoms of polyarteritis nodosa, systemic lupus erythematosus, Wegener's granulomatosis, scleroderma, and essential mixed cryoglobulinemia should be sought because these systemic diseases often involve the kidney. Hepatosplenomegaly and macroglossia suggests renal amyloidosis. (***Luke R, 2003)***