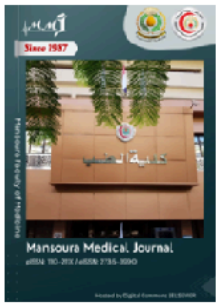
MANSOURA MEDICAL JOURNAL

ISSN - Print: 1110-211X - Online: 2735-3990

journal homepage: mmj.mans.edu.eg



Volume 21 | Issue 1 Article 15

SOME OBSERVATIONS ON GOLUCOSYLATED HEMOGLOBIN IN CHRONIC RENAL FAILURE AND THE INFLUENCE OF HEMODIALYSIS

Osama Salama

Clinical Pathology Depts. Mansoura Faculty of Medicine

Nabil Laymon

*Internal Medicine** Depts. Mansoura Faculty of Medicine*

Hassan Risk

Internal Medicine Depts. Mansoura Faculty of Medicine

Fardous Abdelfattah

Internal Medicine Depts. Mansoura Faculty of Medicine

SOME OBSERVATIONS ON GOLUCOSYLATED HEMOGLOBIN IN CHRONIC RENAL FAILURE AND THE INFLUENCE OF HEMODIALYSIS

By

Salama, O. S.*; Lymon, N. E., Rizk, H. M.** and Ramadan, F. A.****

From

Clinical Pathology and Internal Medicine** Depts.*

Mansoura Faculty of Medicine

Received for Puplication : 1/2/1992

INTRODUCTION

Glucosylated hemoglobin is a model of non enzymatic protein modification forming a minor component of human hemoglobin (Peterson & Jones, 1977). It is formed by irreversible post synthetic transformation of the native Hb-A in which a sugar moiety is attached to the N-terminal valine in each B chain of otherwise normal Hb-A (Bunn, 1981). It comprises approximately 6.8% of the total human hemoglobin. This minor fraction is composed of many subfractions namely : HbA_1a_1, HbA_1b, HbA_1c which comprise approximately 1.6, 0.8 and 4% of the total adult human erythrocytes respectively and are collectively called fast hemoglobins (Gambino, 1981). Thus, HbA_1c is the largest fraction of glucosylated hemoglobins (Bunn et al., 1976) making up to 80% of the minor hemoglobins and is formed when glucose is slowly non enzymatically and irreversibly linked to HbA. The other glucosylated hemoglobins HbA_1a_1, HbA_1a_2 and HbA_1b have not been so clearly characterized. During the 120 day life span of the erythrocytes, a progressive increase of HbA_1c occurs reaching a constant equilibrium over several weeks (Gallop & Baz, 1985). The percent of HbA_1 in the blood is proportional to the integrated blood glucose (Bunn et al., 1988). Therefore, it is tho most reliable test to assess the control of glycemia in diabetics during the remote weeks to

months (Gonen et al., 1976).

Several studies revealed that glucosylation is a direct reflection of the levels of different metabolites within the red cells as well as the rate at which these metabolites react with Hb within the red cells. Therefore, glucosylated Hb is generally believed to reflect an integrated record of a timed averaged plasma glucose concentrations over the antecedent 2-3 months indicating a long term of metabolic control of diabetes (Gonen et al., 1977). There is presently no other test that can provide this kind of objective information (Paisy et al., 1980).

Uremia is known to be associated with a lot of metabolic drangements particularly in diabetics. The significance of glucogylated hemoglobin as an indicator fr uremia in diabetics and non diabetics has however been questioned. The role of glucosylated Hb in uremia is however unclear and controversial (Smith et al., 1989). Some authorg have shown a significant correlation between HbA_1 and serum urea (Fluckiger et al., 1981) and serum creatinine as well (Kovarik et al., 1981), whereas others failed to confirm these findings (deBair et al., 1980). Therefore, the target of this study was to assess the value of estimating glucosylted Hb in diabetic uremic patients and the consequences of hemodialysis on its level.

MATERIAL AND METHODS

The material of this study comprized 30 patients with end stage renal disease. They were 18 males and 12 females and their ages ranged from 30 to 50 years. They were divided into 2 groups, each included 15 patients (9 males and 6 females). The first group comprised uremic patients at diagnosis (before dialysis or any therapeutic intervention) while the second group included patients on frequent hemodialysis (12 sessions/month). Each group was further subcategorized into a and b according to the presence or absence of diabetes mellitus as follows:

Group I : CRF (not dialysed):

a) CRF non diabetics : 10 patients (6 males and 4 females).

b) CRF diabetics : 5 patients (3 males and 2 females).

Group II : CRF on frequent hemodialysis:

a) Non diabetics : 10 cases (6 males and 4 females).

b) Diabetics: 5 cases (3 males and 2 females).

In addition, 5 diabetic non uremic patients (3 males and 2 females) were selected, besides 10 normal healthy subjects (6 males and 4 females) of matched age were included as a reference groups.

All members included in this work were subjected to the following investigations:

* Complete hemogram (Dacie & Lewis, 1991).

* Fasting and post-prandial blood glucose, serum creatinine, BUN, liver functions profile, urine analysis. according to the standard assay methods.

* Quantitative assay of glucosylated hemoglobin using Helena Glyco-Tek affinity microchromatographic column method described by Klenk (1982).

RESULTS

It was clear that GHb showed a significant reduction in CRF as compared to the control, while it was significantly increased in CRF associated with diabetes (table 1). After hemodialysis, GHb level was still significantly higher in CRF diabetics as compared to either the control or CRF groups (tablo 2). On comparing GHb levol in CRF patients before dialysis with its value in the patients after dialysis, a significant increase in GHb lovel could be noticed in CRF after dialysis than before it. On the otherhand, a non significant change could be observed in GHb in CRF diabetics after dialysis as compared to its lovel before dialysis in the same patients. Meanwhile, a positive correlation could be observed between GHb level and both blood sugar as well as serum creatinine in CRF and CRF diabetics before dialysis. Moreover, a positive correlation was still present between GHb and serum creatinine in CRF after dialysis.

DISCUSSION

Chronic renal failure is well known to be associated with numerous metabolic abnormalities particularly when combined with diabetes mellitus. Glucosylated hemoglobin is a model of non enzymatic post-synthetic protein modification (Peterson & Jones, 1977). Its level is proportionate with the integrated blood glucose concentration (Bunn et al., 1988). The role of glucosylated Hb in uremia is however, unclear and controversial (Smith et al., 1989). Moreover, the effects of uremia on Hb glucosylation were shown to be more complicated. Fluckiger ot al. (1981), reported normal levels of HbA_1 in CRF whereas, Dandona et al. (1979), reported a low level of HbA_1 in uremic patients. Lantz et al. (1981) and Salovanta ot al. (1986) described elevated levels of glucosylated Hb in nondiabetic uremic patients. They attributed that to the influence of the renal dysfunction on HbA_1 resulting in: firstly, carbamylation of Hb in the presence of high urea concentration which generates a hemoglobin complex that chromatographically can not be distinguished from glucosylated Hb, secondly, the increase of HbA_1 level may reflect a true impairment of glycemic control which had been documented in uremic patients.

In our study, a significantly reduced glucosylated Hb level was observed in CRF patients. This could be Consistent with the well proved shortened erythrocyte survival in uremia with a consequent clearance of any accumulated glucosylated Hb from the circulation. This finding was found to be in agreement with that reported by Dandona et al. (1979) and Sabater et al. (1991). In contrast to that, other workers reported high levels of glucosylated Hb in CRF, but this may not be due to a true glucosylation, but rather to hemoglobin carbamylation as a consequence of urea dissociation into ammonia and cyanate. This carbamylation do interfere with chromatographic determination of glucosylated Hb giving an apparant or false elevation.

In CRF diabetes, a highly significant increase in glucosylated Hb was observed when compared to either the

control or CRF groups. This could be attributed to glucose intolerance (DeFranzo et al., 1981) or to the associated hyperglycemia in such patients (Casparie & Miedema, 1977). However, other investigators found no abnormality in glucosylated Hb in uremics (Panzett et al., 1983).

When hemodialysis was considered in CRF groups, it yielded a significant increase in glucosylated Hb level in uremic patients as compared to their values before dialysis. Again this may be refferred to the improved survival of the red cells and a consequent prologation of the erythrocyte life span leading to more accumulation of glucosylated Hb. In CRF, most patients have an impaired glucose metabolism, but this did not found to play a major role in the formation of glucosylated Hb (Casparie & Miedema, 1980) and those on chronic hemodialysis are usually dialysed against a fluid with a high glucose content that might be the cause of the increased glucosylated Hb in dialysis patients. On the otherhand, Roger et al. (1986) reported that the high glucosylated Hb level in end stage renal disease in all chronic hemodialysis patients was not related to the glucose content of dialysis fluid and the mode of dialysis did not appear to effect glucosylated Hb level in CRF.

In the present study, a positive corrolation has been revealed between glucosylated Hb and serum creatinine level in CRF as well as CRF diabetics before hemodialysis. Moreover, this correlation was still valid in CRF diabetics after dialysis. Accordingly, glucosylated Hb assay could be a landmark in the diagnosis of CRF in doubtful or boderline cases. Fluchiger et al. (1981) and Oimomi et al. (1981) reported a significant correlation between HbA_1 and serum urea. Kovarik et al. (1981) also reported a positive correlation between Hb_1A and serum creatinine while other investigators failed to confirm those findings (deBaer et al., 1980).

SUMMARY AND CONCLUSIONS

Glucosylated Hb is a model of non enzymatic postsynthetic protein modification proportionate with blood

glucose level. Its role in uremia is however unclear. Moreover, the effect of uremia on Hb glucosylation was shown to be more complicated. Therefore, the aim of this study was to clarify the reflection of uremia on glucosylated Hb level. The material of this study included 30 patients with CRF and CRF diabetics besides 5 non uremic diabetics and 10 healthy controls. Glucosylated Hb was assayed in all subjects and was reported after in uremic cases. We concluded that the level of glucosylated Hb has been significantly reduced in CRF which could be due to shotened red cell survival, while in CRF diabetics it was higher due to their high blood glucose. Moreover, hemodialysis resuited in elevation of glucosylated Hb due to the improved red cell survival. A positive correlation has been revealed between glucosylated Hb and serum creatinne, a finding that may aid in the diagnosis and follow up of CRF particularly in doubtful cases.

Table (1) : The mean (M) + SD of the studied parameters in the included groups before hemodialysis.

		Control n:10	CRF n:10	CRF-DM n:10	D. M n:10	P			
						P_1	P_2	P_3	P_4
FBG (mg/dl)	Mean	78.00	83.00	129.00	170.00	>0.1	<0.01	<0.01	>0.1
	±SD	7.88	8.57	46.00	34.64				
PPBG (mg/dl)	Mean	115.50	115.00	190.00	300.00	>0.1	<0.01	<0.01	<0.01
	±SD	15.53	9.49	80.32	79.06				
S. CREAT (mg/dl)	Mean	0.51	11.59	7.64	0.46	<0.001	<0.001	>0.1	<0.001
	±SD	0.21	5.99	3.82	0.33				
Hb (G/dl)	Mean	13.54	6.35	8.50	13.50	<0.001	<0.01	>0.1	<0.01
	±SD	1.07	1.92	3.36	0.50				
GHB (%)	Mean	5.95	4.61	9.04	14.97	<0.01	<0.01	<0.01	<0.01
	±SD	0.77	0.84	3.26	3.69				

FBG : Fasting blood glucose.
PPBG : Post-Prandial blood glucose.
S. CREAT : Serum creatinine.
Hb : Hemoglobin concentration.
GHb : Glucosylated hemoglobin.

n : number of cases.
P_1 : CRF versus control.
P_2 : CRF-DM versus control.
P_3 : CRF versus CRF-DM.
P_4 : DM versus CRF-DM.

Table (2) : The effect of hemodialysis in CRF on the studied parameters, a comparison between groups.

		Control n:10	CRF n:10	CRF-DM n:10	P		
					P_1	P_2	P_3
FBG (mg/dl)	Mean	78.00	83.40	118.00	>0.1	<0.001	<0.001
	±SD	7.88	8.44	21.60			
PPBG (mg/dl)	Mean	115.50	117.00	203.00	>0.1	<0.05	<0.001
	±SD	15.54	10.30	58.26			
S. CREAT (mg/dl)	Mean	0.51	8.30	8.28	<0.001	<0.001	>0.1
	±SD	0.21	2.34	3.13			
Hb (G/dl)	Mean	13.54	6.70	8.00	<0.001	<0.001	>0.1
	±SD	1.07	1.48	2.10			
GHB (%)	Mean	5.94	5.97	7.77	>0.01	<0.05	<0.05
	±SD	0.77	0.68	1.20			

P_1 : CRF (after dialysis) versus control.
P_2 : CRF-DM (after dialysis) versus control.
P_3 : CRF (after dialysis) versus CRF-DM (after dialysis) .

Table (3) : Comparison of the hemodialysis effect on the patient subgroups.

		CRF (n:5)		CRF-DM (n:5)		D. M n:5	P		
		Before	After	Before	After		P_1	P_2	P_3
FBG (mg/dl)	Mean ±SD	83.00 8.57	83.40 8.40	129.00 46.15	118.00 21.70	170.00 34.60	>0.1	>0.1	>0.05
PPBG (mg/dl)	Mean ±SD	115.00 9.43	117.00 10.33	190.00 80.30	203.00 58.30	300.00 79.10	>0.1	>0.1	<0.05
S. CREAT (mg/dl)	Mean ±SD	11.59 5.99	8.30 2.35	7.64 3.81	8.28 3.13	0.46 0.33	>0.1	>0.1	<0.001
Hb (G/dl)	Mean ±SD	6.35 1.92	6.70 1.48	8.50 3.40	8.00 2.12	13.50 0.50	>0.1	>0.1	<0.001
GHB (%)	Mean ±SD	4.61 0.84	5.96 0.68	9.04 3.27	7.77 1.18	14.97 3.68	<0.001	>0.1	<0.001

P_1 : CRF before dialysis versus CRF after dialysis.
P_2 : CRF-DM before dialysis versus CRF-DM after dialysis.
P_3 : CRF versus CRF-DM after dialysis.

Table (4) : A correlation between glucosylated Hb and the studied parameters before and after dialysis.

	FBG		PPBG		S. CREAT		Hb		Critical value
	Before	After	Before	After	Before	After	Before	After	
Control r	0.11 -	-0.11 -	0.24 -	0.40 -	0.39 -	0.16 -	0.17 -	0.16 -	±0.62
CRF r	0.63 +	0.55 -	0.67 +	0.33 -	0.81 +	0.18 +	-0.44 -	-0.18 -	±0.62
CRF-DM r	0.92	0.34	0.87	0.90	-0.40	0.08	-0.03	0.54	±0.88
DM r	0.24 -		-0.16 -		0.30 -		0.42 -		±0.88

REFERENCES

Bunn, H. F.; Haney, D. N.; Kamin, S.; Gabby, k. N. and Gallop, P. M. (1976), J. Clin. Invest., 57 : 1652.

Bunn, H. F. (1981): Diabetes, 30 : 325.

Bunn, H. F.; Gabby, K. H. and Gallop, P. M. (1988) : Science 200 : 21.

Casparie, A. F. and Miedema, K. (1977) : Lancet, 2 : 758.

Dacie, J. V. and Lewis, S. M. (1991): Practical Hematology. 7th ed. Churchill Livingstone.

Dandona, P.; Freedman, D. and Moorhead, J. F. (1979) : Br. Med. J., 1 : 1183.

DeBaer, M. J.; Miedema, K. and Casparie, A. F. (1980): Diabetologia, 18 : 437-40.

DeFranzo, R. A.; Abestrand, A.; Smith, D.; Hendler, R. E. and Wahren, J. (1981) : J. Clinical Invest., 67 : 563-8.

Fluckiger, R.; Harman, W.; Meier, W.; Loo, S.. and Gabbay, K. (1981): New Eng.. J. Med. 304 : 823-7.

Gambino, R. (1981): Lab. Report Physians, 3 : 83.

Gonen, B.; Rubenstein, A. H.,; Rcochman, H.; Tanega, S. P. and Horwitz, D. L. (1977): Lancet, 2 : 734.

Gonen, B. and Rubenstein, A. H. (1977) : Diabetologia, 15 : 1-8.

Kovarik, J.; Stummvoll, H. K.; Graft, H. and Muller, M. M. (1981): Diabetologia, 19: 555-6.

Lantz, B.; Wajcman, H.; Beaufils, M.; Meyier, A.; Labic and DiAssan, R. (1981): Diabet. Metabol., 7 : 109-14.

Oimoni, M.; Ishikawa, Kawasaki, T.; Kubota, S.; Yoshimura, Y. and Baba, S. (1981): Diabetologia, 21 : 163.

Paisey, R. B.; McFarlane, D. G.; Sheriff, R. J.; Hartog, M.; Slade, R. R. and White, D. A. (1980): Diabetologia, 19 : 31.

Panzetta, G.; Bassetto, M. A.; Feller, P.; Querena, M.; Sandrini, S.; Franceschi, T. and Vettore, L. (1983): Clin. Nephrol. 20: 259-62.

Peterson, C. M. and Jones, R. L. (1977) : Ann. Int. Med. 87 : 489-9 1.

Roger, J.; Haley, M. D. and David, M. (1986) : National kidney Foundation.

Sabater, J.; Quereda, C.; Herrera, I.; Pascual, J.; Villafruela, J. and Ortuno, J. (1991) : Am. J. Nephrol., 11 : 37-43.

Saloranta, C.; Groop, L.; Kawasaki, T.; Rubota, S.; Yoshimura, Tallgren, L. G. (1986) : Clin. Nephrol., 25 : 186-92.

Smith, W. G.; Holden, M.; Benton, M. and Brown, C. B. (1989): Nephrol. Dial. Transplant. 4: 96-100.

دراسة عن الهيموجلوبين المرتبط بالجلوكوز فى مرضى الفشل الكلوى وتأثير عملية الغسيل الدموى

د. أسامه سعد سلامه* - د. نبيل ليمون**
د، حسان رزق** - د. فردوس عبدالفتاح**
قسم الباثولوچيا الاكلينيكية* - والأمراض الباطنة**
كلية طب المنصورة

الملخص والاستنتاجات :

يعد الهيموجلوبين المرتبط بالجلوكوز نموذجاً لتحور البروتين لا إنزيميا بعد التخليق ويتناسب مع مستوى الجلوكوز بالدم. ودوره فى مرضى الفشل الكلوى غير واضح وكذلك فإن تأثير الفشل الكلوى على ارتباط الهيموجلوبين بالجلوكوز يعد من الأمور المعقدة. وعلى ذلك كان الهدف من هذا البحث هو إيضاح انعكاس الفشل الكلوى على مستوى الهيموجلوبين المرتبط بالجلوكوز. وقد شملت هذه الدراسة ثلاثين مريضاً بالفشل الكلوى وكذلك مرضى الفشل الكلوى ويعانون فى نفس الوقت من مرض السكر بالإضافة إلى ٥ مرضى بالسكر وعشر أشخاص كمجموعة ضابطة وأجرى لجميعهم تعيين مستوى الهيموجلوبين المرتبط بالجلوكوز وأعيد تعيينه فى مرضى الفشل الكلوى بعد إجراء الغسيل الدموى. وقد تم استنتاج انخفاض فى مستوى الهيموجلوبين المرتبط بالجلوكوز فى مرضى الفشل الكلوى مما قد يرجع إلى نقص فترة حياة كرات الدم الحمراء بينما كان مستوى الهيموجلوبين المرتبط بالجلوكوز مرتفعاً فى مرضى الفشل الكلوى فى وجود مرضى السكر نظراً لارتفاع مستوى الجلوكوز بالدم لديهم. وقد نتج عن عملية الغسيل الكلوى ارتفاع نسبة الهيموجلوبين المرتبط بالجلوكو نتيجة لتحسن فترة حياة كرات الدم الحمراء. وقد وجد أن هناك ارتباطاً موجباً بين الهيموجلوبين المرتبط بالجلوكوز ونسبة الكرياتينين بالمصل مما قد يساعد فى تشخيص ومتابعة مرضى الفشل الكلوى خاصة الحالات الغير واضحة.