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CLINICAL APPLICATIONS OF CARBAMYLATED HEMOGLOBIN IN RENAL DISEASES

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ABSTRACT

Carbamylated hemoglobin is formed by reaction of isocyanate (urea dissociation product) with valine residues of Hb chains. Different studies demonstrated that carbamylated hemoglobin level is increased in patients with renal impairment. This study concluded that carbamylated hemoglobin level significantly correlates with serum creatinine (r=0.411, moderate positive) and urea level (r=0.408, moderate positive) (p<0.001). This correlation may be important in clinical settings makes carbamylated hemoglobin good biomarker for renal impairment, and may reflect severity and duration of renal impairment. We also found that carbamylated hemoglobin level is not affected by the diabetes state of the patient.

Keywords: *Carbamylated hemoglobin, urea dissociation products, renal impairment, kidney biomarkers.*

INTRODUCTION

Renal disease is a common health problem that is linked to excess morbidity and mortality worldwide. Estimates of the global burden of disease indicate that

diseases of the kidney account for approximately 830,000 deaths and 18,467,000 disability-adjusted life years annually, ranking them 12th among causes of death and 17th among causes of disability (Ibrahim et al., 2016)

Proteins in the human body, in both health and disease, are exposed to chemical reactions capable of altering their structural and functional properties. Spontaneous post-translational protein modifications are caused by the non-enzymatic attachment of reactive molecules to protein functional groups, as seen, for example, in glycation reactions. Because posttranslational modifications are capable of changing protein structure and function, they can create a mechanistic chemical link to the adverse pathophysiology underlying certain metabolic diseases (Kalim et al., 2014).

Carbamylation is a protein modification that results from constant exposure to urea and its byproduct, cyanate, which both increase as kidney function declines. Urea-driven carbamylation reactions occur not only on proteins but also on free amino acids, and these targets may compete with each other for binding such that amino acid deficiency can exacerbate protein carbamylation. Furthermore, protein carbamylation may not be solely related to urea; recent work shows that cyanate may also be generated by myeloperoxidase (MPO) and peroxide-catalyzed oxidation of thiocyanate (derived from diet and smoking) at sites of inflammation (Berg et al, 2013).

Carbamylated hemoglobin is formed by reaction of isocyanate (urea dissociation product) with valine residues of Hb chains. Carbamylated hemoglobin level is found to be increased in renal failure. Evaluation of carbamylated hemoglobin in renal impairment and its correlations with different parameters may provide clinically significant data regarding prediction and management of renal impairment and its complications.

RESULTS

Our study included 88 persons with wide variety of kidney profiles; 26 person with normal KFTs, 29 patients with AKI, and 33 patient with CKD. Among whole study population, carbamylated hemoglobin significantly ($p<0.001$) correlates with creatinine ($r=0.411$, moderate positive) and urea level ($r=0.408$, moderate positive) ($p<0.001$); but doesn't correlates with Hb concentration ($p=0.49$).

***Table 1**. Relations between carbamylated hemoglobin & laboratory parameters in renal impairment*

Variable	Pearson Correlation Coefficient (r)	Sig.
Cr	.411	<0.001*
Ur	.408	<0.001*
Hb	-.079	0.498

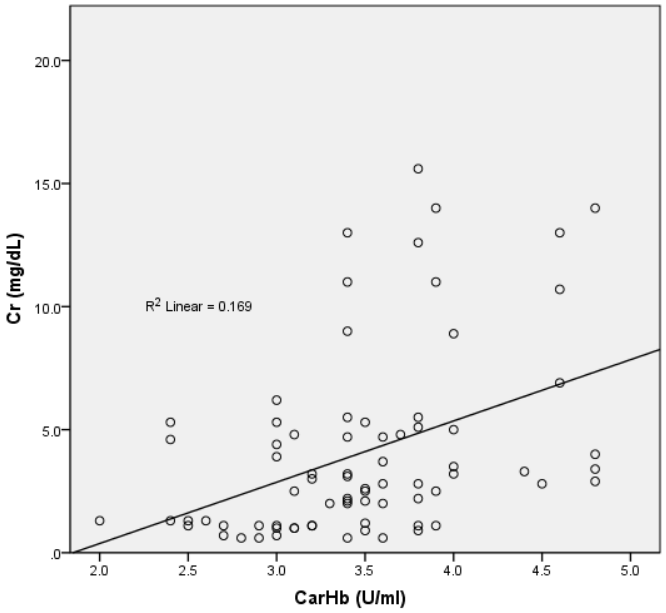

***Figure 1.** Relation between carbamylated hemoglobin & serum creatinine.*

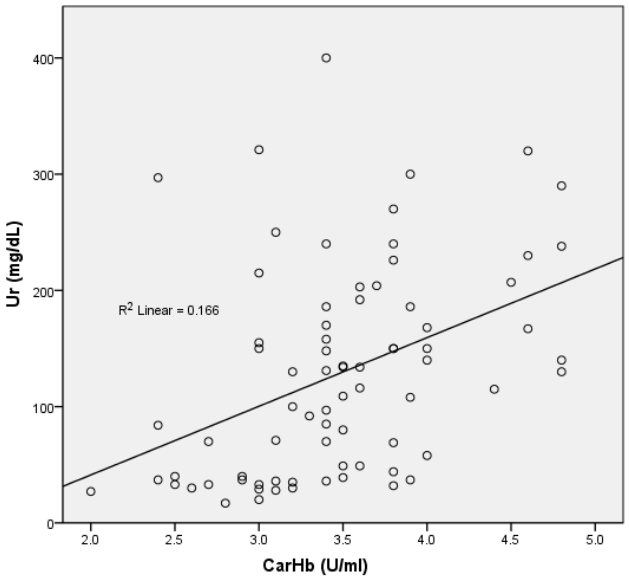

***Figure 2**. Relation between carbamylated hemoglobin & blood urea level*

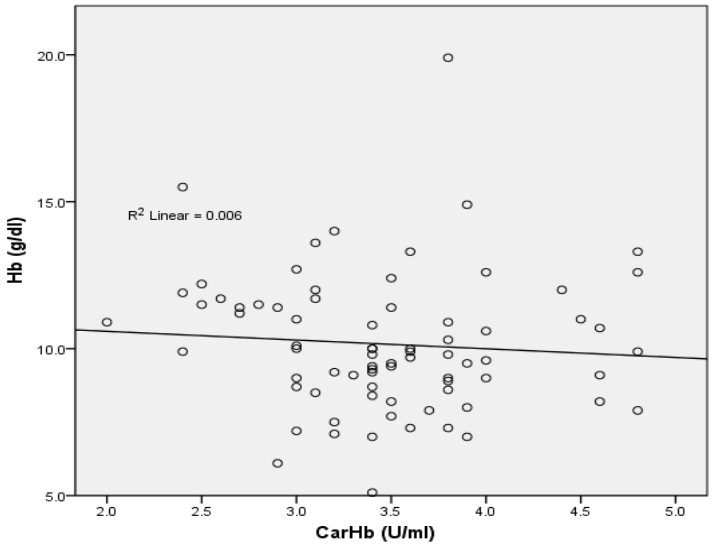

Figure 3. *Relation between carbamylated hemoglobin & blood hemoglobin level*

There is also no significant correlation with age (r= 0-.114; p= 0.325). No significant difference in mean. carbamylated hemoglobin between male and female. No statistically significant difference between mean carbamylated hemoglobin in diabetics (3.4±0.65) and nondiabetics (3.5±0.60) (p=0.99)

Table 2. *Mean carbamylated hemoglobin level in males and females*

Sex	Mean±SD carbamylated hemoglobin (U/mL)	Sig.
Female	3.39±0.64	0.206
Male	3.57±0.59	

Table 3*. Mean carbamylated hemoglobin level in diabetic and nondiabetic patients*

Diabetes	Mean±SD carbamylated hemoglobin (U/mL)	Sig.
Diabetics	3.4±0.65	0.99
Non-Diabetics	3.5±0.60	

DISCUSSION

Renal impairment is a common presentation in outpatient clinic and emergency room. Great effort is directed toward developing novel biomarkers of renal impairment helping in diagnosis and management (Murray et al., 2014). This study aimed to describe the correlation of carbamylated hemoglobin level with different laboratory parameters that is clinically important in renal impairment;

these relations may verify the clinical applications of carbamylated hemoglobin assessment in renal disorders. Identification of such correlation may help to predict, and manage renal disorders and their complications. Our study included 88 persons with different renal profiles; 26 people with normal KFTs, 29 patients with AKI, and 33 patients with CKD.

Among whole study population, carbamylated hemoglobin significantly ($p<0.001$) correlates with creatinine ($r=0.411$, moderate positive). Such this correlation may be important in clinical settings makes carbamylated hemoglobin good biomarker for renal impairment, and may reflect severity and duration of renal impairment. This was in agreement with Jonathan et al., who noticed correlation between carbamylated hemoglobin and creatinine in the same study groups (Jonathan et al., 1992). But against that; A weak positive insignificant ($r = +0.121$, $P=0.319$) relationship between carbamylated hemoglobin and creatinine was notice by Tahora S. et al, 2021. Also, no correlation was observed ($r = 0.157$, $P = 0.333$) by Naresh et al., 2018 and earlier by Stim et al., 1995. These different findings is thought to be due to different study population, different methods of carbamylated hemoglobin assessment, and difference in testing correlation in whole study population or within groups. As carbamylation reflect the effect of urea derived isocyanate, urea / creatinine ratio is to be revised as this may explain the different findings in these studies.

Unlike debates in creatinine, many studies demonstrated good correlation between carbamylated hemoglobin and urea level. We observed moderate positive correlation ($r=0.408$, $p<0.001$) between carbamylated hemoglobin level and urea concentration. This expected agreement is a reflection of pathogenesis of carbamylated hemoglobin, from urea dissociation products. Tahora S. et al, 2021 discovered a significant correlation between urea and carbamylated hemoglobin in both CKD and control group. Carbamylated hemoglobin showed positive correlation ($r = 0.776$, $P < 0.0001$) with concentration urea in renal patient of Naresh et al., 2018 study. Stim et al., studied this correlation in different study groups separately, they observed good correlation in different groups, but described the relationship to be “linear” in AKI & “exponential” in CKD (Stim et al., 1995). Okaka et al., also noticed this correlation, but the difference is that the used time averaged of urea level not only initial assessment, so they concluded that carbamylated hemoglobin may be used to assess severity of kidney disease (Okaka et al., 2012). Jonathan et al., published that carbamylated hemoglobin was found to be raised in correlation with urea irrespective to age, sex, diabetic state and hemodialysis (Jonathan et al., 1992).

No statistically significant difference between mean CarHb in diabetics (3.4 ± 0.65) and non-diabetics (3.5 ± 0.60) ($p=0.99$). In agreement with us, CarHb levels had not been affected by glycemic state (Stim et al., 1995). These results

suggested that glycation has little influence on CarHb assessment, but the opposite is reported in many studies; as Pommerich D et al., who founded that hemoglobin carbamylation has great effect on HbA1c and is to be considered when interpreting glycated Hb level in patient with renal impairment (Pommerich D et al., 2015). Also we noticed that CarHb is not affected by age, sex, or Hb concentration (p=0.49).

CONCLUSION

Carbamylated hemoglobin is formed by reaction of isocyanate (urea dissociation product) with valine residues of Hb chains. Carbamylated hemoglobin level is found to be increased in renal failure. Our study demonstrated that carbamylated hemoglobin level significantly correlates with serum creatinine and blood urea levels, and is not affected by the glycemic state of the patient. This correlation may be important in clinical settings makes carbamylated hemoglobin good biomarker for renal impairment, and may reflect severity and duration of renal impairment. Further studies are recommended to define the validity of carbamylated hemoglobin level assessment in clinical settings and its implication in management of renal disorders.

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