

## FORMATION OF FRUCTOSAMINE IN DIABETIC PATIENTS – WHAT ARE IMPLICATIONS IN TERMS OF ENERGY EXCHANGE

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*Key words:* fructosamine, energy, diabetes

### SUMMARY

*Diabetes mellitus is a frequent disorder affecting individuals of all ages. Monitoring by biomarkers has a key role in the assessment of glycemic control in diabetic patients. Fructosamine is used routinely to assess long term glycemic control in patients with diabetes mellitus. The chemical reaction of glycosylation in the formation of fructosamine has been described for decades. Here, a reappraisal of the bonding energy based on quantum chemical analysis was performed. The bonding energy of the reaction was calculated, showing it to be of the “energy consuming reaction” type. Of interest, the required energy for complex formation per mole of the reaction was equal to that previously reported in the reaction of hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) formation. This could confirm the nature of energy loss in patients with poorly controlled diabetes mellitus.*

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### INTRODUCTION

Diabetes mellitus (DM) is a common disorder affecting individuals of all ages (1). The disease is associated with significant morbidity and mortality and escalating costs, and its prevalence is increasing to epidemic proportions (2). Many studies have consistently documented the importance of glycemic control in delaying the onset and decreasing the incidence of diabetes complications (2). LeRoith and Smith said that although glycemic control was difficult to achieve and challenging to maintain, its impact on disease outcomes was well worth the effort (2).

Monitoring by biomarkers has a key role in the assessment of glycemic control in diabetic patients (3). Several studies have clearly shown that improved glycemic control is strongly associated with a decreased development and/or progression of diabetic complications. Therefore, accurate determination of biomarker for monitoring diabetes control is an important issue for clinical laboratories (3). Of several biomarkers, fructosamine is an effective tool (4). Generally, fructosamine is the result of serum protein glycation (4). Fructosamine is used routinely to assess long term glycemic control in DM patients (4). The chemical reaction of glycosylation in the formation of fructosamine has been described for decades (4,5). Here, the author performed a reappraisal on the

Table 1. Details and required energy for complex formation in each step of fructosamine formation

Items	Alidimine formation	Ketoamine formation
Bond breaking*	1 C-H, 1 C=O, 2 N-H	1 C=N, 1 C-O, 1 O-H
Bond breaking**	1 C-H, 1 C-N, 2 O-H	1 C-N, 1 N-H, 1 C-H, 1 C=O
Getting in energy	100 kcal/mol + 117 kcal/mol + (2 x 390 kcal/mol)	490 kcal/mol + 100 kcal/mol + 110 kcal/mol
Giving out energy	100 kcal/mol + 305 kcal/mol + (2 x 110 kcal/mol)	305 kcal/mol + 390 kcal/mol + 100kcal/mol + 177kcal/mol
Required energy***	432 kcal/mol	-362 kcal/mol

\*Bond breaking getting in energy

\*\*Bond forming giving out energy

\*\*\*Required energy = getting in energy - giving out energy

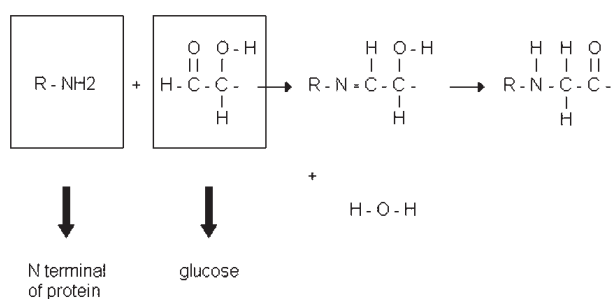
bonding energy based on quantum chemical analysis on the fructosamine formation. In addition, further implications of the findings in poorly controlled DM patients are discussed.

## MATERIALS AND METHODS

### *Pathways for glycosylation reaction*

Concerning glycosylation in the formation of fructosamine, the reaction occurs between the protein N terminal and glucose (Figure 1) (5). The two main steps in the formation of fructosamine are: 1) formation of Schiff base; and 2) linkage rearrangement, known as Amadori rearrangement, to form more stable ketoamine (4,5).

Figure 1. Glycosylation reaction process



### *Quantum chemical analysis for bonding energy*

The quantum chemical analysis for overall reaction was performed according to the classic chemical bonding theory. The required energy for complex formation in each pathway was calculated.

## RESULTS

The details and the required energy for complex formation of fructosamine are presented in Table 1. The required energy for complex formation is 70 kcal/mol.

## DISCUSSION

Glucose molecules are joined to protein molecules to form stable ketoamines, or fructosamines, through glycation, a nonenzymatic mechanism involving a labile Schiff base intermediate and the Amadori rearrangement (5). The concentration of fructosamine in serum thus reflects the degree of glycemic control attained by the diabetic patient and is useful in monitoring the effectiveness of therapy in diabetes over a period of several weeks (5). The amount of fructosamine in serum is increased in DM due to the abnormally high concentration of blood sugar (6,7). In the presence of excess plasma glucose, serum protein becomes increasingly glycosylated, making fructosamine a useful index of glycemic control (6,7).

The glycosylation reaction in the formation of fructosamine is a type of chemical bond formation. Here, the author calculated the bonding energy of the reaction and found it to be of the “energy consuming reaction” type. This finding may have a number of implications in clinical medicine. Physiologically, poor glycemic control in diabetic patients can lead to the state of energy loss. Poor nutritional status, muscle waste, and functional impairment can be seen in poorly controlled diabetic patients (8).

Wiwanitkit has recently proposed that energy loss be expected in diabetic patients with poor control (9).

The nature of energy consuming reaction in the formation of fructosamine could also be seen in this study. Of interest, the required energy for complex formation *per* mole of the reaction was equal to that previously reported in the reaction of the hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) formation (9). This can confirm the nature of energy loss in poorly controlled DM patients. Indeed, the formation of HbA<sub>1c</sub> has a similar reaction to the formation of fructosamine. The difference is the original substrate, hemoglobin and protein. Indeed, hemoglobin is a type of protein and it may be said that HbA<sub>1c</sub> is a subtype of fructosamine. The American Diabetes Association (ADA) notes that fructosamine

may be useful in situations where HbA<sub>1c</sub> cannot be reliably measured, e.g., in diabetic pregnancy and hemoglobin disorder. Considering molecular weight, the required energy *per* gram in the formation of HbA<sub>1c</sub> is higher than that of fructosamine (the molecular weight of hemoglobin is usually less than that of serum protein). This implies that the increase in HbA<sub>1c</sub> quantity can better reflect energy disturbance and subsequent complications. According to this study, the previous hypothesis that energy acquisition from the nearby cellular compartment might be an important pathological process in poorly controlled diabetes (9) could be confirmed.

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