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Research Article

Glycated Albumin Value and Its Relation with The Improvement of Diabetic Ulcers: Pilot Study

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Abstract.
Diabetic ulcer refers to a complication of chronic hyperglycaemia. When treating hyperglycaemia, it is necessary to well and immediately monitor the average level of glucose, i.e. glycated albumin (GA) value. This study investigated the correlation between GA values and the improvement of diabetic ulcers. A clinical, cross-sectional study. Thirty patients with Diabetic Foot Ulcer (DFU) were involved as the subjects of this study and they were selected by accidental sampling with the following criteria: (1) patients with Type 2 DM with DFU according to grade 2 and 3 PEDIS degrees; (2) aged 30-60 years; (3) diagnosis criteria for DM and DM type 2 in accordance to the American Diabetes Association 2012; (4) IMT value: 18.5-22.9. Data collection technique was by checking GA levels, while monitoring the improvement of diabetic ulcers was by using PEDIS degrees. Meanwhile, data analysis used Spearman's rho. The results of this study showed that most of research subjects had the values of GA failure with PEDIS 2 degree, i.e. 8 (26.7%) and there was no normal GA value with the degree of PEDIS 1, 2 and 3. There was a significant correlation between GA values and PEDIS degree ($p = 0.001$, $p < 0.05$). The findings revealed a correlation of GA values and improvement in diabetes ulcers. GA control is needed for the improvement of diabetes ulcers under nursing care.

Keywords: Glycated Albumin; diabetic ulcers; DFU; chronic hyperglycaemia

1. Introduction

Diabetes Mellitus (DM) refers to a group of symptoms found in a person for the increasing blood glucose levels due to a progressive decrease in insulin secretion [1]. Patients with DM frequently experience problems in the lower extremities precipitated by ulcers, infections and gangrene. In every year, more than one million patients with DM must lose their legs in which mostly they experience an amputation due to foot ulcers [2]. Monitoring glucose level in short, medium or long term is highly needed to prevent any complication accompanying it. The short-term monitoring can be done through blood glucose examination, fasting blood glucose, blood glucose 2 hours after meals and oral

glucose tolerance test (OGTT) [3]. Meanwhile, medium-term monitoring might be in the form of fructosamine and GA and for the long term it can be in the form of haemoglobin glycate (HbA1c) that today becomes the recommended examination for glucose levels monitoring for patients. HbA1c is a good examination parameter to monitor DM and it has become a standard for the Diabetes Mellitus examination. Also, it is used to monitor on the average of 2-3 months earlier [4].

During treatment, monitoring of the average glucose level is needed properly and immediately to find out the response of the therapy carried out. The three months required to observe the changes in HbA1c values are often seen less rapid. For this, there is a need for other glycate proteins that can describe the average level of blood glucose in a shorter time, such as fructosamine and GA. Unfortunately, fructosamine describing the glycation of total serum protein has many flaws including: absolute value (able to be determined by serum protein levels), large differences among individuals and determined by other serum protein levels such as globulin. At the moment, GA seems to be the best option [5-6]. An important thing in the treatment of ulcers is related to its development. Some researchers have proposed a number of methods to assess such improvement, predicted healing and evaluating the ulcer treatment through the measurement of ulcer area [7-9]. The identification of wound edges and measurement of ulcer areas, however, is not something simple. In response, the International Working Group of the Diabetic Foot (IWGDF) developed the UKD classification into 5 categories: perfusion, extent, depth, infection, sensation (PEDIS). This classification is very relevant to the pathogenesis and development of DFU [2]. The aim of this study was to assess the GA values and its relation with the improvement of diabetic ulcers.

2. Methods

This research has been designed to conduct a clinical and cross-sectional study. There were 30 patients with diabetic ulcers involved as the subjects in this study and they were selected by quota sampling with the following criteria: (1) Patients with type 2 DM with diabetic ulcers with PEDIS degrees 2 and 3; (2) aged 30-60 years; (3) diagnosis criteria for Type 2 DM in accordance to the American Diabetes Association 2015 [1]; (4) IMT value: 18.5 - 22.9. Technique in collecting data was performed by GA examination, while monitoring the improvement of diabetic ulcers was by means of PEDIS degrees. A statistical analysis was performed using software and normality was determined by the Kolmogorov-Smirnov test with a reliability of $p < 0.05$. Also, Spearman's rhowas used to

determine the association between GA values and the improvement of diabetic ulcers with the use of a reliability of $p < 0.05$.

3. Results and Discussion

In this research, there were 30 patients with diabetic ulcer that fulfilled the inclusion and exclusion criteria. Table 1 presents the demographic data and characteristics of research subjects and Table 2 presents the correlation data between GA values and PEDIS degrees. Of thirty patients with diabetic ulcer participated in this study, demographic data and characteristics of the subjects showed an average of aged 54.07 ± 8.09 years. By sex, the majority of subjects were women, i.e. 10 (33.3%) while men were in a small proportion i.e. 20 (66.7%). For education level, most of the subjects had the educational background at high school level, which is 18 (60%) in contrast to elementary school, which is 2 (6.7%). Meanwhile, in terms of occupation, the subjects mostly worked at private business that accounted for 15 (50%); while the occupation as the civil servants only accounted for 1 (3.3%). Body weight and body mass index (BMI) respectively were 56.43 ± 8.21 kg and 21.68 ± 1.30 kg/m2 on average. Then, the length of DM had an average of 8.50 ± 6.29 years. The mean random plasma glucose levels and 2 hour postprandial were 236.6 ± 33.88 mg/dl and 259.13 ± 33.13 mg/dl respectively. The mean GA value was $25.98 \pm 12.25\%$ and all of the subjects received antidiabetic drugs (OAD). The mean duration of diabetic ulcers was 23.73 ± 33.37 weeks meanwhile, the average degree of PEDIS was 2.03 ± 0.67. The results of this research showed that most of the subjects had the failure GA value with a degree of PEDIS 2, i.e. 8 (26.7%). There was no normal GA value with degree of PEDIS 1, 2 and 3. A significant relationship was found between the GA value and the degree of PEDIS ($p = 0.001$, $p < 0.05$).

Increasing age is a major risk factor for wound healing disruption. Clinical and animal studies at both cellular and molecular level showed a relationship between increasing age and the delay in wound healing [10-11]. In general, some differences are found in wound healing between young and old age. Theoretically, there is a relationship between age and delay in wound healing as indicated by an increase in platelet aggregation, secretion of inflammatory mediators, the delay of infiltration of macrophages and lymphocytes, impaired macrophage function, decreased secretion of growth factors, delayed re-epithelisation, decreased angiogenesis, collagen deposition, collagen and wound strength [10]. Sex hormones also contribute to the wound healing disruption; in this case in relation to the age. The acute wound healing in older women and men will be delayed in view of the decreased estrogens (estrone and 17β-estradiol),

TABLE 1: Socio-demographic and clinical characteristics of the participants (n = 30).

	Frequency (%)	Mean±SD	Minimum	Maximum
Age		54.07±8.09	35	65
Sex Male Female	10 (33.3) 20 (66.7)			
Education Level Elementary School Middle School High School Higher Education	2 (6.7) 6 (20) 18 (60) 4 (13.3)			
Occupation Housewife Private Civil Servant Retired	12 (40) 15 (50) 1 (3.3) 2 (6.7)			
Weight (Kg)		56.43±8.21	43	70
Body Mass Index (kg/m2)		21.68±1.30	19.50	24
Length of DM (year) ≤10 >10	23 (76.7) 7 (23.3)	8.50±6.29	1	28
Plasma glucose level (mg/dl) Random 2 hour PP		236.6±33.88 259.13±33.13	201 210	316 330
GA Value % Normal Excellent Good Acceptable Failure	0 10 (33.3) 5 (16.7) 3 (10) 12 (40)	25.98±12.25	11.57	57.24
Time Length of Diabetic Ulcer (Week)		23.73±33.37	1	144
PEDIS Degree 1 2 3	9 (30) 10 (33.3) 11 (36.7)	2.03±0.67	1	3
Antidiabetic Drugs (OAD) Yes No	30 (100) 0			

TABLE 2: GA Value and Its Relation With PEDIS Degree.

Variable	PEDIS Degree				P-value
GA value	1	2	3	Total	
Normal : 11-16 %	0	0	0	0	0.001[a]
Excellent : ≤ 18 %	3 (10%)	5 (16.7%)	2 (6.7%)	10 (33.3%)	
Good : 18.1 – 21 %	1 (3.3%)	2 (6.7%)	2 (6.7%)	5 (16.7%)	
Acceptable : 21.1 – 24%	0	2 (6.7%)	1 (3.3%)	3 (10%)	
Failure : ≥ 24.1 %	2 (6.7%)	8 (26.7%)	2 (6.7%)	12 (40%)	
Total	6 (20%)	17 (56.7%)	7 (23.3%)	30 (100%)	

[a] Significant at p < .05 (Spearman's rho)

androgens (testosterone and 5α-dihydrotestosterone, DHT) and a precursor steroid Dehydroepiandrosterone (DHEA) [12].

The results of the research showed a number of differences between old men and young men in regulating estrogenic gene expression in wounds. Estrogens influence wound healing by regulating various genes related to regeneration, matrix production, protease inhibitors, epidermal function and genes related to inflammation [13]. This

research also showed that most of the subjects had high school education background and worked at private business. Education is an important factor for understanding management, adherence to blood sugar control, handling any appearing symptoms with proper treatment and preventive measures for complications. Education in general is correlated to knowledge. Patients with higher education tend to have better knowledge about diabetes and its effects on health; thus leading them to respond positively and to maintain health [14].

However, higher education does not give any guarantee that the experience gained will be high in consideration to the determination of socio-cultural factors that can influence a person to act based upon his or her experience. Customs, norms, and encouragement from the closest people are some of the factors affecting a person to decide to act. The education level is also related to the work level that in turn will determine the amount of income. The low income due to the work level eventually can create a tendency to have an irregular and unhealthy diet in which it can lead to a routine to consume unhealthy food [15]. Work is related to physical activities and sports activities. Housewives, for instance, do some house cores such as washing, cooking and cleaning the house as well as many other activities that cannot be described. In this case, a physical activity can decrease insulin resistance [16].

This research showed that the mean BMI among the subjects did not show obesity. Obesity itself brings an impact on wound healing, as proven in animal experiments where obesity is accompanied by impairments in collagen structure and function, collagen deposition, and wound healing. It is assumed that this is related to the change in the structure of fat tissues [17]. The length of time with DM is correlated to microvascular complications and neuropathy [3]. In this case, the prolonged DM can result in exposure to chronic hyperglycaemia, triggering an increase in microvascular permeability during the initial and later phases of the disease. The changes in capillary structure and function can cause the disruption of molecular exchange through the endothelial membrane to the interstitial [18]. Based on the clinical data, the random plasma glucose levels, 2 hour postprandial glucose and GA values indicated the uncontrolled hyperglycaemia. Hyperglycaemia can trigger the formation of advanced glycation end-products (AGEs) later on causing the impaired diabetic ulcers healing in mice [19].

In this study the failure GA value, the length of time with diabetic ulcer ($\pm$ 24 mg) and the level of PEDIS 2 showed chronic ulcers that failed to follow the sequence of the normal wound healing [20]. All patients with diabetic ulcer receive antidiabetic drugs (Insulin, Metformin, and Glibenclamide). It is indicated that insulin is able to improve the diabetic ulcers healing [21], by increasing angiogenesis [22], and accelerates the

re-epithelialization [23]. Metformin, meanwhile, can accelerate epithelialization in mice with diabetic ulcer [24]. Glibenclamide can accelerate epithelialization and the formation of granulation tissues Glibenclamide can accelerate epithelialization and the formation of granulation tissues [25].

The results showed that most of the subjects had the failure GA value with PEDIS 2 and there was no normal GA value with PEDIS degrees 1, 2 and 3. Both the GA value and PEDIS degree showed a significant relationship. Failure GA value indicated chronic hyperglycaemia. Hyperglycaemia can cause oxidative stress as the ROS production exceeds the antioxidant capacity [26]. The formation of AGEs as a result of hyperglycaemia can cause the impaired diabetic ulcers healing in mice [19]. Diabetic wound will experience an impaired cellular function, including a decrease in T cells and dysfunction of fibroblast cells and epidermal cells, making the wound healing impaired Diabetic wound will experience an impaired cellular function, including a decrease in T cells and dysfunction of fibroblast cells and epidermal cells, making the wound healing impaired [27-28]. AGEs play a role in the pathogenesis of diabetic neuropathy and angiopathy, eventually potential to directly or indirectly hinder the healing process [29]. The AGEs accumulation and their interactions with specific receptors, such as receptors for advanced glycation end-products in wound tissue contributes to decrease of neutrophil migration. Also, AGEs can increase the oxidative stress and decrease antioxidants [30]. Several studies reported the ability of AGEs to change an interaction between cells and extracellular matrix (ECM) and the number of ECM constituents; thus, AGEs can cause the structural changes in collagen I [31]. Hyperglycaemia has a biological impact on fibroblast cells, i.e. the decrease of migration and proliferation of fibroblast cells, so the amount of collagen also decreases [32]. Hyperglycaemia and its associated factors, such as AGEs, have an important role in inhibiting the diabetic ulcers healing [33].

4. Conclusions

The results of this study indicated the correlation of the GA values and the improvement of diabetic ulcers. In addition, the GA control is needed to improve the diabetic ulcers under nursing care.

Acknowledgments

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