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Evaluation of procollagen 1N propeptide for predicting osteomyelitis and epithelial neutrophil activator-78 for early wound healing in patients with diabetic foot

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Osteomyelitis (OM) is a frequent side effect of diabetic foot infections and/or ulcers. Hemostasis, inflammation, proliferation, remodelling, many cell types, intricate signalling processes, and a variety of growth hormones are all part of the complicated process of wound healing. Therefore, this study's objective is to assess the amounts of procollagen type 1N propeptide for osteomyelitis diagnosis and epithelial neutrophil activator-78 for early wound healing in patients with diabetic foot. This study was included 138 participants (46 patients with the diabetic foot and 52 patients with type 2 diabetes without foot ulcer), their ages ranged from 45-70 years. In addition, healthy people (40) participants were included as a control group. Measurements of lipid profile, blood urea, and creatinine were done by spectrophotometry methods (Spinreact, 2 Spain), whereas measurements concentration of epithelial neutrophil activator-78 (ENA-78) and procollagen type I N-terminal peptide (PINP) were conducted by ELISA methods. This study revealed a highly significant increase of fasting blood glucose (FBG), HbA1c, ENA, and PINP ($P<0.01$) in type 2 diabetes mellitus and diabetic foot when compared with healthy control and between each other, while other parameters did not show any significant difference. There were marked elevations of serum P1NP & ENA-78 in patients of diabetes only and diabetic foot and they had highly beneficial to diagnosis, risk stratification, and assessment the severity of these diseases.

KEYWORDS

Diabetes mellitus; diabetic foot; PINP; ENA-78; osteomyelitis.

Introduction

Diabetes mellitus is a metabolic illness with numerous etiologies that is defined by persistent hyperglycemia and changes in the metabolism of carbohydrates, fats, and proteins. These disturbances are brought on by errors in insulin production, action, or both. Diabetes mellitus results in long-term harm, malfunction, problems, and failure in several organs [1].

Diabetes foot is out of control complex metabolic pathways, sensory loss brought on by peripheral neuropathy, ischemia brought on by peripheral arterial disease, or a combination of these may produce foot ulcers are all ways that diabetes contributes to the development of neuropathy and peripheral arterial disease [2]. Diabetic foot ulcer (DFU) is the leading cause of disability and mortality as one of the most serious chronic

consequences of diabetes. DFU has a poor clinical diagnosis and prognosis. Clinician notices a decrease in hospitalization, disability, and death rates if they can identify diabetes patients at risk for early DFU. To reflect novel biomarkers for therapeutic intervention outcomes, DFU risk and severity should be considered [3].

Osteomyelitis is a prevalent consequence of diabetic foot ulcers and/or infections; in individuals with diabetic foot issues, it is usually overlooked and underdiagnosed. Making a diagnosis requires a high degree of clinical suspicion since OM frequently results in the dreaded consequence of limb amputation if it is left undetected and untreated. Acute diabetic infections have a four times greater risk of amputation when OM is present compared with soft tissue infection alone [4]. With a molecular weight of roughly 35,000 kDa, pro-collagen type I N-propeptide (PINP) is a trimeric peptide made up of two type 1 procollagen-1 chains and a procollagen-2 chain that are non-covalently connected [5]. Procollagen I molecule is synthesized by osteoblasts, and the pro-peptide extensions at the amino- and carboxy-terminals (PINP and PICP, respectively) of the procollagen molecule are cleaved off and released into circulation when collagen molecule is laid down to form the osteoid matrix during bone formation. They are frequently employed as indicators of collagen synthesis in blood. These pro-peptides' concentration indicates how quickly type I and III collagens are produced. The kinds I and III collagens generated and deposited by fibroblasts during wound healing improve the tensile strength of the wound. Diabetes mellitus is the primary pathogenic disease in individuals with poor wound healing. They are commonly used as markers of blood collagen production. The concentration of these pro-peptides reflects the rate of synthesis of type I and III collagen. When a wound is healing, fibroblasts produce and deposit types I and III collagen, which increases the tensile strength of the wound. The main pathogenic illness in those with poor wound healing is diabetes mellitus. High blood sugar levels in diabetics inhibit cell division and decrease collagen production in foot ulcers, which can result in limb amputation [7,8]. This study aims to estimate serum levels of procollagen type1N propeptide as a biomarker for diagnosis of osteomyelitis, risk stratification, and assess disease severity, and also to evaluate epithelial neutrophil activator-78 as predictor for early wound healing in patients with diabetic foot.

Materials and methods

A case-control study, conducted at Al-Faiha Diabetic Food Center, Basra, Iraq, from September 15, 2021 to March 22, 2022. This study was included (138) participants-(46) patients with diabetic foot (26 males and 20 females) and (52) patients with only diabetic mellitus type 2 (27 males and 25 females). In addition, 40 healthy individuals were included (17 males and 23 females) as a control group. All patients and healthy subjects were given consent to participate in the research.

Serum total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, glucose, urea, and creatinine were all measured using spectrophotometric reagent kits from Spinreact/Spain. According to the manufacturer's instructions, human ELIZA kits were used in Fine Test®, China, to measure ENA and PINP in serum.

Statistical analysis was carried out utilizing Microsoft Office Excel 2019 and the statistical package for social sciences (SPSS) version 26. Standard deviations and the mean were used to represent the data (SD). The statistical significant was found at p-value less than 0.05.

Results and discussion

Anthropometric and biochemical characteristics of the current study were summarized in Table 1.

TABLE 1 Anthropometric and biochemical characteristics of the study

Variables	Control (No.=40) Mean ± SD	DM* (No.=52) Mean± SD	DF (No.=46) Mean ± SD	P-value
Age (years)	54.3 ± 7.87	59.8 ± 8.24	60.3 ±7.73	0.001
BMI (kg/m²)	29.13±4.46	28.60±5.23	28.38±5.27	0.752
Systolic	122.29±14.76	128.68±19.31	134.0±17.38	0.001
Diastolic	88.86±11.24	93.15±13.18	108.13±11.79	0.163
Sex Males (No. %)	17 (51.4)	27 (50.9)	26 (54.2)	
Females(No.%)	23 (48.6)	25 (49.1)	20 (45.8)	0.941
Total (No. %)	40 (100)	52 (100)	46 (100)	
Hb%	12.14±2.68	12.24±1.99	11.26±1.88	0.172
RBS (mg/dl)	103.14±46.33	232.51±102.49	242.04±88.95	0.0001
HbA1c (%)	5.20±0.54	9.13±2.07	9.62±2.11	0.0001
Urea	37.41±36.57	36.61±22.69	39.61±19.82	0.073
Creatinine	0.72±0.50	0.75±0.39	0.87±0.63	0.124
Cholesterol (mg/dl)	183.91±51.17	185.79±76.46	195.17±80.40	0.823
Triglycerides (mg/dl)	163.51±71.60	172.12±81.07	192.88±95.47	0.390
LDL (mg/dl)	113.68±32.12	114.73±46.84	129.18±54.74	0.353
HDL (mg/dl)	50.79±22.32	46.64±16.14	40.08±12.08	0.061
VLDL (mg/dl)	33.87±15.09	36.51±16.86	38.35±18.98	0.636
PINP	1.39±0.23	1.46±0.22	1.57±0.33	0.001
ENA-78	0.28±0.15	0.33±0.28	0.39±0.21	0.002

*__DM:__ diabetes, **DF:** diabetic foot, **SBP**: systolic blood pressure, **DBP**: diastolic blood pressure, **PINP**: procollagen type I N-terminal peptide, and **ENA-78**: epithelial neutrophil activating peptide 78.

Based on Table 1, compared healthy control with type 2 diabetes mellitus (T2DM) and diabetic foot disease (DF) patients, the result showed that the level of procollagen type I N-terminal peptide was significantly increased ($p<0.01$). These results were consistent with a large-scale cross-sectional study performed in Germany supported this conjecture [9].

In addition, the results showed that the level of epithelial-neutrophil activating peptide indicated highly significantly increased ($p<0.01$). It has been linked to a number of illnesses, including acute coronary syndromes, subclinical atherosclerosis, obesity, and diabetes [10],[11]. The healing of diabetic feet was independently and significantly correlated with ENA-78. According to the results of this study, an early indicator of wound healing in DFU patients was the exudate level of ENA-78 [12].

Based on the earlier research, CXCL5 is engaged in angiogenesis, and the absence of ENA-78 impacts angiogenesis. Nevertheless, further prospective investigations will be needed to pinpoint the specific molecular mechanism behind ENA-78's influence on the development of wound healing. Furthermore, a prior study found that the exudate ENA-78 level is a possible early indicator of diabetic foot patient wound healing, with the potential to create methods for the prevention or treatment of diabetes [8]. As shown in Table 2, the comparison between diabetes and diabetic foot.

TABLE 2 Comparison between diabetes and diabetic foot

Variables	DM (No.=52) Mean± SD	DF (No.=46) Mean ± SD	P-value
Age (years)	59.8±8.24	60.3±7.73	0.738
BMI (kg/m2))	28.60±5.23	28.38±5.27	0.752
Systolic	128.68±1.93	134.27±1.73	0.000
Diastolic	93.15±1.31	108.12±11.79	0.163
Sex Male	27 (50.9)	26(54.2)	
Female	25 (49.1)	20 (45.8)	0.737
Total	57 (100)	46 (100)	
HB%	12.24±1.99	11.62±1.88	0.172
RBS (mg/dl)	232.51±102.49	242.04±88.90	0.000
HbA1c (%)	9.13±2.07	9.62±2.11	0.000
Urea	36.61±22.69	39.61±19.82	0.073
Creatinine	0.75±0.39	0.87±0.63	0.124
Cholesterol (mg/dl)	185.79±76.46	195.17±80.40	0.823
Triglycerides (mg/dl)	172.12±81.07	192.88±95.47	0.390
LDL (mg/dl)	114.73±46.84	129.18±54.74	0.353
HDL (mg/dl)	46.64±16.14	40.08±12.08	0.061
VLDL (mg/dl)	36.51±16.86	38.35±18.98	0.636
PINP	1.46±0.22	1.57±.33	0.001
ENA-78	0.33±0.28	0.39±0.21	0.002

As presented in Table 2, when comparing DM with DF showed a highly significant increase ($p<0.01$) of FBG, HbA1c, this indicates a long-term increase in glucose in groups diabetic of foot more than in groups of diabetes mellitus patients. A multiorgan systemic condition of glucose metabolism with many vessels and nonvascular complications is diabetes mellitus [13]. Diabetes, a multisystemic illness, has a significant foot as a target organ. High mechanical stresses can cause breakdown, the creation of soft tissue and the foot's bone joint system as well as various foot disorders in diabetes individuals who also have peripheral neuropathy and peripheral vascular disease [14].

When comparing lipid profile levels of diabetes mellitus groups with diabetic foot groups, no significant difference was found ($p>0.05$), (Table 3). According to the earlier research, people with diabetic foot problems not only have foot ulcers and concurrent infections that may delay the healing of wounds, but they also have greater cumulative rates of lower limb amputation and impairment (Singh *et al*., 2005). As a result, abnormalities in the blood supply, particularly those related to blood lipids and lipid ratios, play a major role in the development of diabetic foot. These individuals may also experience vascular damage to their heart, brain, kidney, and other organs. These serious cardiovascular disease (CVD) problems, which include myocardial infarction, stroke, and renal failure are the main causes of death in T2DF patients, and they might ultimately arise from these vascular injuries [16,17].

As listed in Table 3, procollagen type I N-terminal peptide (PINP) of DM when compared with DF, showed a highly significant difference ($p<0.01$). There is no similar result to this research. The significant increase in serum P1NP in diabetic foot ulcers with bone infection may help to identify osteomyelitis (DFO). There are differences in a marker for bone production and turnover in diabetic foot ulcers with osteomyelitis, the controls, and diabetic foot ulcers without osteomyelitis. The P1NP effectiveness in identifying DFO

compared with other widely used inflammatory markers was another goal [18].

ENA-78 epithelial-neutrophil activating peptide showed the same result, a highly significant increase ($p<0.01$), when comparing DM with DF. The healing of diabetic feet was independently and significantly correlated with ENA-78. ENA-78 may therefore be used as an early indicator of wound healing in DFU patients. According to the patient characteristics, it was discovered that DF patients had substantially higher FBG and HbA1c levels, indicating that glycemic management is crucial for wound healing. According to Spearman's correlation study, there are negative correlations between HbA1C and ENA-78 (plasma or exudate); when HbA1c rises, ENA-78 levels fall, making it harder to cure wounds.

The AUC of ENA-78, which was determined by ROC curve analysis to be 0.705, provided the additional proof that ENA-78 is crucial to the prediction model for DFU wound healing. Hemostasis, inflammation, proliferation, and remodelling are all involved in the intricate process of wound healing [19]. In each step of wound healing, several cell types, intricate signalling processes, and a variety of growth factors are all involved [8,20].

Table 3 indicates the comparison among control, diabetes, and diabetic foot.

TABLE 3 Comparison among control, Diabetes and diabetic foot

Variables	DM			DF		
	Control (n=40)	Total patients (n=52)	P-Value	Control (n=40)	Total patients (n=46)	P-Value
Age (years)	54.3±7.87	59.8±8.24	0.002	54.3±7.87	60.3±7.73	0.001
BMI (kg/m^2)	25.13±9.46	28.6011±5.23	0.0438	26.13±7.46	29.38±5.27	0.0417
Hb%	12.14±2.68	12.24±1.99	0.0487	12.14±2.68	11.6292±1.88205	0.407
RBS (mg/dl)	103.14±46.33	232.51±102.49	0.000	103.14±46.33	242.04±88.950	0.000
HbA1c (%)	5.20±0.54	9.13±2.07	0.000	5.20±0.54	9.62±2.11	0.000
Urea	37.41±36.57	36.61±22.69	0.357	37.41±36.57	39.61±19.82	0.025
Creatinine	0.72±0.50	0.75±0.39	0.494	0.72±0.50	0.87±0.63	0.041
Cholesterol (mg/dl)	183.91±51.17	185.79±76.46	0.604	183.91±51.17	195.17±80.402	0.967
Triglycerides (mg/dl)	163.51±71.60	172.12±81.074	0.641	163.51±71.60	192.88±95.47	0.232
LDL (mg/dl)	113.68±32.12	114.73±46.84	0.679	113.68±32.12	129.18±54.74	0.376
HDL (mg/dl)	50.79±22.32	46.64±16.146	0.800	50.79±22.32	40.08±12.08	0.065
VLDL (mg/dl)	33.78±15.09	36.51±16.86	0.385	33.78±15.09	38.35±18.98	0.444
PINP	1.39±0.23	1.46±0.22	0.123	1.39±0.23	1.57±0.33	0.001
ENA-78	0.28±0.15	0.33±0.28	0.510	0.28±0.15	0.39±0.21	0.002

As shown in Table 3, when comparing healthy control with DM, and healthy control with DF were showed highly significant increases of HbA1c and FBS ($p<0.01$), these analyses were used for the initial diagnosis of diabetes. High blood glucose or HbA1C, increase in the complications of diabetes, especially the diabetic foot, until it reaches the stage of amputation.

Comparison of healthy control with DM, and healthy control with diabetic foot were shown no significant differences ($p>0.05$) in the mean of serum cholesterol, TG, LDL and VLDL, while the results of serum levels of HDL showed significant decrease ($p<0.05$), which may be due to low sample size of groups.

The comparison of healthy control with DF showed a highly significant increase ($p<0.01$). The body's initial line of cellular defense,

neutrophils react promptly to tissue damage and invader microbial agents [21]. Antigen-antibody complexes, the fundamental pathogenic mechanism in autoimmune illnesses, cause neutrophil infiltration, which sets off an inflammatory response [22]. The high significant difference of ENA-78 was found between the control and diabetic foot patients because of lower immunity in diabetic foot.

The comparison of healthy control with DM, and healthy control with DF showed highly significant increases of PINP ($p<0.01$), (Table 3). It is unknown how beneficial the P1NP will be in evaluating DFO. Despite this, no research has been done to evaluate the P1NP effectiveness in distinguishing soft-tissue inflammations from diabetic foot bone infection osteomyelitis DFO [23]. Analysis of the Receiver-operating characteristic (ROC) curve was done for blood biomarker diagnostic values for DF in all patients (data was not shown). ROC curve corresponded to FBG and HbA1c levels were 0.952 and 0.99, respectively. FBG and HbA1c tests were therefore found to be strongly predictive for individuals with DF in the current investigation, which was in line with [24]. These biomarkers play an important role in the decision-making process, and HbA1c levels are extensively used for diabetic foot clinical outcomes and settings [25]. As displayed in Figure 1, HbA1c and FBS have high accuracy, sensitivity (93.48 and 95.65), and specificity (100.00 and 94.29), respectively, so the HbA1c and FBS were excellent predict a diagnosis of diabetic foot or general diabetic mellitus, and HbA1c was more accurate predictor than FBS.

The sensitivity and specificity of PINP's ROC analysis level were low (56.52 and 77.14%, respectively), which may have been caused by the small sample size that allowed them to be utilized interchangeably. Calculators for assessing fracture risk do not presently use bone turnover indicators since they are not advised for this purpose with regard to treating osteoporosis [5].

The diagnostic precision of ENA-78 for wound healing was also confirmed using ROC curve analysis, or receiver operating characteristic analysis. The best cut-off point for ENA-78 was >312, which might be utilized as a diagnostic cut-off point in wound healing. The area under the curve (AUC) of ENA-78 was 0.714. Sensitivity was 63.04% and specificity was 80.00% at this level. Further proof that ENA-78 is crucial to the DFU prediction model for wound healing was provided by the ROC curve study of ENA-78. According to the study, the lower ENA-78 level will cause the wound to take longer to heal [5]. The findings of this study was agreed with previous studies [26,27], who reported that ENA-78 and PINP good indicators for a diagnosis of diabetic foot. In addition, some studies reported that, ENA-78 and PINP were fair predictors of a diagnosis of diabetic foot or general diabetic mellitus [28-29]. The association between the ENA-78 and diabetes was possibly involved of neutrophil activation, though the mechanism of $CXCL_5$ action in diabetes, which requires further investigation.

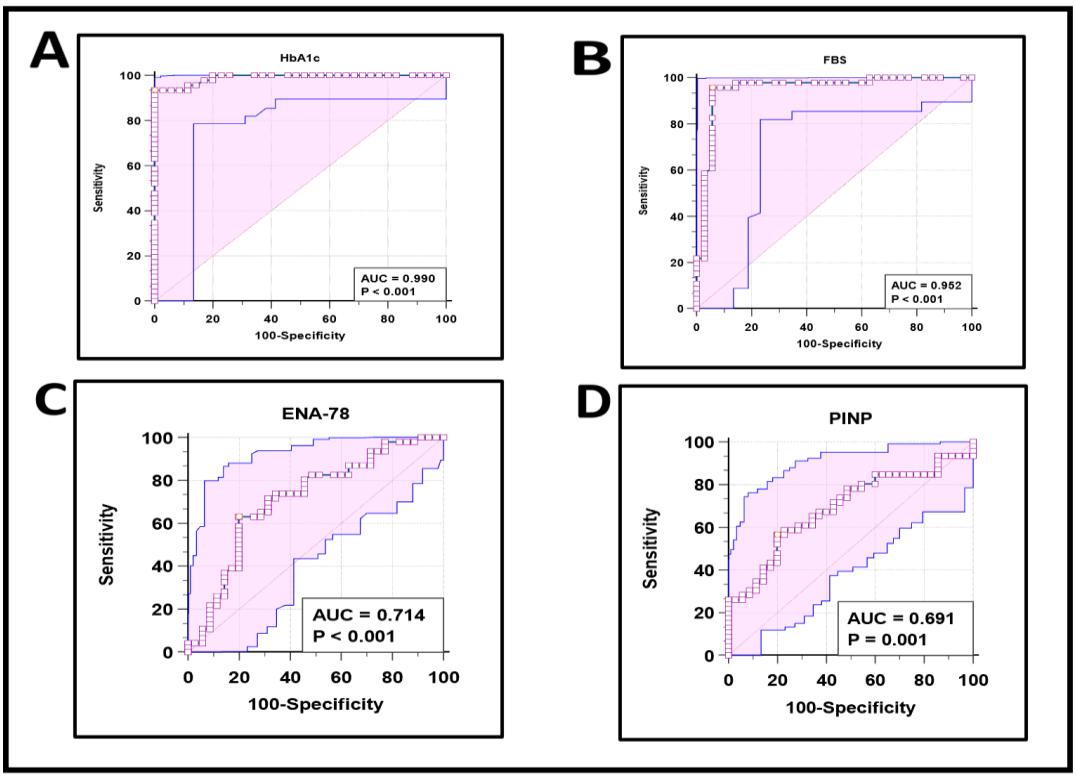

FIGURE 1 Receiver operator characteristic (ROC) curve analysis of: A- HbA1c, B- FBS, C- ENA-78, D- PINP

Conclusion

The current study demonstrated that P1NP and ENA-78 showed highly significant increases in patient with DF and they might be good indicators for DF diagnosis.

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Conflict of Interest

The authors have no conflict of interest.

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