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The Association of the Neutrophil-Lymphocyte Ratio with Diabetes Mellitus and Diabetic Foot Ulcer: A Review Article

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ABSTRACT

Introduction: Diabetes mellitus (DM) is inappropriately elevated blood glucose levels. Diabetic foot ulcer (DFU) is the most common complication of diabetes mellitus. Many research studies found that the neutrophil-lymphocyte ratio (NLR) has a positive correlation with HBA1C, blood glucose, and the outcome of diabetic foot ulcers. Methods: The literature searches using online databases such as PubMed, ScienceDirect Elsevier, and Google Scholar. Result: After doing an online search, we found 39 articles were relevant to this review topic. Analysis: Many research studies have found that increased HbA1C (≥6,5) and increased blood glucose (random blood glucose ≥ 200mg/dL and/or fasting blood glucose ≥126 mg/dL) in patients with diabetes mellitus have a positive correlation with increased NLR. There were increased NLR values in patients with diabetic foot ulcers and NLR values were higher (NLR≥6) in non-healing ulcers than in healing ulcers. Conclusion: NLR can be used as a screening tool for determining the evaluation of diabetes mellitus and as a screening tool for determining the outcome of diabetic foot ulcers

Keywords: Diabetes Mellitus, Diabetic Foot Ulcer, Neutrophil Lymphocyte Ratio.

ABSTRAK

Pendahuluan: Diabetes melitus (DM) adalah peningkatan kadar glukosa darah secara tidak wajar. Ulkus kaki diabetik (UKD) merupakan komplikasi diabetes melitus yang paling umum. Banyak penelitian menemukan bahwa rasio neutrofil limfosit (RNL) mempunyai korelasi positif dengan HBA1C, glukosa darah, dan hasil keluaran dari ulkus kaki diabetik. Metode: Pencarian literatur menggunakan database online seperti PubMed, ScienceDirect Elsevier, dan Google Schoolar. Hasil: Setelah melakukan pencarian online, kami menemukan 39 artikel yang relevan dengan topik review ini. Analisis: Banyak penelitian yang menemukan peningkatan HbA1C (≥6,5) dan peningkatan glukosa darah (glukosa darah sewaktu ≥ 200mg/dL dan/atau glukosa darah puasa ≥126 mg/dL) pada pasien diabetes melitus mempunyai korelasi positif dengan peningkatan RNL. Dan terjadi peningkatan nilai RNL pada pasien ulkus kaki diabetik dan nilai RNL lebih tinggi (RNL≥6) pada ulkus yang tidak sembuh dibandingkan dengan ulkus yang sudah sembuh. Kesimpulan: RNL dapat

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digunakan sebagai alat skrining untuk menentukan evaluasi diabetes melitus dan sebagai alat skrining untuk menentukan outcome ulkus kaki diabetik

Kata Kunci: *Diabetes Mellitus, Rasio Neutrofil Limfosit, Ulkus Kaki Diabetik.*

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1 Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by inappropriately elevated blood glucose levels or what we usually call hyperglycemia due to impairment of insulin secretion, defective insulin action, or both.[1]-[4] Diabetic foot ulcer (DFU) is the most common complication of diabetes, which is due to microvascular damage. Diabetic foot ulcers are a prevalent cause of osteomyelitis of the foot and amputation of lower limbs. It has been found that >50% of all nontraumatic amputations of the lower extremities that occur in patients with diabetes are related to diabetic ulcers.[5]-[10]

Triad pathologic mechanisms of diabetic foot ulcers are neuropathy, vascular insufficiency, and secondary infection. Hyperglycemia produces oxidative stress on nerve cells and leads to neuropathy. Motor neuron dysfunction may lead to an imbalance of flexors and extensors, anatomic deformities, and eventual skin ulcerations. Damage to autonomic nerves impairs sweat gland function, and the foot may develop decreased ability to moisturize skin, leading to epidermal cracks and skin breakdown. In sensory neuropathy, diabetes induces neuronal autonomic dysfunction that results in impaired sweat production, leaving the foot susceptible to dryness, skin cracking, and fissuring, patients may not notice foot wounds because of decreased peripheral sensation. In vascular insufficiency, hyperglycemia induces changes in the peripheral arteries of the foot and begins on the cellular level. Endothelial cell dysfunction leads to a decrease in vasodilators, plasma thromboxane A2 levels become elevated. The result is vasoconstriction and plasma hypercoagulation in peripheral arteries leading to ischemia and increased risk of ulceration. Secondary infection is usually due to trauma of the foot.[11]-[14]

Diabetic foot ulcers are characterized by an increase in the number of leukocytes in the blood as a physiological response to stress in the circulation. Neutrophils are active inflammatory mediators, which serve as the first line of defense and a high neutrophil count is a nonspecific marker of the inflammatory process. Lymphocytes can control and regulate the inflammatory response as well as anti-atherosclerosis. Systemic inflammatory conditions in diabetic patients, especially in patients with diabetic foot ulcers can be assessed by inflammatory markers such as the neutrophil-lymphocyte ratio (NLR).[11]-[14]

Many research studies found that increased HbA1C has a positive correlation with increased neutrophil-lymphocyte ratio (NLR) and increased fasting blood glucose in patients with diabetes mellitus.[15]-[18] Some studies showed that NLR has been associated with microvascular and

macrovascular complications in diabetes. One of the macrovascular complications is peripheral arterial disease which NLR values increase, the combined effect of peripheral arterial disease with neuropathy is the most common cause of diabetic foot ulcers.[15],[19]-[23]

Many studies have shown a significant association between diabetic foot ulcers and NLR, there was an increased NLR value in patients with diabetic foot ulcers and NLR values were higher in non-healing ulcers than in healing ulcers.[6][7][14]

This review article will provide a review of the NLR between healing and non-healing ulcers and then also aims to determine the association of the NLR with the outcome of diabetic foot ulcer and determine the association of the NLR with evaluation of diabetes mellitus.

2 Methods

This review article uses a Mixed Methods Review. Mixed Methods Review refers to a combination of review approaches for example combining quantitative with qualitative research or outcome with process studies. Requires either a very sensitive search to retrieve all studies or separately conceived quantitative and qualitative strategies.[24]

The literature searches using online databases such as PubMed, ScienceDirect Elsevier, and Google Scholar. Published literature relating to DM and NLR was obtained using the keywords “diabetes mellitus”, “diabetic foot ulcer”, “neutrophil-lymphocyte ratio”, “complication of diabetes mellitus”, “neutrophil-lymphocyte ratio” in association with “diabetes mellitus” and “neutrophil-lymphocyte ratio” in association with “diabetic foot ulcer”. The articles must be in English and published in 10 years (2014 until 2023). Studies in non-English language and performed on animals were excluded from this review. The selected articles were carefully reviewed and analyzed to extract essential insights about the topic under discussion.

3 Results

Table 1 Total number of articles applying inclusion criteria

Online Database	Keyword	Number of Result
PubMed	Diabetes Mellitus	133.235
	ComplComplicationsiabetes Mellitus	682
	Diabetic Foot Ulcer	1283
	Neutrophil Lymphocyte Ratio	2774
	Neutrophil Lymphocyte Ratio, Diabetes Mellitus	122
	Neutrophil Lymphocyte Ratio, Diabetic Foot Ulcer	2
Science DirectElsevierr	Diabetes Mellitus	229.541
	CComplicationsof Diabetes Mellitus	2.593
	Diabetic Foot Ulcer	4.870
	Neutrophil Lymphocyte Ratio	3.651
	Neutrophil Lymphocyte Ratio, Diabetes Mellitus	733
	Neutrophil Lymphocyte Ratio, Diabetic Foot Ulcer	6
google scholar	Diabetes Mellitus	1.460.000
	CComplicationsof Diabetes Mellitus	12.000
	Diabetic Foot Ulcer	20.200
	Neutrophil Lymphocyte Ratio	19.800
	Neutrophil Lymphocyte Ratio, Diabetes Mellitus	12.000
	Neutrophil Lymphocyte Ratio, Diabetic Foot Ulcer	173

After doing an online search on PubMed, ScienceDirectElsevierr, and Google Scholar. We found that 42 articles were relevant to this review topic. The articles were reviewed and analyzed to extract essential insights about the topic under discussion.

4 Discussion

4.1 Diabetes Mellitus

Diabetes mellitus is taken from the Greek word diabetes, meaning siphon - to pass through, and the Latin word mellitus meaning sweet. Diabetes mellitus is a metabolic disorder characterized by inappropriately elevated blood glucose levels or what we usually call hyperglycemia due to impairment of insulin secretion, defective insulin action, or both. Genetic and environmental risk factors impact inflammation, autoimmunity, and metabolic stress. These states affect b-cell mass and/or function such that insulin levels are eventually unable to respond sufficiently to insulin demands, leading to hyperglycemia levels sufficient to diagnose diabetes. In some cases, genetic and environmental risk factors and gene-environment interactions can directly impact b-cell mass and/or function. Regardless of the pathophysiology of diabetes, chronic high blood glucose levels are associated with microvascular and macrovascular complications that increase morbidity and mortality for people with diabetes. This model positions b-cell destruction and/or dysfunction as the necessary common factor to all forms of diabetes. DM is classified as Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Gestational Diabetes Mellitus, monogenic diabetes mellitus, and other less common conditions, such as diabetes related to pancreatic disease, drug-induced, or rare insulin resistance, and mitochondrial syndromes. [1]-[4]

4.2 Diabetic Foot Ulcer

Diabetic foot ulcer is the most common complication of diabetes, which is due to microvascular damage. This can lead to both morbidity as well as mortality. Diabetic foot ulcers are one of the most prevalent consequences of poorly treated diabetes mellitus. Diabetic foot ulcers are a prevalent cause of osteomyelitis of the foot and amputation of lower limbs. A diabetic foot ulcer is a localized foot ulcer that is associated with neuropathy and/or peripheral arterial disease of the lower limb in patients with diabetes. It has been found that >50% of all nontraumatic amputations of the lower extremities that occur in patients with diabetes are related to diabetic ulcers. [1],[5]-[10]

Diabetic foot ulcers frequently result from a person with diabetes simultaneously having two or more risk factors, with diabetic peripheral neuropathy and peripheral artery disease usually playing a central role. The neuropathy leads to an insensitive foot, loss of protective sensation, foot deformities, and limited joint mobility can result in mechanical trauma in some areas which usually causes thickened skin (callus). Finally, frequent trauma of the callus results in subcutaneous hemorrhage and eventually becomes an ulcer. In diabetic microenvironments neutrophils dysregulated release granular molecules to kill foreign pathogens in ulcers, causing a proinflammation and overproduction of cytokines and superoxide, which delay wound healing. [8][13][25] - [27]

Table 2 Wagner's classification of diabetic foot ulcers[13][27]

Grade	Characteristic
Wagner grade 0	No ulcer but high-risk foot
Wagner grade 1	Partial or full-thickness ulcer (superficial)
Wagner grade 2	Deep ulcer extending to ligament, tendon, joint capsule, bone, or deep fascia without abscess or osteomyelitis
Wagner grade 3	Deep abscess, osteomyelitis, or joint sepsis
Wagner grade 4	Partial/localized foot gangrene e.g. toe, heel, etc
Wagner grade 5	Extensive gangrene involving the whole foot

4.3 Neutrophil Lymphocyte Ratio with Diabetes Mellitus and Diabetic Foot Ulcer

NLR is the ratio of the absolute neutrophil count to the absolute lymphocyte count. It is regarded as a marker of the body's immune response to offending agents. It is also regarded as a rapid and simple parameter indicative of systemic inflammation and stress. Neutrophilia or lymphopaenia results in high NLR while lymphocytosis or neutropaenia results in low NLR. Overall the normal range of NLR is in the range of 0.8–3. The values above 3.0 and below 0.7 in adults are pathological. However, NLR in the grey zone of the range of 2.3–3 may serve as a warning that there is a pathological process present in organisms, such as cancer, atherosclerosis or ischemic heart disease, psychiatric disorders, subclinical infection, and/or inflammation.[28]-[31]

Many research studies have found that increased HbA1C (≥6,5) and increased blood glucose (Random Blood Glucose ≥ 200mg/dL and/or Fasting Blood Glucose ≥126 mg/dL) in patients with

diabetes mellitus have a positive correlation with increased NLR. NLR has been found higher in uncontrolled diabetes mellitus than in controlled diabetes mellitus.[15]-[19][32]-[42]

Some studies showed that NLR has been associated with microvascular and macrovascular complications in diabetes, most importantly in disease progression and metabolic impairment.[15][19]-[22][42]-[44] One of the macrovascular complications is a peripheral arterial disease in which NLR values definitely increased and also found increased NLR values in diabetic peripheral neuropathy, the combined effect of peripheral arterial disease with neuropathy is the most common cause of diabetic foot ulcers.[45]-[49]

Many studies have shown a significant association between diabetic foot ulcers and NLR, there was an increased NLR value in patients with diabetic foot ulcers and NLR values were higher (NLR≥6) in non-healing ulcers than in healing ulcers.[6][7][14][37][50]-[52] NLR significantly increased in patients with diabetic foot ulcer, compared with type 2 diabetes mellitus patients without diabetic foot ulcer and higher NLR values were an independent factor for wound healing. And the NLR value was significantly higher in grade 5 and lowest in grade 2 indicating that there was a significant relationship between NLR and Wagner's classification.[14][32]

Elevated NLR in patients with diabetic foot infections increased the risk of amputation and sepsis.[32][53] NLR has high specificity and sensitivity in predicting the prognosis of patients with diabetic foot, increased NLR value was found to be a reliable predictive biomarker of mortality in diabetic foot ulcer patients following amputation.[52][54]-[58] A correlation has been found between the degree of diabetic foot ulcers according to Wagner's classification with NLR, patients with high NLR values have a higher degree of diabetic foot ulcer, and the need for vascular treatment and amputation is much higher than patients with low NLR value.[59][60]

5 Conclusion

In these articles, we found many studies had shown increased NLR values in uncontrolled diabetes mellitus (HbA1C ≥6,5 and/or Random Blood Glucose ≥ 200mg/dL and/or Fasting Blood Glucose ≥126 mg/dL). In these review articles, we also found many studies had shown a significant association between diabetic foot ulcers and NLR, there was an increased NLR value in patients with diabetic foot ulcers and NLR values were higher (NLR≥6) in non-healing ulcers than in healing ulcers. So, NLR can be used as a screening tool for determining the evaluation of diabetes mellitus and NLR can be used as a screening tool for determining the outcome of diabetic foot ulcers.

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