Metabolism Open 23 (2024) 100315

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

Identification of phase angle and Triglyceride-Glucose index as biomarkers for prediction and management of diabetic foot disease

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ARTICLE INFO

Keywords:
Diabetic foot
Phase angle
Triglyceride glucose index
Biomarkers
Diabetes management. insulin resistance
Glycemic control
Peripheral arterial disease
Chronic ulcer
Hyperglycemia
Neuropathy
Diabetic
Wound healing
Amputation
Inflammatory markers
Foot ulcer

ABSTRACT

Introduction: Approximately 25 % of diabetic patients develop diabetic foot ulcers (DFUs), significantly increasing morbidity, mortality, and healthcare costs. Effective control and prevention are crucial.
Objective: This study aims to identify easily measurable parameters for predicting DFU risk by assessing the correlation between Phase Angle (PA) and the Triglyceride-Glucose (TyG) index with DFU risk.
Materials and methods: A comparative case-control study was conducted at the General Hospital of Elche from March to June 2023 with 70 participants (33 with diabetes, 37 without). Cases had diabetes for over five years and a diabetic foot risk grade of 0, 1, or 2 (IWGDF 2019). Exclusion criteria included inability to walk, prior use of orthoses, and severe complications like edema or wounds. Predictive variables were PA, TyG index, body composition, and biochemical markers. Statistical analyses included Pearson/Spearman tests for correlations, Student's t-test/Mann-Whitney test for group comparisons, and ANOVA/Kruskal-Wallis tests for normally and non-normally distributed variables.
Results: PAand TyG index were strongly linked to diabetic foot risk, supporting their potential as biomarkers. Significant relationships with other relevant biomarkers were also confirmed.
Conclusion: PA and TyG index are valuable, easily measurable biomarkers for assessing diabetic foot risk, and can be monitored in primary care settings. Implementing these biomarkers in routine practice could enhance the management of diabetic complications, particularly in resource-limited settings, by enabling early detection and intervention, thus improving patient outcomes and reducing the burden of advanced complications.

1. Introduction

Diabetes mellitus is a serious chronic condition characterized by elevated blood glucose levels due to inadequate or ineffective insulin production. In 2021, it was estimated that 537 million people had diabetes, with projections reaching 643 million by 2030 and 783 million by 2045 [1].

Poor glycemic control can lead to various macrovascular and microvascular complications, such as retinopathy, neuropathy, diabetic kidney disease, and diabetic foot ulcers (DFUs) [2,3]. DFUs are among the most feared complications of uncontrolled diabetes as they can result in severe outcomes like amputations or death [4]. Approximately 25 % of diabetic patients develop DFUs in their lifetime, with a 5-year mortality rate 2.5 times higher than that of diabetic patients without foot ulcers [5,6]. Healing rates of DFUs vary from 65 % to 77 %, but some patients never achieve wound closure [7]. Skeletal muscle dysfunction, including sarcopenia, significantly affects diabetics, increasing the risk of DFUs and mortality [8,9], and contributing to osteoporosis development [10].

Most DFUs are initially asymptomatic due to reduced foot sensation

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https://doi.org/10.1016/j.metop.2024.100315
Received 11 August 2024; Received in revised form 28 August 2024; Accepted 28 August 2024
Available online 30 August 2024

from peripheral artery disease and neuropathy, delaying treatment until ulcers fail to heal. Preventive strategies, such as annual diabetic foot screening and foot care interventions, have been implemented to identify high-risk patients early [11]. The International Working Group on the Diabetic Foot (IWGDF) recommends identifying at-risk feet, regular inspections, patient education, appropriate footwear, and treating risk factors [12].

Identifying diabetic patients at risk of ulceration, assessing early signs of skin breakdown, initiating appropriate management, and referring patients as needed are crucial [13]. A healthy lifestyle, including a high-quality diet and physical activity, reduces the risk of microvascular complications in diabetics [14]. The Mediterranean diet is associated with lower cardiovascular disease incidence and microvascular complications [15], and physical activity significantly improves DFU outcomes by enhancing nerve conduction velocity, peripheral sensory function, and foot peak pressure distribution [16]. Conversely, sarcopenia and dynapenia are linked to underweight and low adherence to the Mediterranean diet [17].

Although data is limited, it appears that DFU patients are more prone to frailty, impairing ulcer healing and increasing rehospitalization risk. Patients with DFUs and sarcopenia have higher rates of amputations and postoperative mortality [18], along with lower healing rates, more pain, and worse mobility at follow-up [19]. DFUs significantly impact patients' health and socioeconomic well-being, as well as the quality of life of their families [5,19]. As diabetes prevalence grows, the projected implications of DFUs become alarming. Current treatments are expensive, posing a barrier, particularly in low and middle-income economies [5].

Recent evidence suggests that certain biomarkers are related to diabetic foot ulcer (DFU) risk and could play a crucial role in preventing this complication. One such biomarker is the phase angle (PA), a key indicator in cellular health assessment, which is independently associated with DFU risk [20]. PA is obtained through bioimpedance analysis, a simple, quick, painless, and non-invasive technique that reflects the integrity of cellular membranes and nutritional status, both of which are fundamental in managing chronic diseases like diabetes [21]. The relevance of PA lies in its ability to capture subtle changes in cellular health that are not easily detectable through traditional biomarkers [20].In the context of diabetic complications, such as DFU, cellular dysfunction and alterations in body composition are common underlying phenomena [22]. The inclusion of PA in studies of DFU is justified by its demonstrated capacity to predict risks associated with these complications, complementing other metabolic measurements and providing a more comprehensive evaluation of the patient's health status [23]. Another notable biomarker is the Triglyceride-Glucose (TyG) index, which has been associated with DFU severity [24] and is positively correlated with all-cause mortality in diabetic patients with DFUs [25]. These biomarkers, which are both easily obtainable and low-cost, are ideal for routine monitoring of diabetic patients in primary care settings.

2. Methods

2.1. Design

This comparative case-control study was conducted at the General Hospital of Elche (Alicante, Spain) from March to June 2023. Participants were divided into two groups: those with diabetes (cases) and those without (controls), aiming to identify predictive biomarkers for diabetic foot risk. Cases had diabetes for over 5 years, aged 18–80, attending clinical follow-ups, and a diabetic foot risk of 0, 1, or 2 (IWGDF), with a recent blood test. Controls were non-diabetic, aged 18–80, residing in the hospital's Health Department, with a recent blood test. Exclusion criteria included walking/standing difficulties, previous plantar orthosis treatment, lower extremity edema, or wounds at electrode sites. Cases with a diabetic foot risk level of 3 were also excluded.

2.2. Data collection

Patients had two visits within three days. At the first visit, they were informed about the study, signed the consent form, had their feet assessed, and were assigned a diabetic foot risk grade. The second visit included body composition measurement (anthropometry and bioimpedance), hand dynamometry, and collection of biochemical parameters from recent blood tests.

2.3. Ethics approval and consent to participate

The study adhered to the Declaration of Helsinki. Ethical approval (protocol PI 138/2022) was obtained from the Research Ethics Committee on January 31, 2023. All participants provided signed informed consent.

2.4. Variables

2.4.1. Outcome variable: Risk grade of diabetic foot

We used the 2019 IWGDF risk stratification system [26] to assign a diabetic foot risk grade to each participant in the case group based on the presence of loss of protective sensitivity in the feet, arterial disease, or other severe complications such as foot ulcers, lower limb amputation, or end-stage renal disease [26].

2.4.2. Predictive variables

We used the TANITA MC-780MA Segmental Multi-Frequency Analyzer and collected the following data: fat mass, muscle quality, total body water, metabolic age, basal metabolism, and PA. The TANITA also provides indices such as body mass index, and visceral fat index. Bioimpedance data were collected following strict, standardized methodology: no heavy physical exercise 24 h before, no large meals 2–4 h before, no coffee or alcohol at least 8 h before, and an empty bladder before measurement [21].

Additionally, the difference between metabolic age and actual age was calculated, and the sarcopenia risk index was estimated using the algorithm proposed European Working Group on Sarcopenia in Older People (EWGSOP) [17], which assesses walking speed, muscle strength, and muscle mass. Walking speed was assessed by measuring habitual walking speed in meters/second over a 4-m distance, using <0.8 m/s as the cut-off point for poor physical performance. Muscle strength was assessed by grip strength of both hands using an ActivForce 2 mechanical dynamometer (ActivForce, San Diego, CA, USA).

The measurement was performed in triplicate, and the average of the 2 highest readings was recorded. Low muscle strength was defined as <30 kg as per EWGSOP guidelines.

Muscle mass was estimated using calf circumference and mid-arm muscle circumference (MAMC). MAMC was calculated using the formula [27]:

$$\text{MAMC} = \text{mid-upper arm circumference} - (3.14 \times \text{tricipital skinfold}) \{1\}$$

Tricipital skinfold was measured at the midpoint of the arm's length, with the arm relaxed and hanging parallel to the body axis.

Waist and hip circumferences were recorded in centimeters following World Health Organization (WHO) guidelines [28]. Waist circumference was measured between the midpoint of the lower rib and iliac crest. Hip circumference was measured at the widest point above the greater trochanters. A seca fiberglass measuring tape (seca, Hamburg, DEU) was used for all measurements to the nearest 0.1 cm, and a Bozeera plicometer (Bozeera, DEU) was used for tricipital skinfold measurements. In the case of dynamometry, the average of 3 measurements was taken for each variable. Abizanda et al. (2012) evaluated the validity and utility of hand-held dynamometry for measuring muscle strength in community-dwelling older adults. This study found that three attempts are recommended for all strength measurements using

hand-held dynamometry to ensure reliability and validity of the results [29].

Biochemical variables were obtained from routine clinical follow-up blood tests: albumin, total lymphocytes, glucose, triglycerides and glycosylated hemoglobin (HbA1C). The TyG index was calculated using the formula [30]:

$$\text{TyG index} = \text{Ln (fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/ 2)} \quad \{2\}$$

The Controlling Nutritional Status (CONUT) score was estimated based on the sum of serum albumin score, total lymphocyte score, and total cholesterol score [31].

2.5. Statistical analysis

The sample size was calculated using Epi Info™, considering 13,182 diabetic individuals in the department and a 6 % expected ulcer frequency. A 95 % confidence level and 9 % confidence limit determined a minimum of 26 patients per group, but over 30 subjects with and without diabetes were recruited.

Data were analyzed using R software. Pearson or Spearman tests examined correlations, and group comparisons used the Student's t-test or Mann-Whitney test based on data distribution. For variables that were normally distributed, or close to normal (normality confirmed through Shapiro-Wilk test and visual inspection of histograms and Q-Q plots), parametric tests such as Pearson correlation, Student's t-test, and one-way ANOVA were used, given their greater power under these conditions. However, for variables with borderline normality or non-normal distribution, non-parametric tests like Spearman correlation, Mann-Whitney test, and Kruskal-Wallis test were selected to ensure robustness and minimize the risk of biased results. Significance was set at $p < 0.001$ (high) and $p < 0.05$ (medium). Multiple comparisons corrections and multiple imputation methods were applied to handle missing data.

To compare controls (C), risk level 0, and combined risk levels 1 and 2, one-way ANOVA with Tukey post-hoc tests were used for normally distributed variables, and Kruskal-Wallis with Dwass-Steel-Critchlow-Fligner post-hoc tests for non-normal variables.

A two-phase methodology evaluated correlations between variables and diabetic foot risk. Initially, all variables were analyzed in the complete sample, assigning a diabetic foot risk of 0 to controls. Significant associations were identified in this larger sample (Tables 2–4). Subsequently, the sample was stratified into cases and controls for significant variables, confirming the validity and independence of the biomarkers (Tables 5 and 6).

This methodological approach, combining global analyses with detailed stratifications, allows for a more robust evaluation of the findings. It leverages the initial analysis to detect potential correlations and then validates these associations through detailed stratification. This provides a more comprehensive and precise understanding of the relationships between the studied variables and diabetic foot risk, ensuring both internal validity and clinical applicability of the results.

2.6. Handling missing data

In this study, missing data accounted for less than 5 % of the total collected data. The nature of the missing data was evaluated and determined to be 'Missing Completely at Random' (MCAR), indicating that the absence of data was not related to either observed or

Table 1
Participants' socio-demographic characteristics including cases-controls, gender, age, educational status and income.

	n	%
Cases-Controls	70	
Cases	33	47.1
Controls	37	52.9
Type of diabetes	33	
Type 1	5	15.2
Type 2	28	84.8
Gender	70	
Men	27	38.6
Women	43	61.4
Age	59	
45–64 years old	29	42.0
>65 years old	27	39.1
≤44 years old	13	18.8
Educational Status	69	
Unschooled	5	7.2
Primary school	28	40.6
Secondary school	18	26.1
Higher education (university)	18	26.1
Income	69	
Medium	55	79.7
Low	14	20.3

Table 2
Correlations between the studied variables and the diabetic Foot Risk for the whole sample (N = 70).

Predictive variable	Correlation	P value[a]	R^2	P value[b]
Relaxed arm circumference	0.064	0.604	0.0040	0.604
Hip circumference	0.237	**<0.05***	0.0513	0.061
Waist circumference	0.443	**<0.001****	0.1960	**<0.001****
Tricipital skin fold	0.213	0.119	0.0453	0.119
Right hand dynamometry	0.138	0.254	0.0272	0.172
Left hand dynamometry	−0.340	**0.004****	0.0786	**0.019***
Glucose	0.532	**<0.001****	0.2620	**<0.001****
HbA1c	0.560	**<0.001****	0.3400	**<0.001****
Triglycerides	0.345	**0.004****	0.0674	**0.034***
TYG Index	0.454	**<0.001****	0.1910	**<0.001****
BMI	0.333	**0.005****	0.0968	**0.009****
Visceral Fat Index	0.293	**0.015***	0.0756	**0.022***
Sarcopenia Risk Index	0.178	0.143	0.0159	0.302
CONUT	0.430	**0.008****	0.2810	**<0.001****
PA	−0.332	**0.005****	0.0969	**0.009****
Basal Metabolism (Kcal)	0.068	0.580	0.0045	0.581
Metabolic Age	0.370	**0.002****	0.1370	**0.002****
Age	0.299	**0.012***	0.0833	**0.015***
Muscular Quality	−0.311	**0.009****	0.0969	**0.009****
Tot. Body Water (%)	−0.264	**0.028***	0.0697	**0.028***

[a] P values by Pearson's coefficient for normal variables and Spearman's for non-normal variables.
[b] P values Linear Regression.

Table 3
Correlations between the studied variables and PA for the whole sample.

Predictive variable	Correlation	P value[a]	R^2	P value[b]
Relaxed arm circumference	0.336	**0.005****	0.113	**0.005****
Hip circumference	−0.022	0.857	0.005	0.546
Waist circumference	−0.089	0.469	0.007	0.469
Tricipital skin fold	−0.139	0.317	0.0193	0.317
Right hand dynamometry	0.331	**0.006****	0.109	**0.006****
Left hand dynamometry	0.339	**0.004****	0.115	**0.004****
Glucose	−0.052	0.677	0.0027	0.677
HbA1c	−0.251	**0.047***	0.0682	**0.039***
Triglycerides	0.075	0.547	0.0009	0.811
TYG Index	0.054	0.666	0.0006	0.837
BMI	0.091	0.457	0.2333	0.211
Visceral Fat Index	0.049	0.688	0.0004	0.871
Sarcopenia Risk Index	0.330	**0.006****	0.0926	**0.011***
CONUT	−0.457	**0.005****	0.244	**0.002****
Basal Metabolism (Kcal)	0.350	**0.003****	0.102	**0.007****
Metabolic Age	−0.477	**<0.001****	0.160	**<0.001****
Age	−0.547	**<0.001****	0.258	**<0.001****
Muscular Quality	1.000	**<0.001****	0.999	**<0.001****
Tot. Body Water (%)	0.391	**<0.001****	0.123	**0.003****

[a] P values by Pearson's coefficient for normal variables and Spearman's for non-normal variables.
[b] P values Linear Regression.

Table 4
Correlations between the studied variables and TyG Index for the whole sample.

Predictive variable	Correlation	P value[a]	R^2	P value[b]
Relaxed arm circumference	0.140	0.262	0.0693	0.033
Hip circumference	0.139	0.265	0.0617	0.044
Waist circumference	0.571	**<0.001****	0.3160	**<0.001****
Tricipital skin fold	0.034	0.813	0.0390	0.160
Right hand dynamometry	−0.037	0.763	0.0078	0.476
Left hand dynamometry	0.407	**<0.001****	0.0098	0.425
Glucose	0.693	**<0.001****	0.5330	**<0.001****
HbA1c	0.543	**<0.001****	0.2820	**<0.001****
Triglycerides	0.925	**<0.001****	0.6410	**<0.001****
PA	0.054	0.666	0.0006	0.837
BMI	0.418	**<0.001****	0.2310	**<0.001****
Visceral Fat Index	0.473	**<0.001****	0.2910	**<0.001****
Sarcopenia Risk Index	0.372	**0.002****	0.2090	**<0.001****
CONUT	−0.457	**0.005****	0.0190	0.416
Basal Metabolism (Kcal)	0.272	**0.027***	0.1520	**0.001****
Metabolic Age	0.370	**0.002****	0.1290	**0.003****
Age	0.200	0.105	0.0290	0.168
Muscular Quality	0.054	0.666	0.0006	0.835
Tot. Body Water (%)	−0.017	0.892	0.0004	0.862

[a] P values by Pearson's coefficient for normal variables and Spearman's for non-normal variables.
[b] P values Linear Regression.

Table 5
One-way ANOVA (Fisher's) and tukey post-hoc test.

Variables	ANOVA		Post Hoc	
	F	P value[a]	Comparisons	P value[b]
Phase Angle (°)	6.99	**0.002** **	C vs 0	0.999
			C vs 1-2	**0.002** **
			0 vs 1-2	**0.029** *
Fat Mass (%)	3.42	**0.039** *	C vs 0	0.985
			C vs 1-2	**0.036** *
			0 vs 1-2	0.210
Fat-Free Mass (%)	3.24	**0.045** *	C vs 0	0.996
			C vs 1-2	**0.044** *
			0 vs 1-2	0.205
Muscle Quality	6.99	**0.002** **	C vs 0	0.999
			C vs 1-2	**0.002** **
			0 vs 1-2	**0.029** *
Total Body Water (%)	3.79	**0.028** *	C vs 0	0.996
			C vs 1-2	**0.027** *
			0 vs 1-2	0.156
Metabolic Age	5.53	**0.006** **	C vs 0	0.956
			C vs 1-2	**0.008** **
			0 vs 1-2	**0.037** *

[a] P value ANOVA Test.
[b] P value Tukey post-hoc test.

Table 6
Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner pairwise comparisons.

Variables	Kruskal-Wallis		Dwass-Steel-Critchlow-Fligner	
	χ^2	P value[a]	Comparisons	P value[b]
TyG Index	20.06	**< 0.001** **	C vs 0	0.060
			C vs 1-2	**<0.001** **
			0 vs 1-2	0.999
BMI (kg/m^2)	8.50	**0.014** *	C vs 0	0.864
			C vs 1-2	**0.008** **
			0 vs 1-2	0.407
Muscle Mass Index	6.72	**0.035** *	C vs 0	0.966
			C vs 1-2	**0.034** *
			0 vs 1-2	0.218
Visceral Fat Index	6.28	**0.043** *	C vs 0	0.943
			C vs 1-2	**0.024** *
			0 vs 1-2	0.555

[a] P value Kruskal-Wallis test.
[b] P value Dwass-Steel-Critchlow-Fligner pairwise comparisons.

unobserved variables.

To handle the missing data, we employed the Multiple Imputation by Chained Equations (MICE) technique, implemented in the R software. This approach is widely recognized for its effectiveness in handling missing data by generating multiple imputed datasets (five imputations in our case), thus preserving the inherent variability of the original data and minimizing the risk of bias.

The predictor variables included in the imputation process encompassed all relevant variables in our model, both demographic and clinical, ensuring that the imputation was based on the most comprehensive information available. After imputation, checks were performed to ensure that the distributions of the imputed variables were consistent with the original distributions, and that no significant biases were introduced.

Subsequent statistical analyses were conducted on each of the imputed datasets, and the results were combined using Rubin's rules, allowing for precise and reliable estimates.

3. Results

3.1. Sample characteristics

Table 1 shows the socio-demographic characteristics of the 70 participants: 61 % were women, 52.9 % (n = 37) were controls and 47.1 % (n = 33) were cases mostly with mostly with type 2 diabetes. Most participants were between 45 and 64 years old (42 %) with medium income (79 %), 40 % had primary school education, and 26 % each had secondary or university education.

3.2. Biomarker analysis

Correlation analysis revealed that higher diabetic foot risk (Table 2) significantly correlated with increased waist circumference ($r^2 = 0.196$, p = <0.001), glucose ($r^2 = 0.262$, p = <0.001), HbA1 ($r^2 = 0.340$ p = <0.001), triglycerides ($r^2 = 0.067$, p = 0.004), TyG index ($r^2 = 0.191$, p = <0.001), BMI ($r^2 = 0.097$, p = 0.005), metabolic age ($r^2 = 0.137$, p = 0.002), and CONUT ($r^2 = 0.281$, p = 0.008). Significant negative correlations included left-hand dynamometry ($r^2 = 0.079$, p = 0.004), muscle quality ($r^2 = 0.097$, p = 0.009), PA ($r^2 = 0.097$, p = 0.005). Moderate associations were found for hip circumference (r = 0.237, $r^2 = 0.051$, p = 0.05), visceral fat index ($r^2 = 0.076$, p = 0.015), age ($r^2 = 0.083$, p = 0.012), and total body water percentage ($r^2 = 0.069$, p = 0.028).

Higher PA (Table 3) significantly correlated with relaxed arm circumference ($r^2 = 0.113$, p = 0.005), right-hand dynamometry ($r^2 = 0.109$, p = 0.006), left-hand dynamometry ($r^2 = 0.109$, p = 0.006), basal metabolism ($r^2 = 0.102$, p = 0.006), sarcopenia risk index ($r^2 = 0.093$, p = 0.006), muscle quality ($r^2 = 0.999$, p = <0.001), and total body water percentage ($r^2 = 0.123$, p = <0.001). Negative correlations included HbA1c ($r^2 = 0.068$, p = 0.047), CONUT ($r^2 = 0.244$, p = 0.005), metabolic age ($r^2 = 0.160$, p = <0.001), and age ($r^2 = 0.258$, p = <0.001).

Higher TyG index (Table 4) significantly correlated with waist circumference ($r^2 = 0.316$, p = <0.001), glucose levels ($r^2 = 0.533$, p = <0.001), HbA1c ($r^2 = 0.282$, p = <0.001), triglycerides ($r^2 = 0.641$, p = <0.001), BMI ($r^2 = 0.231$, p = <0.001), and visceral fat index ($r^2 = 0.291$, p = <0.001). Positive correlations were also found with the sarcopenia risk index (, $r^2 = 0.209$, p = 0.002), basal metabolism ($r^2 = 0.152$, p = 0.027), metabolic age ($r^2 = 0.129$, p = 0.002) and left-hand dynamometry ($r^2 = 0.009$, p = <0.001).

ANOVA results (Table 5) showed significant differences in PA (F = 6.99, p = 0.002), fat mass (F = 3.42, p = 0.039), fat-free mass (F = 3.24, p = 0.045), muscle quality (F = 6.99, p = 0.002), total body water (F = 3.79, p = 0.028), and metabolic age (F = 5.53, p = 0.006) among DFU risk groups. Tukey post-hoc tests indicated significant differences between the control group (C) and risk levels 1–2 (1–2) for PA (C vs 1–2, p

= 0.002; 0 vs 1–2, p = 0.029), fat mass (C vs 1–2, p = 0.036), fat-free mass (C vs 1–2, p = 0.044), muscle quality (C vs 1–2, p = 0.002; 0 vs 1–2, p = 0.029), total body water (C vs 1–2, p = 0.027), and metabolic age (C vs 1–2, p = 0.008; 0 vs 1–2, p = 0.037).

Kruskal-Wallis results (Table 6) indicated significant differences in TyG Index ($\chi^2 = 20.06$, p = <0.001), BMI ($\chi^2 = 8.50$, p = 0.014), Muscle Mass Index ($\chi^2 = 6.72$, p = 0.035) and Visceral Fat Index ($\chi^2 = 6.28$, p = 0.043) among DFU risk groups. Pairwise comparisons showed significant differences between control (C) and risk levels 1–2 (1–2) for TyG Index (C vs 1–2, p = <0.001), BMI (C vs 1–2, p = 0.008), Muscle Mass Index (C vs 1–2, p = 0.034), and Visceral Fat Index (C vs 1–2, p = 0.024) (Fig. 1).

4. Discussion

The primary aim of this study was to identify easily measurable parameters relevant for the prognosis of diabetic foot disease and to verify that both the PA and TyG indices correlate with diabetic foot risk. Our findings indicate a strong correlation between these indices and diabetic foot risk, suggesting their potential utility as biomarkers in daily clinical practice for preventing diabetic foot complications. Additionally, both parameters are associated with an increased risk of sarcopenia and variables typically altered in metabolic syndrome, adding a new dimension to risk assessment in diabetic patients.

4.1. TyG index and diabetic foot risk

The association between diabetic foot risk and the TyG index has been demonstrated in several studies, showing that a higher TyG index is associated with a greater risk of ulcer development, severity, and mortality [24,25]. However, one study reported lower TyG levels in diabetic patients with ulcers, likely due to malnutrition in their sample [32], which was not the case in our study. We also found a positive correlation between diabetic foot risk and HbA1c, consistent with literature linking HbA1c with the TyG index as a biomarker of insulin resistance (IR) [33–36]. This relationship is particularly useful in clinical practice in settings where HbA1c tests are infrequent due to high costs [37]. The TyG index can serve as an indicator of IR and diabetic foot risk, improving patient follow-up. Our statistical analysis using the Tukey Post-Hoc Test indicated significant differences in TyG index values between the control group and risk groups 1 and 2 (p < 0.001), but not between the control group and risk group 0 (p = 0.060), nor between risk groups 0 and 1/2 (p = 0.999). This suggests that the TyG index is particularly effective at distinguishing between those at moderate to high risk (groups 1 and 2) versus those at low or no risk (control and group 0), which is crucial for early intervention strategies.

4.2. PA and diabetic foot risk

Our results and the scientific literature show an association between PA and sarcopenia in patients with T2DM [22,38]. While the relationship between PA and diabetic foot risk has been less studied, our findings support this association [21,38]. The weak and non-significant correlation between PA and the TyG index suggests that these biomarkers reflect different aspects of diabetic disease. The TyG index relates to IR and poor glycemic control, leading to microvascular damage and neuropathies [25,34], whereas PA is associated with nutritional status and overall body composition, indirectly affecting diabetic foot risk. Adequate nutritional status is essential for wound healing and maintaining skin integrity [39]. The lack of correlation between PA and the TyG index highlights the need for a comprehensive approach to assessing diabetic foot risk, considering multiple biomarkers to gain a holistic understanding of the patient's health status.

Additionally, the costs associated with determining these biomarkers, TyG and PA, are more economical than HbA1c. In our health department, the unit cost per procedure for HbA1c is 5.85 euros, compared to 0.75 euros for TyG [40] and 0.026 euros for PA, according to data provided by Tanita Europe [41]. This cost-effectiveness highlights the practicality of incorporating these biomarkers into routine assessments.

Although measuring PA involves the use of advanced and costly technology, its inclusion in high-level clinics could provide valuable insights into patients' metabolic and vascular health. PA reflects the state of cellular function and inflammation, offering a detailed view of the underlying processes that predispose patients to ulcer development. Studies have shown that physical activity has a significant impact on metabolic syndrome markers in adults with Type 2 diabetes. For instance, aerobic exercise was found to significantly reduce waist circumference, although its effects on other metabolic syndrome markers such as blood pressure, triglycerides, high-density lipoprotein, and fasting blood sugar were not statistically significant [42]. Additionally, the global prevalence of metabolic syndrome among patients with Type 1 diabetes highlights the importance of addressing this condition to reduce the risk of diabetic complications [43]. Moreover, the

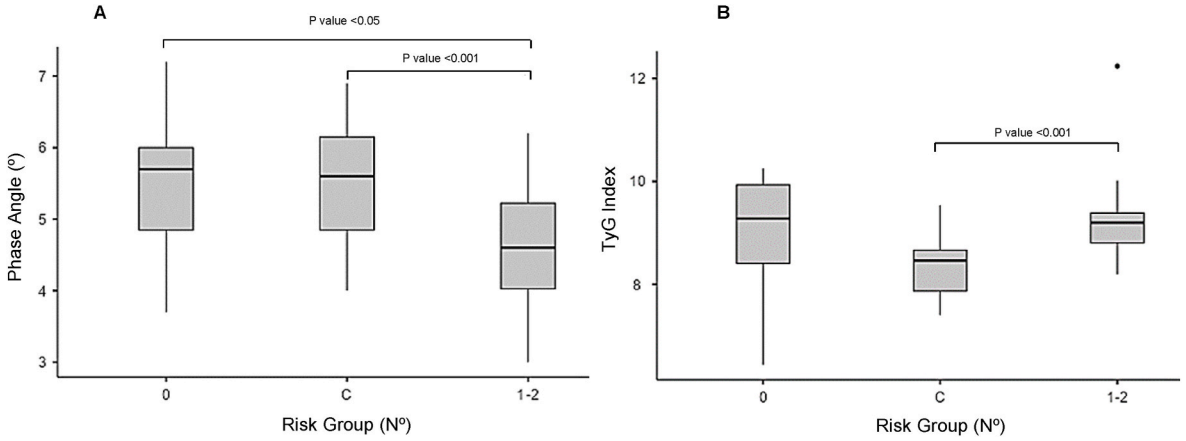

Fig. 1. Boxplots of Risk Group and Variables: Phase Angle (A) and TyG Index (B). (A) The boxplot illustrates the distribution of Phase Angle (°) across different diabetic foot risk groups: control (C), risk grade 0, and risk grades 1–2. Statistical comparisons were performed using one-way ANOVA followed by Tukey post-hoc tests. The median Phase Angle for risk grades 1–2 is significantly lower than that for the control group (p < 0.001) and risk grade 0 cases (p < 0.05). (B) The boxplot shows the distribution of the TyG Index across the same diabetic foot risk groups. Statistical significance was assessed using the Kruskal-Wallis test followed by Dwass-Steel-Critchlow-Fligner post-hoc comparisons. The median TyG Index is significantly higher in risk grades 1–2 compared to both the control group and risk grade 0 cases (p < 0.001). Outliers are indicated with dots.

epidemiology of metabolic vascular syndrome and its coincidence with Type 2 diabetes and cardiovascular diseases in various European countries underlines the critical need for effective management strategies [44]. This complementarity would allow multidisciplinary healthcare teams to predict the onset of diabetic foot ulcers (DFUs) and intervene early and effectively, optimizing outcomes and reducing the risk of future complications. Implementing these biomarkers could significantly improve the quality of life for diabetic patients, preventing disabilities and reducing the costs associated with treating advanced complications.

4.3. Multifactorial approach to diabetic foot risk

People with diabetes often develop other metabolic syndrome pathologies [45,46]. Our results show an association between higher diabetic foot risk and higher waist circumference, triglyceride levels, fat mass, and fat-free mass. The TyG index, a predictor of metabolic control and IR in T2DM [46,47] and obesity, explains its correlation with diabetic foot risk [48]. The relationship between these factors and diabetic foot risk underscores the interconnected nature of metabolic syndrome components, suggesting that interventions targeting these areas may simultaneously reduce the risk of diabetic foot complications.

Metabolic syndrome and diabetes can lead to altered nutritional, physical, and hormonal parameters, evoking conditions like sarcopenia [49]. Diabetes accelerates aging, increasing the risk of premature sarcopenia [50]. Loss of muscle mass worsens glycemic control due to reduced glucose uptake, increasing insulin secretion and resistance [49]. This decline in muscle quality is associated with higher diabetic foot risk [50]. The observed correlation between the muscle quality index and PA in our results is due to the inclusion of PA in the muscle quality calculation, which integrates multiple measurements from bioelectrical impedance analysis (BIA), emphasizing PA as a critical parameter of cellular integrity and fluid distribution.

4.4. Study limitations and future research

The relatively small sample size of 70 participants is a primary limitation of our study, potentially restricting the statistical power to detect small effect sizes, particularly given the heterogeneity of the diabetic population. Although the sample size was calculated using Epi Info™, considering a substantial reference population, we acknowledge that this sample may not be sufficient to identify subtle associations, which can be crucial in clinical settings where even minor effects may have significant implications for patient care. This limitation is especially pertinent concerning the limited representation of participants with type 1 diabetes, which prevented a robust comparison between diabetes types.

Additionally, our study did not assess handedness, which constrains our ability to fully explore the relationship between left-hand dynamometry and diabetic foot risk. Furthermore, the lack of foot dynamometry measurements limits the comprehensive evaluation of muscle function in diabetic patients.

Beyond these, other potential confounding factors must also be acknowledged. The use of medications, such as insulin and other antidiabetic agents, could have influenced the glycemic control and metabolic parameters of participants, potentially affecting the observed relationships between the biomarkers studied and diabetic foot risk. Comorbidities like hypertension, dyslipidemia, and cardiovascular disease, common in diabetic populations, could have independently contributed to the risk of diabetic foot complications, confounding the impact of the studied biomarkers. Moreover, lifestyle factors such as diet, physical activity, and smoking or alcohol consumption are known to influence both metabolic health and wound healing, yet were not controlled for in this study.

To address these limitations, future research should aim to include larger and more diverse samples, taking into account these confounding factors, as well as handedness, allowing for a more detailed analysis of both types of diabetes independently. Longitudinal studies are also needed to validate the use of Phase Angle (PA) and the Triglyceride-Glucose (TyG) index as long-term predictive biomarkers, and to examine their impact on the progression of diabetic foot risk. Expanding the scope of research to involve multiple centers and more diverse populations could further enhance the generalizability of the findings and their applicability across different clinical settings.

5. Conclusions

This study identifies the PA and TyG indices as relevant and easily measurable biomarkers for evaluating diabetic foot risk, with potential application in daily clinical practice. The TyG index, a reliable marker of insulin resistance (IR), is particularly useful in resource-limited settings where HbA1c tests are not feasible, providing a practical tool for monitoring the risk of diabetic complications. PA, on the other hand, offers valuable insights into cellular health and inflammation, further enriching the assessment of diabetic foot risk. By jointly utilizing these biomarkers, healthcare providers can achieve a more comprehensive and precise diagnosis and monitoring of diabetic foot risk, addressing the gap in affordable and accessible biomarkers for diabetic foot evaluation. Implementing these indices in clinical practice can significantly enhance the prevention and management of diabetic foot, ultimately improving patient outcomes and quality of life.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Ethical approvals were obtained from the Research Ethics Committee. Participants were informed of the study's objective and provided signed written informed consent.

Consent for publication

"Not applicable".

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study was supported by grants from the Agència Valenciana de la Innovació (INNEST/2021/365) and the promoter POLISABIO (POLISABIO22_AP05).

CRediT authorship contribution statement

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J. Saiz: Visualization, Supervision. **G. Prats-Boluda:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **R. Santoyo Pérez:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation.

Declaration of competing interest

The authors report no conflict of interest.

Acknowledgements

"Not applicable".

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