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Comparative Responses of Achilles Tendinopathy to Selected Physiotherapy Approaches and the Modulating Influence of ABO Blood Group Phenotype in Nigerian Footballers: a Randomized Control Study

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SUMMARY

Background. Genetic factors have been implicated in Achilles Tendinopathy (AT) and the response to different management strategies in Caucasian populations. To account for racial differences, this study investigated the ABO blood group disposition to AT and effects on selected physiotherapy interventions in Nigerian footballers.
Methods. Participants included 56 footballers made up of 28 confirmed cases of AT and 28 matched controls. Royal London Hospital test and ultrasonography were used to screen for AT. Demographic data as well as outcome variables were determined at baseline. ABO blood grouping was done by conventional serotyping. Participants with AT were randomized into three groups and managed for eight weeks using Intrasound Therapy, Therapeutic Ultrasound and Eccentric Exercises. The outcome variables of the three physiotherapy approaches in the different ABO groups were assessed and statistically analyzed using IBM SPSS 22 at the end of eight weeks.
Results. Blood group O responded significantly in all outcome parameters ($p < 0.05$) regardless of the modality used. Blood group A had the highest OR of 3.000 ($p = 0.051$) while blood group B had the lowest OR of 0.625 ($p = 0.758$). However, all the treatment strategies were effective in the management of AT.
Conclusions. The differential treatment outcomes according to ABO blood group in footballers suffering from AT may help in the development of treatment algorithms.
Studyregistration. South African Medical Research Council (PACTR201909524416162).

KEY WORDS

Achilles tendinopathy; blood groups; intrasound therapy; therapeutic ultrasound; eccentric exercises.

INTRODUCTION

Achilles tendinopathy (AT) is a major foot and ankle overuse injury which is prevalent in running and jumping sporting activities, especially in football that has witnessed increased participation in recent times (1). It is degenerative and causes abnormal collagen structure with eventual tendon rupture (2, 3). Clinically, AT presents with symptoms of pain, swelling, impaired function during sporting activities and activities of daily living and poor quality of life (4).

Major risk factors for AT are a combination of extrinsic and intrinsic factors with ABO blood groups implicated as an important intrinsic factor in an individual's susceptibility to AT (4-6). The ABO blood groups have been implicated in a number of human diseases and the risk of developing some diseases is influenced by alleles or phenotypes of ABO blood

groups; for instance, blood groups have been reported to have a correlation with the overall risk of tendon rupture, with blood groups O and A more likely to experience a tendon rupture (7). However, beyond their role in blood transfusion, alleles and phenotypes of the ABO system show racial and population-based variations with available data on Achilles tendinopathy limited to Caucasians population (8-11).

The management of AT lacks evidence-based support, and tendinopathy sufferers are at risk of long-term morbidity with unpredictable clinical outcome (12). The non-surgical treatment available to patients with acute and chronic AT are non-steroidal anti-inflammatory medications (NSAIDs), steroid or platelet-rich plasma injections, autologous whole blood injections, prolotherapy and sclerotherapy (13). These therapies offer unpredictable results, and in the case of steroids, can lead to serious side effects and more rapid degeneration of the tendon (13). Physiotherapy is accepted as the first line approach for managing AT because it is non-invasive and offers a more comprehensive rehabilitation of the affected tendon and surrounding tissues (14). Physiotherapy management of AT includes Eccentric exercises and electrotherapeutic modalities such as Therapeutic ultrasound, Intrasound therapy and Low-level laser therapy among others (15, 16). These are often used in a multimodal approach for the purpose of alleviating symptoms and promoting functional recovery (16).

The response of individuals to treatment has been found to be influenced by their genetic disposition and genetic information now available has opened up the possibility to systematically study inter-individual differences in drug response using genome-wide association (GWA) studies (17). Results of these efforts have so far led to pharmacogenomics which is the tailoring of drug treatments to people's genetic makeup and a form of "personalized medicine". Genetic investigation is needed to develop treatment and therapies that can selectively modulate AT by understanding the genetic variation that may influence the prognosis of the management. The blood group phenotype and other associated genetic expressions can enhance the understanding of individual differences in disease presentation and responses to intervention. Differential response to treatment can determine the type and preference of treatment and studies on response to treatment with the use of physiotherapy approaches in the management of AT are sparse. There is a dearth of studies on the association between ABO inheritance and tendinopathy in black Africans, hence the need for this study in order to account for racial variations. The purpose of this study therefore was to determine the ABO blood groups predisposition to Achilles tendinopathy and their responses to treatment with selected physiotherapy approaches in a population of Nigerian footballers.

MATERIALS AND METHODS

Study population

This study involved fifty-six (56) football players who were recruited from some football clubs under the Lagos Junior League in Lagos, Nigeria. The participants had written informed consent and had played football actively in the last 6 months and engaged in full football training and match responsibilities at the time of the commencement of the study. Excluded were participants who had undergone prior surgical repair of the Achilles tendon. Assessments and data collection took place at two different stadia in Lagos metropolis. Ethical approval was obtained from the institutional Health Research and Ethics Committee (HREC/06/19/536). The study was also registered with South African Medical Research Council (PACTR201909524416162).

Study design and research procedure

This was a randomized case-control study that involved 28 participants who tested positive to Achilles tendinopathy through both the Royal London Hospital Test (RLHT) and Musculoskeletal Ultrasonography and 28 age-matched controls who tested negative to AT. Participants who met the inclusion criteria were purposively recruited and those who tested positive to AT were randomized into 3 groups as seen in the flow chart **figure 1**).

The sample size was determined using the protocol developed by Kumar (18). The study was done in two phases.

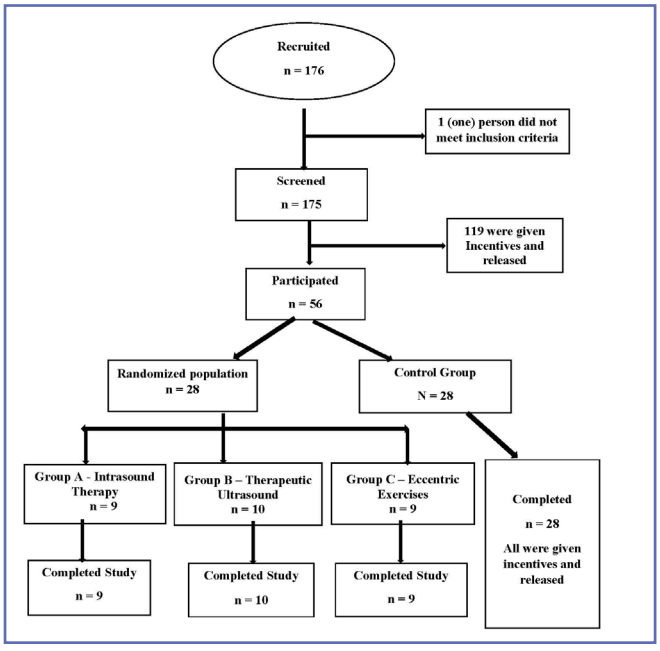

Figure 1. Flow Chart of participants from recruitment to completion of study.

Phase 1: determination of intrinsic risk factors for Achilles tendinopathy

Demographic data which included age, gender, football club, ethnicity, height, weight and leg dominance were obtained for each participant with the use of the data form. The presence of Achilles tendinopathy was assessed using the Royal London Hospital Test (RLHT) (19), in prone lying position on a plinth/flat surface. Diagnostic Ultrasound Machine (XARIO 200, China) equipped with a 5-12 MHz 50 mm linear array transducer was used to image the Achilles tendon to confirm AT for participants who tested positive and their age matched controls who tested negative to RLHT. Ten milliliters (10 ml) of blood were obtained by venipuncture from participants who tested positive to both RLHT and ultrasonography using a collecting set, plain EDTA bottles. Blood groups were determined using Antigen-Antibody principle (20).

Phase 2: intervention using physiotherapy approaches

Participants who tested positive to the RLHT and confirmed with ultrasonography were randomized into 3 treatment groups using a computer-generated random sequence. Baseline assessment was done which included: "Range of Motion" (Goniometry) (21), "Pain" (VAS) (22), "Quality of Life" (SF-12) (23), "Severity of injury" (VISA-A) (24) and "Foot Function" (FAAM) (25).

Group A: this group received Intrasound Therapy only 3 times a week for 8 weeks.

Group B: this group received Therapeutic Ultrasound only 3 times a week for 8 weeks.

Group C: this group received Eccentric Exercises only 3 times a week for 8 weeks.

Treatment procedure

Group A

Intrasound Therapy (Novasonic Sonic Wave SK2 device, from USA): participants were asked to lie prone on a plinth with the ankle hanging over the edge of the plinth which is a zero-angle position for the ankle joint. The Intrasound therapy device was plugged in and set at moderate intensity for the participants. The Intrasound probe was moved over the affected part of the Achilles tendon in circular motion for 10 minutes with a water-soluble coupling medium (K-Y gel) (26) to transmit the sound waves down into the Achilles tendon. Participants reported any feeling they had during the procedure and were monitored for any adverse reaction to treatment.

Group B

Therapeutic Ultrasound (Ultrason 101-ML device, from India): participants were asked to lie prone on a plinth with the ankle hanging over the edge of the plinth which is a neutral position for the ankle joint. The ultrasound machine was plugged in, with intensity at 1 MHz and continuous mode frequency for the participants. The ultrasound probe (1 MHz probe) was moved over the affected part of the Achilles tendon in circular motion for 10 minutes with a water-soluble ultrasound gel to transmit the sound wave down into the Achilles tendon (27). Participants reported any feeling they had during the procedure and were monitored for any adverse reaction to treatment.

Group C

Eccentric Exercises: participants in this group received moderate intensity eccentric strengthening and stretching exercises of the triceps surae. The eccentric loading program was previously described and it included 3 sets of 15 slow repetitions (28). The gastrocnemius muscle was eccentrically loaded (standing on the toes) with both knees in full extension, to maximize the activation of the soleus muscle. Also, with the knee extended (affected leg), the Achilles tendon was in full elongation (heels down and toes pointing upwards) at the edge of a stair. The third set was with the knee flexed at the edge of a stair, the Achilles tendon was elongated (heels down and toes pointing upwards). Each exercise was repeated 5 times. Assessment of the outcome parameters were done post-intervention at the end of 8 weeks of treatment.

Data analysis

Data was analyzed using the Statistical Package for Social Sciences version 22.0 and summarized using descriptive statistics of mean, standard deviation, frequencies and percentages. Independent t-test was used to determine the mean difference of parameters among study group and controls. Paired t-test was used to compare pre and post intervention outcome variables of group A, B and C. One-way Analysis of Variance (ANOVA) was used to assess improvement across all three blood groups and treatment groups. Level of significance for all inferential statistics was set at $p \leq 0.05$.

RESULTS

A total of fifty-six football players completed the study: 28 cases of Achilles tendinopathy and 28 matched controls. The Median (Interquartile range) of their ages (years), heights (m), weights (Kg) and BMI (Kg/m^2) were 21 (19-25), 1.72 (1.65- 1.78), 63.8 (57-71) and 21.6 (19.7-23.3) respectively. The Blood Group distribution in AT is seen in **figure 2**.

The distribution of the ABO blood groups has been repeatedly investigated in various populations all over the world and their frequencies exhibited considerable variation with blood group O showing the highest frequency and blood group AB the least frequency (29). Anifowoshe *et al.* (30) reported the distribu-

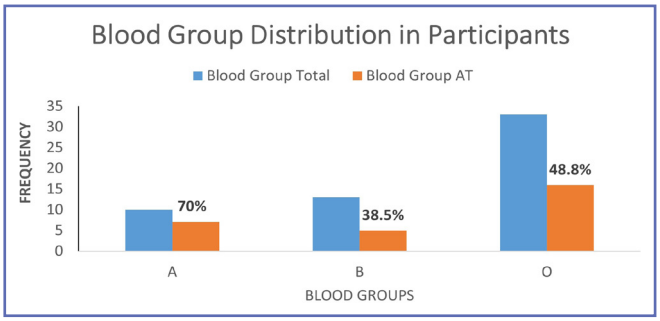

Figure 2. Distribution of ABO Blood Group in AT.

tion of the ABO blood groups in the Nigerian population with frequencies in the order O > A > B > AB as 52.93%, 22.77%, 20.64% and 3.66% respectively. This study was not an exception to the findings as blood group O showed the highest frequency and AB the least. In the randomized population of study however, there was no blood group AB both in cases and control which could be explained by the low percentage in the general population. Blood group A had the highest odd ratio with a value of 3.000, blood group B had the lowest odd ratio with a value of 0.625 at 95% confidence interval **table I**).

Table II shows the responses of the various blood groups to the outcome parameters. Improvement recorded in blood groups were measured regardless of the treatment received. At the end of 8 weeks of treatment, the outcome parameters based on the responses of the different blood groups to the treatment modalities are depicted in **table II**. Blood group O significantl improved in all the outcome variables regardless of the treatment modality received.

One-way Analysis of variance (ANOVA) showed there was no significant difference across treatment modalities received in all three groups. However, pre- and post intervention analysis within the groups showed that treatment with therapeutic ultrasound significantly improved almost all the outcome parameters (**table III**).

Table I. Blood group predisposition to Achilles tendinopathy.

Blood Group	Odd Ratio (95% CI)	P-value
A	3.000	0.051
B	0.625	0.758
O	0.941	0.967

*Significance at $p < 0.05$

Table II. Comparison of blood group responses to outcome parameters.

Parameters	Blood Group A	Blood Group B	Blood Group O	F-value	P-value
VAS					
Pre-Rx	5.33 ± 1.75	4.80 ± 1.92	5.38 ± 2.03	0.170	0.845
Post-Rx	1.17 ± 1.33	1.00 ± 1.73	1.63 ± 1.67	0.371	0.694
	t = 8.730, p ≤ 0.001*	**t = 6.517, p = 0.003***	**t = 5.724, p ≤ 0.001***		
ROM-DF					
Pre-Rx	19.67 ± 6.50	21.40 ± 6.54	17.63 ± 7.27	0.617	0.548
Post-Rx	23.50 ± 4.68	25.40 ± 10.92	21.31 ± 6.02	0.749	0.990
	t = - 4.053, p = 0.010*	**t = - 1.807, p = 0.145**	**t = - 3.405 p = 0.004***		
ROM-PF					
Pre -Rx	17.50 ± 4.23	17.50 ± 3.39		0.010	0.484
Post-Rx	23.17 ± 2.14	21.80 ± 5.22	17.25 ± 4.85	0.710	0.582
	t = - 2.688, p = 0.043*	**t = - 1.844, p = 0.139**	20.88 ± 4.18		
			t = - 3.896, p = 0.001*		
VISA-A					
Pre-Rx	61.67 ± 6.41	52.20 ± 12.21	61.81 ± 17.52	0.391	0.681
Post-Rx	85.00 ± 13.86	87.40 ± 19.09	76.38 ± 16.06	1.204	0.317
	t = - 4.295, p = 0.008*	**t = - 3.112, p = 0.036***	**t = - 2.471, p = 0.026***		
FAAM-ADL					
Pre-Rx	83.50 ± 13.38	79.60 ± 13.08	77.44 ± 13.53	0.448	0.644
Post-Rx	97.00 ± 4.98	94.00 ± 9.82	93.50 ± 7.81	0.458	0.638
	t = - 3.166 p = 0.025*	**t = - 4.330 p = 0.012***	**t = - 3.904 p = 0.001***		
FAAM-SP					
Pre-Rx	69.50 ± 20.35	70.60 ± 20.49	67.56 ± 23.52		
Post-Rx	88.67 ± 13.35	91.40 ± 13.41	83.13 ± 17.52	0.042	0.959
	t = - 3.153, p = 0.025*	**t = - 3.570, p = 0.023***	**t = - 2.167, p = 0.047***	0.603	0.555

Parameters	Blood Group A	Blood Group B	Blood Group O	F-value	P-value
SF12-PSC					
Pre-Rx	46.41 ± 5.93	45.12 ± 6.84	45.86 ± 5.99	0.060	0.942
Post-Rx	53.13 ± 3.14	54.44 ± 5.08	52.88 ± 4.36	0.256	0.776
	t = - 3.154 p = 0.025*	**t = - 5.423 p = 0.006***	**t = - 5.374 p = 0.001***		
SF12-MSC	49.04 ± 13.37	53.46 ± 11.21		0.677	0.518
Pre -Rx	57.42 ± 4.38	56.21 ± 4.57	47.23 ± 9.71	0.114	0.893
Post-Rx	**t = - 2.109, p = 0.089**	**t = - 0.639, p = 0.557**	56.18 ± 6.11		
			t = - 4.422, p = 0.001*		

*Significance at p < 0.05. VAS: Visual Analogue Scale; ROM: Range of Motion; DF: Dorsiflexion; PF: Plantarflexion; VISA-A: Victorian Institute for Sports Assessment-Achilles; FAAM: Foot and Ankle Ability Measure; ADL-SC: Activity of Daily Living-Subscale; SP-SC: Sport Subscale; SF-12: Short Form-12; PSC: Physical Subscale; MSC: Mental Subscale.

Table III. Comparison across treatment groups at baseline and 8th week.

Parameters	INTRASOUND	ULTRASOUND	ECCENTRIC Exs.	F-value	P-value
VAS					
Pre-Rx	6.11 ± 1.36	5.40 ± 2.07	4.22 ± 1.72	2.669	0.089
Post-Rx	1.89 ± 1.27	1.30 ± 1.42	1.00 ± 1.94	0.756	0.480
	t = 6.185 p = 0.001*	**t = 7.235 p = 0.001***	**t = 3.884 p = 0.005***		
ROM-DF					
Pre-Rx	16.33 ± 7.05	20.10 ± 6.19	19.22 ± 7.43	0.762	0.477
Post-Rx	20.67 ± 6.86	23.20 ± 7.61	23.22 ± 5.95	0.418	0.663
	t = - 7.211, p = 0.001*	**t = 1.849, p = 0.097**	**t = 3.098 p = 0.015***		
ROM-PF	15.00 ± 3.43	19.05 ± 4.66	17.39 ± 4.12		
Pre-Rx	21.00 ± 4.12	21.90 ± 3.87	23.22 ± 5.95	2.296	0.121
Post-Rx	**t = - 3.753, p = 0.006***	**t = - 2.543 p = 0.032***	**t = - 2.710 p = 0.027***	0.144	0.867
VISA-A					
Pre-Rx	61.56 ± 16.47	62.89 ± 15.73	62.89 ± 15.73	0.218	0.806
Post-Rx	75.33 ± 17.39	83.78 ± 18.44	83.78 ± 18.44	0.684	0.514
	t = - 2.166, p = 0.062	**t = - 4.458, p = 0.002***	**t = - 2.149, p = 0.064**		
FAAM-ADL					
Pre-Rx	74.89 ± 12.66	81.60 ± 12.05	81.56 ± 14.45	0.802	0.460
Post-Rx	94.00 ± 5.48	95.10 ± 6.92	93.78 ± 9.99	0.082	0.921
	t = - 5.065, p = 0.001*	**t = 4.573, p = 0.001***	**t = - 1.935, p = 0.089**		
FAAM-SP	62.67 ± 22.74	70.00 ± 23.99	70.33 ± 19.12	0.351	0.708
Pre-Rx	80.56 ± 15.20	91.30 ± 9.76	85.56 ± 20.76	1.116	0.343
Post-Rx	**t = - 2.102, p = 0.069**	**t = - 2.850, p = 0.019***	**t = - 1.923, p = 0.091**		
SF12-PSC					
Pre-Rx	45.32 ± 5.11	46.39 ± 6.48	45.59 ± 6.30	0.082	0.922
Post-Rx	52.16 ± 3.98	53.53 ± 3.90	53.50 ± 4.95	0.311	0.735
	t = - 3.713, p = 0.001*	**t = - 3.979 p = 0.003***	**t = - 6.879 p = 0.001***		
SF12-MSC	47.95 ± 11.20	49.83 ± 10.93	49.69 ± 11.57	0.080	0.923
Pre-Rx	56.41 ± 6.31	57.84 ± 4.77	55.82 ± 5.67	0.331	0.721
Post-Rx	**t = - 2.845, p = 0.022***	**t = - 2.498, p = 0.034***	**t = - 2.360, p = 0.046***		

*Significant at p < 0.05. VAS: Visual Analogue Scale; ROM: Range of Motion; DF: Dorsiflexion; PF: Plantarflexion; VISA-A: Victorian Institute for Sports Assessment-Achilles; FAAM: Foot and Ankle Ability Measure; ADL-SC: Activity of Daily Living-Subscale; SP-SC: Sport Subscale; SF-12: Short Form-12; PSC: Physical Subscale; MSC: Mental Subscale.

DISCUSSION

In the last 20 years, there has been increasing evidence that blood groups have a role to perform biologically and have been used as genetic markers in studies and correlations with various diseases (31). The ABO blood types have been shown to have significant ties to race and are known to play important roles in the susceptibility and outcome of numerous disease processes. Studies have identified certain ABO blood types as potential risk factors for a variety of disease processes including certain patterns of musculoskeletal injuries (32, 33). However, the findings of this study indicate that the ABO phenotype does not show significant predisposition to AT, although blood group A had a higher odd ratio while blood group B showed the lower odd in our study population. This agrees with the findings of Kujala *et al.* (34). However, this is at variance to the previous findings that blood group A or O was more at risk of Achilles tendon injury (7). Similarly, prior studies from other populations; Hungary, Finland and Scotland reported preponderance of blood group O to AT (35, 36). This variance between the previously reported Caucasian's data and our African population might be important racial factors in the prevention and management of AT in different population groups. Therefore, comparative study with larger study population may be imperative to determine the blood group that is most at risk of AT especially among black Africans.

Interestingly, we observed improved outcome of all variable parameters in blood group O regardless of the modality used. This suggests that footballers with blood group O who present with Achilles tendinopathy may be effectively managed with any of the selected physiotherapy approaches. Blood group A in this study also appeared to improve in most of the considered parameters but not in mental subscale of quality of life (QoL). Blood group B on the other hand had the weakest response as parameters like range of motion (ROM) for both dorsiflexion and plantarflexion in addition to mental subscale of the QoL were not improved. The reason for this differential responses need to be elucidated in a larger cohort study. However, this study provides evidence of differential responses to management by the different Blood group genotypes with potential for new management strategies. We described the efficacy of all the three interventional strategies in the treatment of AT as Pre and Post intervention comparison within each group showed improvement in most of the treatment outcome parameters. However, we observed differential response outcome of the treatment modalities in respect of their blood group phenotype.

Therapeutic ultrasound (TU) appears to be the most effective for the management of Achilles tendinopathy because there was significant improvement in all the outcome parameters (VAS, ROM-PF, VISA-A, FAAM, SF-12) except the ankle dorsiflexion. This ultimately suggests that TU may be effective in the management of AT. *In vitro* studies have demonstrated that ultrasound can stimulate cell migration, proliferation, and collagen synthesis of tendon cells that may benefit tendon healing (37). Therapeutic ultrasound has been previously reported to reduce the swelling in the acute inflammatory phase of soft-tissue injuries, relieve pain, and increase function in patients with chronic tendon injuries and may enhance tendon healing (38). These positive effects of therapeutic ultrasound on tendon healing revealed by *in vivo* and *in vitro* studies may be responsible for the physiologic responses to this physical modality.

Pain (VAS) was most significantly improved in the Intrasound therapy (IST) group and the ankle range of motion (ROM) for dorsiflexion and plantarflexion were also improved. The overall quality of life (QoL) improved in both domains after 8 weeks. It was however observed that there was no improvement in severity of injury (VISA-A) in this group. Furthermore, there was 50% improvement in the foot activity (FAAM) of players who received IST as only the activity of daily living (ADL) subscale was improved while the Sports subscale was not improved. Intrasound therapy may be able to modulate tenocyte activity at the cellular level as reported by previous studies since tenocytes play a key role in tendon repair because they lay down the extracellular matrix and the strength of the repaired tissue is attributed to their population at the site of injury (13, 39, 40). However, the duration of management for a more satisfactory outcome requires further studies.

Frizziero *et al.* (41) suggested that more RCTs are needed to compare the existing protocols and establish the possible relative effectiveness of different dosages of EE. Eccentric exercises (EE) improved pain (VAS) experience, ROM for dorsiflexion and plantarflexion and overall QoL significantly in this study. Eccentric exercises have been associated with clinical benefit in improving pain, tendon structure and function and modulating muscle control and tendon loading in patients with tendinopathy (16, 42). However, there was no improvement in foot activity (FAAM) and severity (VISA-A) of injury. VISA-A measures pain and flexibility during sporting activities while FAAM emphasizes functionality (in both sport activity and ADL). The lack of improvement

in functionality and flexibility of the tendon among the participants in this group may be because of strain for an extended period as players continued in their sport activities after treatment. The best way to approach this may be for the players not to engage in any form of sport activity for best results. A study reported that the severity (VISA-A) of Achilles tendinopathy improved when EE was combined with Laser therapy (43). In a prospective cohort study of individuals with symptomatic Achilles tendinopathy, ultrasonographic tendon structure improved following eccentric loading, and normalized to values of a matched control group after 24 weeks (16, 44). However, another systematic review reported strong evidence that disagrees with structural changes as an explanation for the improvement of tendinopathy with exercise, challenging the belief that improving the structure will automatically improve function (16, 45). Considering the t-value (t = - 6.879, - 2.360) however, eccentric exercises gave the best result in the improvement of the QoL. This agrees with the findings of De Vos *et al.* (46), who reported that patient satisfaction improved by 63% in the EE only group compared to other groups and Mafi *et al*. (4), who reported satisfaction and return to activity significantly by 82% in the EE group.

CONCLUSIONS

The study demonstrated that differential responses to treatment of AT is influenced by ABO blood group phenotypic inheritance with Blood group O recording improved treatment outcome regardless of the interventional modality used. Furthermore, all the 3 physiotherapy modalities used; Intrasound therapy, Eccentric exercises and therapeutic ultrasound were effective for the management of Achilles tendinopathy. However, differential responses were recorded irrespective of the blood phenotype. Therefore, a differential treatment algorithm of combined ABO phenotypes and selected modality based on subject specific symptom needs may allow precision rehabilitation and improve management strategy.

FUNDINGS

None.

DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

OIO, AAI, AO: conceptualization, study design. OIO, AAI, AO: manuscript preparation. OIO, SAM, AO: clinical studies. OIO, AAI, SAM, AO: intellectual content. OIO, AAI, SAM: data acquisition.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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