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Randomized, Double-Blind, Double-Masked, Parallel Group Clinical Study to Compare the Effectiveness of Diclofenac Potassium 150 mg, LP OD, vs Diclofenac Potassium 50 mg, TID, Three Times a Day, in Knee Osteoarthritis

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Abstract

Background: Osteoarthritis is a chronic disease associated with pain, inflammation, stiffness and synovial effusion, with progressive functional limitation, compromising quality of life. It progressively leads to loss or decrease in joint function. Pharmacological and non-pharmacological therapy seeks symptomatic management, complicated by a lack of adherence. After acetaminophen, non-steroidal anti-inflammatory drugs such as diclofenac are the most widely used medications. **Objectives:** The primary objective compared the analgesic effect of diclofenac 150 mg once daily vs. 50 mg three times daily in patients with knee osteoarthritis. The secondary objective assessed changes in quality of life. **Method:** One group received diclofenac 150 mg OD with placebo TTD. Another group received placebo OD and 50 mg active diclofenac (reference) TTD, both for 30 days. The evaluation of pain was carried out by a visual analog scale (VAS), at the beginning, 2, 3, 4, 15 and 30 days, quality of life (the WOMAC scale) and adverse effects, at 15 and 30 days. **Results:** Pain decreased significantly on days 15 and 30, compared to day 0, in both groups, without differences between groups. The total results in the WOMAC scale showed a very marked improvement at 15 and 30 days, without differences between groups. The most frequent adverse effects were constipation 6% in the reference group, and gastric discomfort 30.3% in the reference group vs 28.1%, in the Test group. **Conclusions:** Prolonged-release

diclofenac 150 mg OD is as effective as diclofenac 50 mg TID for the treatment of patients with knee osteoarthritis.

Keywords

Knee Osteoarthritis, Diclofenac, Visual Analog Scale, WOMAC Scale

1. Introduction

Osteoarthritis is a chronic disease where cartilage damage and inflammation of the synovial membrane combine with sudden crises of pain, inflammation, stiffness and synovial effusion. It is the most common of joint diseases, which progressively leads to a loss or decrease in joint function. This entity can affect 85% of the 70-year-old population and 20% of the general population [1].

In this pathology, pain and inflammation converge as main symptoms; its therapy is focused on pharmacological and non-pharmacological treatments, aimed at symptomatic management [1].

The aging of the population, and obesity, are the greatest risk factors for osteoarthritis, which gradually increases after the age of 30, and can reach up to 80% around the age of 65 and even 95% at older ages [2].

It occurs primarily in weight-bearing joints, such as the hip and knee, because they are sites exposed to joint overload, trauma, biomechanical alterations, or infection, not to mention the important role of heredity [3].

It presents with pain and progressive functional limitation; it constitutes, in addition to a usual reason for medical consultation with the consequent high costs for its care and treatment, a frequent cause of deterioration in the quality of life (QoL) [4].

There are studies that show that, in people with symptomatic osteoarthritis, up to 50% of them suffer some degree of disability [5].

After acetaminophen, nonsteroidal anti-inflammatory analgesics (NSAIDs) are the most frequently used medications in patients with osteoarthritis [6].

In order to assess the safety and efficacy of diclofenac, a Network Meta-Analysis (NMA) was performed in patients with osteoarthritis [7], in which randomized controlled trials (RCTs) of diclofenac, lasting at least 4 weeks for the treatment of osteoarthritis (OA), were identified from 'legacy' studies conducted by Novartis, but not published in a peer-reviewed journal or included in any previous conjoint analysis. Nineteen RCTs (5030 patients) were included, 18 of which were double-blind and one single blind. All studies were conducted before cyclooxygenase 2 (COX-2) inhibitors were marketed. The data allowed a robust comparison of efficacy between diclofenac and ibuprofen. Diclofenac 150 mg/day was more effective than ibuprofen 1200 mg/day and probably had favorable results for pain relief compared to ibuprofen 2400 mg/day [7].

Diclofenac has a systemic absorption directly proportional to the dose within the range of 25 to 150 mg. Multiple-dose administration produces absorption

characteristics that are similar to those observed after a single administration [8] [9] [10] [11] [12]. The absolute bioavailability of 90 ± 11.6% after oral administration of a single 50-mg dose of $^{[14C]}$Diclofenac suggests that diclofenac undergoes first-pass metabolism with approximately 60% of the ingested dose reaching the systemic circulation [10] [11] [12].

The control of many chronic diseases, such as osteoarthritis, in which it is necessary to make changes in lifestyle, diet, or permanent pharmacological treatment, is sometimes difficult to achieve [13].

Among the causes identified that can influence the lack of adherence, it is worth mentioning the complexity of the treatment (several doses per day, difficult schedules to comply with), and the fear of side effects [14].

The advancement of new galenic formulation techniques has allowed the development of pharmaceutical products, which, while maintaining a known range of effectiveness, offer advantages in relation to conventional forms, such as less frequent administration, as occurs in extended-release forms.

In Venezuela, LETI Group, through its company Biocontrolled, has developed a new formulation of 150 mg of potassium diclofenac, which releases 50 mg in the first hour and 100 mg delayed (dual action), with the intention of accelerating the onset of pain relief (**Figure 1**).

Taking this into consideration, this study is carried out in order to compare the efficacy of diclofenac potassium LP 150 mg, administered once a day, versus diclofenac potassium 50 mg immediate-release tablets, TID, to evaluate its efficacy in pain and quality of life in patients with knee osteoarthritis.

2. Materials and Methods

A randomized, double-blind, double-dummy, parallel group study was carried out.

The patients signed the informed consent to participate in it, and the protocol was approved by an Institutional Ethics Committee and by the country's Health Authorities.

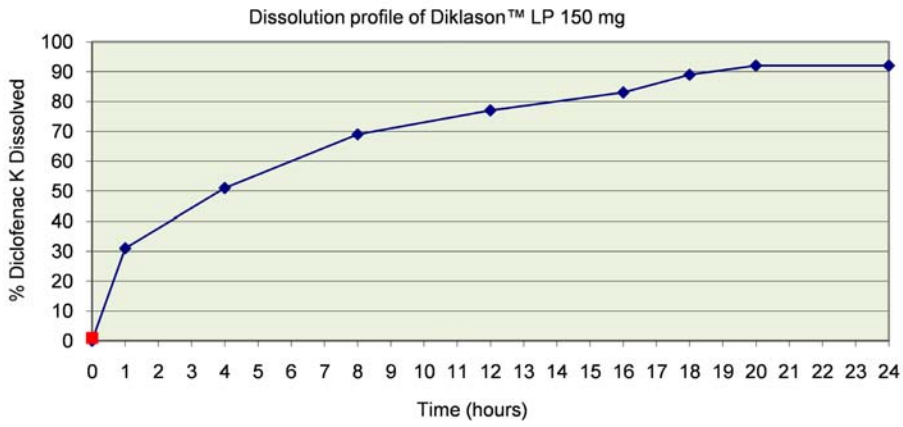

Figure 1. Dissolution profile of prolonged release diclofenac.

2.1. Inclusion Criteria

1) Patients of both sexes diagnosed with osteoarthritis of the knee were admitted according to the criteria of the American Society of Rheumatology [15].

2) Knee pain and three or more of the following findings:

a) More than 50 years;

b) Morning stiffness less than 30 minutes;

c) Crepitation, bone pressure pain, bone hypertrophy, lack of joint heat.

3) Class I to class III radiological lesion (Radiological Classification of Osteoarthritis, Kellgren and Lawrence) [16].

2.2. Exclusion Criteria

a) Patients with kidney disorders, liver function disorders or coagulation disorders;

b) Uncontrolled arterial hypertension, poorly controlled diabetes, patients with MI or cerebral stroke, 6 months prior to the start of the investigation;

c) Knee replacement or other intra-articular surgery, arthrocentesis within three months prior to trial;

d) Diagnosis of fibromyalgia, rheumatoid arthritis, ankylosing spondylitis, active gout, or other inflammatory joint disorders other than osteoarthritis;

e) Patients with active gastrointestinal disease: peptic ulcer disease, inflammatory bowel disease (Crohn's disease or ulcerative colitis) or any other disease that, in the investigator's opinion, discourages the use of NSAIDs;

f) Patients with a history of malignant disease;

g) Patients who had received, in the 8 weeks prior to the study, treatment with I. M. or intra-articular steroids, or those who have received intra-articular Hyaluronic Acid;

h) Patients who have received analgesic therapy 24 hours prior to study entry, for short-acting analgesics, and 7 days prior for long-acting analgesics;

i) Patients with hypersensitivity or allergy to NSAIDs;

j) Proven pregnancy, or lactating women.

2.3. Evaluations

The primary endpoint was pain at baseline (baseline), 2, 3, 4, 5 days, and 30 days. The secondary objectives were to evaluate the quality of life through the WOMAC scale at 0, 15 and 30 days.

The evaluation of pain intensity (Pain Intensity/PI) was performed using the Visual Analog Pain Scale (VAS: 0 - 10), in the two study groups (Group A or B), where 0 is the total absence of pain and 10 is the maximum possible pain. It was measured immediately before the administration of study drugs (time 0, baseline) and at 15 and 30 days. The evaluation of quality of life was evaluated using the WOMAC questionnaire, in the same periods of time [17] [18].

Patients received one of two blinded clinical supply boxes (treatments) during the study: a) a group with diclofenac potassium 150 mg PL OD (active) and dic-

lofenac potassium 50 mg TID (placebo); b) diclofenac potassium 50 mg TID (active) and diclofenac potassium 150 mg LP (placebo).

2.4. Statistic Method

The sample size calculation was performed, establishing that to detect a difference of 1.2 on the VAS scale with an accuracy of 99%, a minimum of 30 patients per group was needed.

The VAS scale and the WOMAC scale were analyzed within the group (before and after) using the Wilcoxon Rank scale and between groups using the McWhitney Rank scale.

3. Results

The groups were similar at the beginning of treatment in age, weight, height, BMI, duration of osteoarthritis and there were fewer severe cases of left knee osteoarthritis in the test group. (Table 1, Table 2)

There was a significant decrease in pain measured by VAS 0 - 10 in both groups, with no difference between them at any time of evaluation during the treatment period. (Table 3, Figure 2)

Table 1. Description of the evaluated population.

Parameter	Reference (n = 33)	Test (n = 32)	P between groups
Sex f/m	28/5	22/10	0.00
Menopausal women	76%	60%	0.00
Age	61.5 ± 7.1	58.4 ± 7.3	0.09
Duration of osteoarthritis (years)	8.7 ± 10.4	7.3 ± 7.5	0.54
Weight	76.5 ± 14.8	78.8 ± 12.6	0.65
Height	1.6 ± 0.1	1.6 ± 0.1	0.46
IMC	30.2 ± 6.4	32.9 ± 16.5	0.39
SBP	127.6 ± 7.5	127.9 ± 7.8	0.86
DBP	79.5 ± 5.1	82.4 ± 8.8	0.11
Background	Arterial Hypertension 79% Diabetes 9% Cervical osteoarthritis 3% GI Reflux 3%	Arterial Hypertension 75 %	

Table 2. Affected knee.

	Left			Right		
Radiological class	I	II	III	I	II	III
Reference	29.2%	50.0%	20.8%	23.3%	63.3%	13.3%
Test	44.0%	52%	4.0%	40.91%	54.5%	4.6%
P				0.00	0.84	0.86

Table 3. Evolution of pain.

VAS 0-10						
VAS	**Base**	**Day 2**	**Day 3**	**Day 4**	**Day 15**	**Day 30**
Reference	6.17 ± 2.48	4.05 ± 2.41	3.00 ± 1.97	2.70 ± 2.04	2.55 ± 2.28	1.92 ± 2.72
P from base		0.00	0.00	0.00	0.00	0.00
Test	5.95 ± 2.08	4.10 ± 2.15	2.95 ± 1.68	2.50 ± 1.82	2.29 ± 1.97	1.55 ± 1.99
P from base		0.00	0.00	0.00	0.00	0.00
P between groups	0.709	0.754	0.861	0.805	0.854	0.954

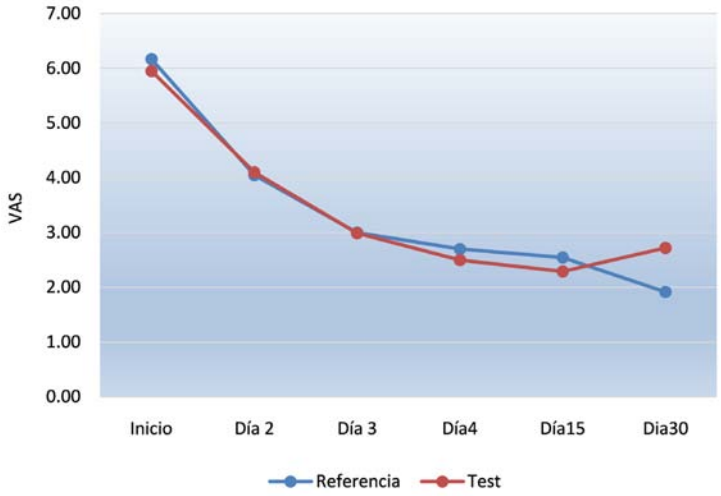

Figure 2. Evolution of the VAS.

No difference was observed in the parameters of the WOMAC scale at any time, except for functional disability, which was statistically lower in the test at the beginning and at the end of treatment. (**Table 4** and **Figure 3**)

There was a decrease in pain at 15 and 30 days of the treatment period without differences between the groups. (**Figure 4**)

There was a statistically significant and clinically important decrease in both groups in WOMAC Global Changes throughout the evaluation period. (**Figure 5**)

The most frequent adverse effects were gastric discomfort 30.3% vs 28.1%, reference vs Test (chi^2 0.53), constipation 6% in the reference group.

The efficacy data on pain, evaluated by VAS, were as follows, for the reference product: baseline: 6.17 ± 2.48, day 3: 2.70 ± 2.04, day 15: 2.55 ± 2.28, day 30: 1.92 ± 2.72. For the study drug, diclofenac LP, the values were as follows: basal pain: 5.95 ± 2.08, at day 3: 2.50 ± 1.82, at day 15: 2.29 ± 1.97 and at day 30: 1.55 ± 1.99. In both groups, there was evidence of a significant analgesic effect of the drug, reaching a decrease in the pain scale of 50% on day three of the study (**Figure 2**).

Changes in disability, using the WOMAC scale, could not be compared due to a statistically significant difference at baseline between the two groups. However, when the total results are observed on the WOMAC scale, a very marked improvement can be seen at 15 and 30 days, with no difference between groups.

Table 4. Evolution of the WOMAC results.

WOMAC	Reference	Test	P Intra group -anterior period Ref.	P Intra group -compared to base Ref.	P Intra group -anterior period Test	P Intra group -compared to base Test	P Between Groups
Initial disability	30.18 ± 12.41	25.32 ± 11.19					0.054
Disability 15 days	13.24 ± 11.69	9.90 ± 9.19	0.000	0.000	0.00	0.00	0.200
Disability 30 days	11.33 ± 11.56	5.63 ± 7.47	0.053	0.000	0.00	0.00	0.024
Initial pain	9.09 ± 4.27	7.81 ± 3.89					0.168
Pain 15 days	3.30 ± 2.94	2.58 ± 2.74	0.000	0.000	0.00	0.00	0.228
Pain 30 days	3.07 ± 3.38	2.36 ± 3.26	0.583	0.000	0.65	0.00	0.258
Initial rigidity	3.64 ± 1.83	3.48 ± 1.61					0.500
Rigidity 15 days	1.27 ± 1.31	1.42 ± 1.65	0.000	0.000	0.00	0.00	0.966
Rigidity 30 days	1.14 ± 1.68	1.08 ± 1.26	0.429	0.000	0.084	0.00	0.887
Initial total score	42.91 ± 17.09	36.61 ± 15.81					0.067
Total score 15 days	17.82 ± 15.30	13.90 ± 12.58	0.000	0.000	0.00	0.00	0.141
Total score 30 days	14.00 ± 15.95	7.94 ± 9.80	0.017	0.000	0.01	0.00	0.097

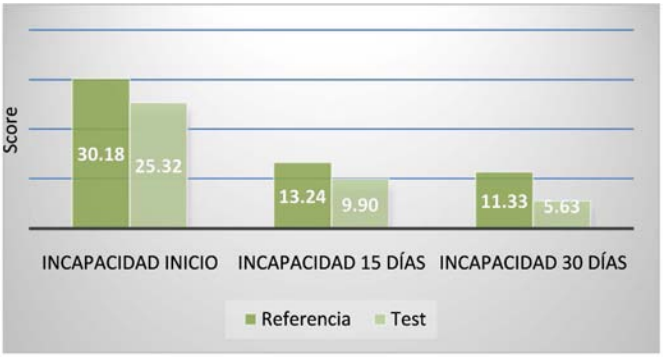

Figure 3. Evolution of WOMAC results: functional disability.

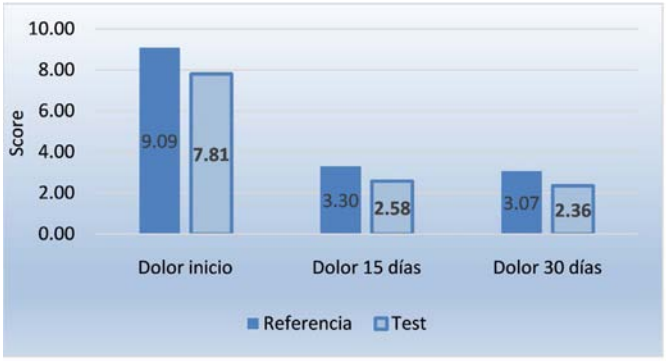

Figure 4. Evolution of WOMAC pain results.

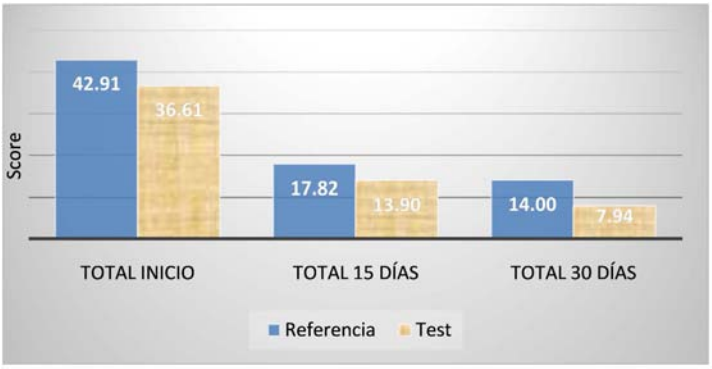

Figure 5. Evolution of the results of the total WOMAC score.

4. Discussion

Osteoarthritis is a chronic disease where cartilage damage and inflammation of the synovial membrane combine with sudden crises of pain, inflammation, stiffness and synovial effusion. This entity can affect 85% of the 70-year-old population and 20% of the general population. [1] It is a pathology which requires chronic treatment, which makes compliance difficult, especially in elderly and polymedicated patients.

The pain and progressive functional limitation constitute a usual reason for medical consultation and frequently causes deterioration in quality of life (QoL) [4]. Its therapy is focused on pharmacological (acetaminophen and NSAIDs) and non-pharmacological treatments, aimed at symptomatic management [1].

The pharmacological treatment of pain in osteoarthritis constitutes a very important challenge for the physician with a great impact on motor function and the consequent disability and deterioration of quality of life. [19] [20].

The control of many chronic diseases, such as osteoarthritis, in which it is necessary to make changes in lifestyle, diet, or permanent pharmacological treatment, is sometimes difficult to achieve. On the other hand, the specific adherence to the pharmacological treatment in this type of diseases is frequently not adequate. In a study published in 2019, carried out in Spain, they evaluated adherence in chronic diseases and the results showed that, in Spanish chronic patients, where approximately three out of four have more than one disease and receive chronic treatments, close to half have poor adherence to treatment. [13]

Reducing the number of daily doses can increase compliance with treatment and improvement of symptoms. A multicenter, randomized, open-label, two-way crossover, phase IV study is the first to evaluate patient preference with a sustained-release paracetamol tablet formulation designed for TID dosing. Compared with standard paracetamol tablets dosed four times daily, the sustained-release formulation was preferred in a 2:1 ratio, provided better overall joint pain relief, resulted in higher levels of satisfaction in subjects with OA of the knee and has the potential to improve patient compliance and, therefore, pain control. [21]

This study allows us to see how the administration of prolonged-release dic-

lofenac potassium at 150 mg, taken once a day, has the same analgesic efficacy in patients with knee osteoarthritis as a dose of diclofenac 50 mg three times a day. Based on this evidence, once a day is much more comfortable for the patient, allowing better adherence to treatment.

Regarding safety, in general, both treatments were well tolerated. The most frequent adverse effects were gastric discomfort 30.3% vs 28.1%, reference vs Test, respectively (chi^2 0.53) and constipation 6% in the reference group.

5. Conclusion

Extended-release diclofenac 150 mg is an effective therapy for the treatment of patients with knee osteoarthritis. Its characteristics and its bioavailability allow a single administration per day vs. the conventional formulation three times a day, with similar analgesic efficacy, which will facilitate better adherence to treatment and will allow better clinical outcomes.

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Conflicts of Interest

Dr. R. Tellez Mendez, Dr L. Cabeza and Dr. J.A. Herrera reveal no conflict of interest. Dr. Maria González Yibirín and Dr. David Rincón Matute work at Laboratorios Leti S.A.V.

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Treatment of Peripheral Neuropathy: Combination Therapy Using LED Light, Extracorporeal Shockwave Therapy, Platelet Rich Plasma, and an Oral Dietary Supplement

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Abstract

Objectives: Peripheral neuropathy (PN) is a significant contributor to disability in the elderly. It is also one of the most prevalent complications of type 2 diabetes, prediabetes and metabolic syndrome. PN is commonly associated with pain, numbness, tingling, burning, and cramping in the feet and legs. Current treatment options are limited to controlling pain, seizures and use of antidepressant medications. These treatments have undesirable side effects and don't stop PN progression. Here we utilized a combination of individual-specific modalities to improve local circulation and relieve PN symptoms. **Methods:** We conducted an open-label, multicenter pilot trial with 34 subjects (19 males and 15 females ranging from 40 - 85 years of age). All of the participants were diagnosed with peripheral neuropathy and had bilateral symptoms in their feet, and many reported the same symptoms (pain, numbness, tingling, burning, and cramping) in their lower legs. The duration of symptoms ranged from four months to over six years. On Day 0, subjects were given a 90-day supply of the oral supplement with dosing instructions and a LED light therapy device. They also received three platelet-rich plasma (PRP) injections in their lower extremities. Subjects also received an extracorporeal shockwave therapy (ESWT) treatment for each foot and subsequently twice per week for the first six weeks, then once weekly for the duration of the study. Subjects filled out the Brief Pain Index (BPI) at weekly intervals. On Day 90, subjects completed the Patient Global Impression of Change (PGIC) survey. **Results:** There were significant responses to pain, as evidenced by BPI scores at weeks 8, 9, 10 and 11 (p = 0.02, 0.01, 0.02, and

0.003, respectively). Analysis of the final day PGIC survey showed a favorable outcome for 73% of participants (p = 0.003), with the majority reporting Very Much Improved. **Conclusions:** By utilizing a multi-modality treatment protocol that includes PRP, LED light therapy, ESWT and an oral dietary supplement, we observed significant reductions in BPI scores. Quality of life and their overall impression of change (PGIC) were significantly improved, and there were no significant side effects.

Keywords

Peripheral Neuropathy, LED Light Therapy Device, Extracorporeal Shockwave Therapy, PRP Injections, Oral Supplement, Multi-Modality Treatment, Pain

1. Introduction

Peripheral neuropathy (PN) is a significant contributor to disability in the elderly and is one of the most prevalent complications associated with type 2 diabetes (T2D), prediabetes, and metabolic syndrome [1]. PN usually affects the feet and legs first, but can also affect the fingers and hands. It is commonly associated with pain, numbness, tingling, burning, and cramping. Although the most prevalent causes of PN are T2D, prediabetes and metabolic syndrome, the exact cause of peripheral neuropathy remains unknown. It has often been postulated that poor circulation, which can be secondary to the weakening of the walls of capillaries caused by elevated blood sugar, plays an important role in the pathogenesis of PN [2].

One approach to PN treatment has involved the use of infrared and red light LED therapy, and such devices are FDA approved and are used to increase local circulation and decrease pain [3]. This effect is believed to be accomplished by dilating vessels to increase local blood circulation and reducing pain by decreasing inflammation.

Platelet-rich plasma (PRP) injections have been shown to promote nerve regeneration [4]. PRP injections act as fillers of nerve conduits or vein-muscle grafts to bridge the nerve gaps after the nerves have been severed by trauma. PRP infiltrates the stumps of the nerve perineurally as well as intraneurally. Moreover, PRP can also act as a scaffold to bridge or wrap nerve stumps [4]. In T2D patients PRP treatments for neuropathy have been shown to decrease neuropathic pain and numbness while increasing nerve function [5]. A recent study also showed promising results by presenting evidence of nerve regeneration of damaged peripheral nerves [6].

Extracorporeal shockwave therapy (ESWT) has also been used to protect nerves against PN development. A study by Seabaugh showed that ESWT, when applied after PRP injections, caused the release of growth factors from platelets and showed beneficial responses. The biological effects of ESWT include: improved vascularization, the local release of growth factors, and local anti-inflam-

matory effects. ESWT has been shown to promote axonal regeneration [7].

Finally, there is evidence that nutritional supplementation can help support damaged peripheral nerves [8]. The oral supplement used in this study consisted of alpha lipoic acid (ALA), methyl B-12, folate, and other components. ALA has been shown to ease the numbness, burning, and pain associated with peripheral neuropathy [9]. It is a powerful antioxidant that improves blood flow and glutathione levels. Methyl B-12 is one of the most critical nutrients for proper nerve function. This B vitamin helps repair and maintain healthy myelin and is associated with decreased PN [10]. Folate has been shown to significantly improve endothelial cell function and normalize blood flow to nerves. Improved nerve conduction velocities are beneficial in treating diabetic polyneuropathy [11]. However, no studies have assessed the efficacy of specific multi-modality treatment of PN. The effects of different individual treatments have been studied for PN, but have not been used together. Our pilot study sought evidence of the benefit from using a combination of modalities to treat PN.

2. Subjects and Methods

We conducted an independent IRB-approved, open-label, multicenter pilot trial with a total enrollment of 39 subjects with a diagnosis (dx) of PN. The clinics that participated in this study were all located in California (cities of Corona, Placentia, and Gardenia). The study recruitment began on August 8, 2021 and final subject finished treatment on July 16, 2022. Before entering the trial each participant signed an Informed Consent document. Five of these subjects were disqualified for failure to comply with home and office treatment schedules. Thirty-four subjects (average age = 67, range 40 - 85 years) completed the study. Both males (n = 20) and females (n = 14) were included in the study. Thirty-one of the participants were diagnosed with T2D with diabetic neuropathy. Three participants presented with prediabetes (total patients, n = 34).

Participants were excluded from the study if they were taking immunosuppressive drugs, they were pregnant or lactating, were outside the age range, had cognitive impairment, or were allergic to any ingredient used in the study supplement. Also excluded were subjects with active cancer(s), HIV, foot ulceration(s), thrombocytopenia, hemodynamic instability, septicemia, septic arthritis, overlying cellulitis, or adjacent osteomyelitis, platelet dysfunction syndrome, high blood pressure (greater than 180/100), fractures or were taking NSAIDS drugs or steroids. This study was conducted per all applicable regulations, including the current U.S. Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, and 56, and Title 45, Part 164. Regulations and guidelines were also observed within the ethical principles described in the current revision of the Declaration of Helsinki.

After the subjects were recruited according to the inclusionary criteria, participants underwent a physical and neurological exam to confirm the diagnosis of PN. The neurological exam included: a pinprick sensation test to the dorsal

and plantar surface of the feet, a 128-Hz tuning fork placement at the base of the great toenail, a Semmes-Weinstein 5.07g monofilament test to the dorsal and plantar surface of the feet, heat perception, deep tendon reflexes tests, muscle strength grading, and gait tests. Participants were scheduled to meet with the study monitor at each clinic location to review and sign the Informed Consent Document.

On Day 0, subjects were given a 90-day supply of the Bedrock Bioscience Nerve Support supplement with dosing instructions and one Bedrock Bioscience LED Light Therapy Device. The Bedrock Bioscience Nerve Support supplement is a vitamin supplement containing ALA, B-12, B-1, B-6, and folate. Bedrock Bioscience LED Light Therapy Device has 60 red light LEDs (660 nm wavelength) and 60 infrared LEDs (880 nm wavelength). Participants were instructed to take two capsules of the Bedrock Bioscience Nerve Support supplement twice daily and use the Bedrock Bioscience LED Light Therapy for twenty minutes in the morning and twenty minutes in the evening throughout the study. Participants were monitored for compliance at home with phone calls, emails, and during office visits. They were also directed to fill out the medical intake form, including the Brief Pain Inventory (BPI) survey on Day 0 and once weekly for 90 days. They also received three PRP injections in both lower extremities on Day 0. Subjects also started receiving an ESWT treatment to each foot on Day 0 and twice per week for the first six weeks, then once weekly for the 90 days. On Day 90, participants were asked to answer questions on an Exit Survey, the Patient Global Impression of Change (PGIC). The subjects were also assessed for side effects and monitored for compliance via phone calls (**Table 1**). The primary endpoints were assessment of the Brief Pain Inventory survey [12], the PGIC survey and their statistical analyses [13] [14]. At the end of the study participants who completed the study were offered compensation.

3. Statistical Analysis

The BPI survey provided most of the data that were analyzed. Descriptive statistics were calculated for each variable, and the frequency was calculated for the categorical variables. The BPI survey was completed throughout the study (12 times), and the pairwise comparisons in BPI scores at each survey were assessed against Baseline. Thirty-four subjects completed the exit survey. The proportion of participants who responded "Moderately Better" and "Very Much Better" was obtained, and a 95% Confidence Limit (95% CL) was calculated.

4. Results

All 34 participants read, understood, and signed the Informed Consent document and completed the BPI and PGIC surveys. Temporary discomfort during ESWT and minor pain during PRP injections were the only minor side effects reported. There were no significant side effects reported. We found a decreasing trend starting at the survey taken on weeks 8 through 11 compared to the BPI

Table 1. Study flow chart summary.

STUDY	Day 0	Week											
		1	2	3	4	5	6	7	8	9	10	11	12
Physical Exam	X												
Medical Intake	X												
Diagnosis	X												
Informed Cons.	X												
LED light therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral supplement	X	X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT													
PRP Injections	X												
TREATMENT													
LED light therapy	2X/day	X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT													
Oral Supplement	2X/day	X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT													
ESWT Wave	X	X	X	X	X	X	X	X	X	X	X	X	X
SURVEYS													
BPI	X	X	X	X	X	X	X	X	X	X	X	X	X
FINAL EXIT													
PGIC													X
Compensation													X

score at the baseline using the Bonferroni-Holm multiple comparison adjustment methods (an unadjusted p-value of 0.003) (Table 2). The estimated means and 95% confidence limits of BPI scores at each survey taken time were obtained and used to construct a figure (Figure 1).

Of the 34 participants, all thirty-four completed the PGIC Exit survey. Figure 2 shows the proportions of patients in each response category of the PGIC Exit survey. Based on the data, the observed proportion of participants who stated "moderately better" and "very much improved" at the end of the study was 73% (95% CL 0.5564, 0.8712). This was statistically significantly higher than the theoretical threshold of 0.5, with a p-value of 0.003.

5. Discussion

The study's objective was to assess whether a multi-modality treatment protocol effectively reduced the pain and other symptoms of PN. The authors postulated from previous clinical observations that a multi-modality approach could have a synergistic effect that would be more beneficial in reducing PN symptoms than

Table 2. The estimated mean differences, p-values and 95% CLs of the BPI score in pairwise comparisons between each time point and at the baseline.

Pairwise Comparison (Time point vs. Baseline)	Time point (week)	The estimated mean difference & 95% CL	The Unadjusted p-value
1 vs. 0	1	−3.79, (−8.17, 0.59)	0.09
2 vs. 0	2	−2.5, (−8.2, 3.2)	0.39
3 vs. 0	3	−1.88, (−8.47, 4.71)	0.57
4 vs. 0	4	−3.05, (−9.41, 3.3)	0.34
5 vs. 0	5	−4.09, (−10.04, 1.85)	0.17
6 vs. 0	6	−1.92, (−8.32, 4.47)	0.55
7 vs. 0	7	−3.7, (−9.75, 2.36)	0.23
8 vs. 0	8	−7.36, (−13.68, −1.03)	0.02
9 vs. 0	9	−7.46, (−13.7, −1.22)	0.01
10 vs. 0	10	−7.92, (−14.33, −1.5)	0.01
11 vs. 0	11	−9.13, (−15.17, −3.09)	0.003

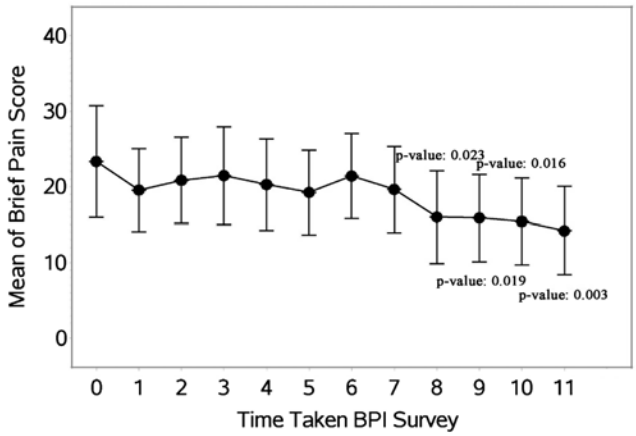

Figure 1. The estimated mean and 95% Confidence limit (95% CL) of the BPI score each time (weeks) the survey was taken.

the use of any one modality alone. The Bedrock Bioscience LED Light Therapy device has been used for over four years in various clinics (over 60,000 treatments). This treatment has been well tolerated. LEDs do not contain ultraviolet rays and have been proven safe for regular use [15]. ESWT has also been proven safe and effective for multiple musculoskeletal conditions. Various clinics have provided over 30,000 ESWT treatments with only transient mild discomfort reported. Other research reported similar results (Wang *et al.* [16]), showing that ESWT effectively reduced foot ulcers and painful diabetic neuropathy. Snyder *et al.* [17] suggested that the ESWT should be used in combination therapies where other therapies alone were not sufficient enough to control diabetic NP. It was shown in their studies that combination therapies with ESWT resulted in a marked reduction in PN pain.

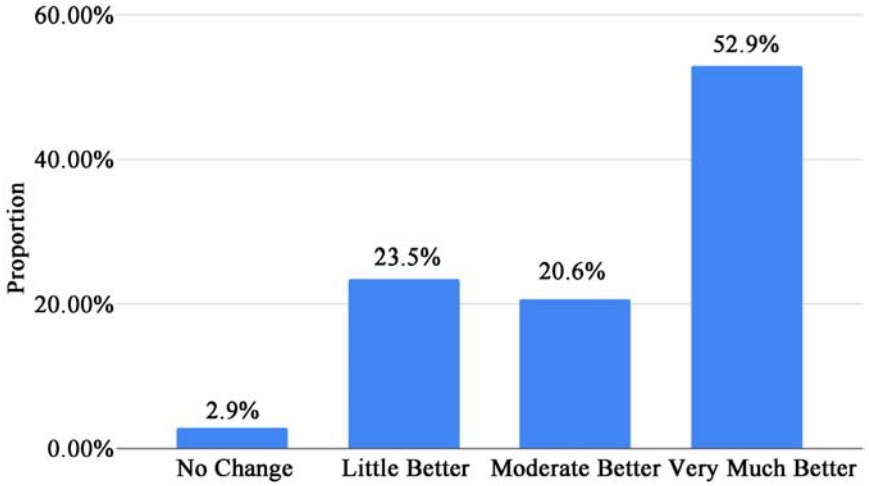

Figure 2. The proportions of patients in each response category of the PGIC Exit survey ($n = 34$, $p < 0.003$).

The Bedrock Bioscience Nerve Support supplement has been utilized in over 2 million doses and contains alpha lipoic acid, B-12, B-1, B-6, and folate. In these patients adverse reactions (ARs) have occurred in less than fifty patients (<0.00003%), and reported ARs were limited to upset stomachs and acid reflux. This is supported by the fact that a recent RCT study showed that a decrease in pain could be achieved safely and effectively compared to other analgesics by supplementing with ALA. There were no side effects reported in the same RCT study [18]. Another study by Boghdadi *et al.* [19] suggested that when combined, ALA and Vitamin B complex are more effective than simple vitamin b12 complex for treating PN. In contrast to these results, we found that although vitamin B12 deficiency has been demonstrated in polyneuropathy, supplementation with B12 has not been effective in controlling NP [20]. However, we added B12 as a component in our combination oral supplement.

PRP injections have also been shown to be an effective treatment for NP. The main ARs include local infection (<1%) and pain at the injection site. Recent studies reported the promising effects of PRP on nerve regeneration [21]. However, the lack of standardization in the PRP preparation makes its evaluation difficult. In addition, there is a lack of well-designed, randomized, placebo-controlled clinical trials (RCT) in this subject area [22].

Our combination therapy was successful for PN, and all the modalities used were effective and safe. We found a significant decreasing trend of NP assessed by BPI starting at the survey taken at weeks 8 through 11. We also found a statistically significant decrease in the mean of BPI scores compared to the Baseline at Day 0.

6. Conclusion

By using a multi-modality treatment therapy protocol for PN patients we demonstrated that the combination of PRP, LED light therapy device, ESWT, and an oral supplement lowered pain scores and significantly improved subjects' im-

pression of change. Seventy-three percent of participants reported either Very Much Improved or Moderately Better at the end of the trial. Twenty-three percent of participants reported Little Improvement, and one reported No Improvement from the treatments. Temporary discomfort during ESWT and minor pain during PRP injections were the only minor side effects reported. There were no significant side effects in the study. Although the results were promising, there were some limitations of the study. A larger number of subjects would be recommended with pre- and post-neurological evaluations. Also, it would be interesting to see if a longer treatment schedule would improve outcomes even more than the results reported here. In this multi-modality study protocol we could not compare the results to individual treatments alone. Most importantly, this study should be eventually repeated with a larger placebo-controlled RCT trial.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Forced Inspiratory Flow Volume Curve in Patients with Obstructive Sleep Apnea-Hypopnea Syndrome

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Abstract

Objective: Obstructive sleep apnea-hypopnea syndrome (OSA) is a disease of obstructive apnea or hypopnea caused by a repeated partial or complete collapse of the upper airway during sleep. The inspiratory part of the flow-volume curve (F-V curve) can be used as an auxiliary means to evaluate upper airway obstruction in adults. This study is to evaluate the ability of the F-V curve to predict the OSA and explore inspiratory indicators related to airway obstruction during sleep. **Methods:** There were 332 patients included in this cross-sectional study, who were accompanied by snoring, daytime sleepiness and other symptoms, with suspicion of OSA. According to the nocturnal polysomnography, the subjects were distributed into mild to moderate OSA group, severe OSA group and non-OSA group. A pulmonary function test was used to collect the subjects' spirometry and F-V curves. **Results:** There was no significant difference in a variety of indices derived from the F-V curve between OSA and normal subjects, including 25% inspiratory flow rate, middle inspiratory flow rate, 75% inspiratory flow rate, peak flow rate, and forced inspiratory flow rate in the first second. The pulmonary function parameters were significantly correlated with the weight, age and sex of the subjects. **Conclusion:** These findings suggest that the inspiratory curve of pulmonary function cannot evaluate the upper airway abnormalities in patients with obstructive apnea-hypopnea syndrome.

Keywords

Apnea-Hypopnea Index, Obstructive Sleep Apnea, Pulmonary Function Test, Inspiratory Flow Volume Curve

1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSA) is a disease of obstructive

apnea or hypopnea caused by a repeated partial or complete collapse of the upper airway during sleep. Abnormalities of upper airway anatomical structure stenosis, neuromuscular function and central respiratory regulation are important factors for the occurrence of sleep apnea. Sleep-disordered breathing due to disease is caused by the obstruction of the upper thoracic airway, which reduces the cross-section of the airway and causes frequent airflow restriction during sleep. [1] [2] It is believed that the mechanisms leading to airway obstruction on sleep-disordered breathing can be summarized in the following four aspects [3] [4]: abnormal morphology of the upper airway; the function of upper airway opening muscle was abnormal; disorders in respiratory drive and regulation; the awakening threshold is abnormal. [5] [6]

Obstructive sleep apnea-hypopnea syndrome may occur in patients with upper airway obstruction. [7] Spirometry is used to diagnose and evaluate respiratory diseases. Pulmonary function examination has important diagnostic value for upper airway obstruction (UAO). [8] [9] [10] In pulmonary function test (PFT), flow volume loop (FVL) is the most valuable one for clinical application. The subjects were instructed to inhale and exhale with maximum strength. The flow volume curve (F-V curve) provided useful information about lung function and the relationship between lung volume and peak flow rate. In particular, when the F-V curve showed a characteristic plateau-like change, upper airway obstruction was highly suspected. [11] There are many factors that affect lung function parameters, including regional and demographic differences, and gender. Height, weight, age, etc. [9] Therefore, for respiratory disease, the percentage of expected values is commonly used to evaluate patients. [9] [10]

During inspiration, the anatomical airway stenosis will lead to the reduction of inhaled air. When exhaling, positive airway pressure will cause trachea dilation and reduce the severity of obstruction. Therefore, for OSA, inspiratory flow measurement is more accurate than expiratory measurement to reflect the pathophysiological abnormalities of upper thoracic airway obstruction. Indicators measured by spirometers may help to distinguish upper respiratory tract obstruction from other respiratory diseases. [8] [12] [13] The inspiratory part of the F-V curve can be used as an auxiliary means to evaluate upper airway obstruction in adults. [12]

The sleep process of OSA patients is an important part of the upper airway muscle relaxation or airway collapse at night. Snoring may increase the work of breathing and the cost of oxygen, and lead to hypoxia. Considering the decrease in ventilatory regulation observed at rest and the activation of the ventilation system during forced vital capacity testing during the day, it is worth investigating whether there are any changes in the ventilatory response and inspiratory flow of OSA patients. Therefore, the purpose of this research is to evaluate airflow restriction and airway obstruction by investigating the relationship between PFT and indicators of PSG, and to determine whether abnormal upper airway anatomy affects the inspiratory index. Subsequently, we analyze the F-V curve of

PFT in OSA patients during the awake period. We are interested in inspiratory lung function parameters (ILPs) (forced inspiratory volume in 1 second (FIV1), forced inspiratory flow at 50% of the vital capacity (FIF50) and peak inspiratory flow (PIF), etc.) and have researched their effects in multiple studies.

2. Materials and Methods

2.1. Study Subjects

In total 332 consecutive subjects (246 males, 86 females) who without a medical history of lung diseases and an expiratory flow limitation, but who were troubled with were snore to various levels or suspicion of OSA were eligible for this study from September 2019 to April 2022. The following exclusion criteria were used: clinical instability (such as patients with major hemoptysis, cancer, respiratory failure, and hemodynamic instability); history of respiratory infection in the last three weeks; evidence of overlap between sleep snoring and chronic airway diseases; and inability to perform (PFT).

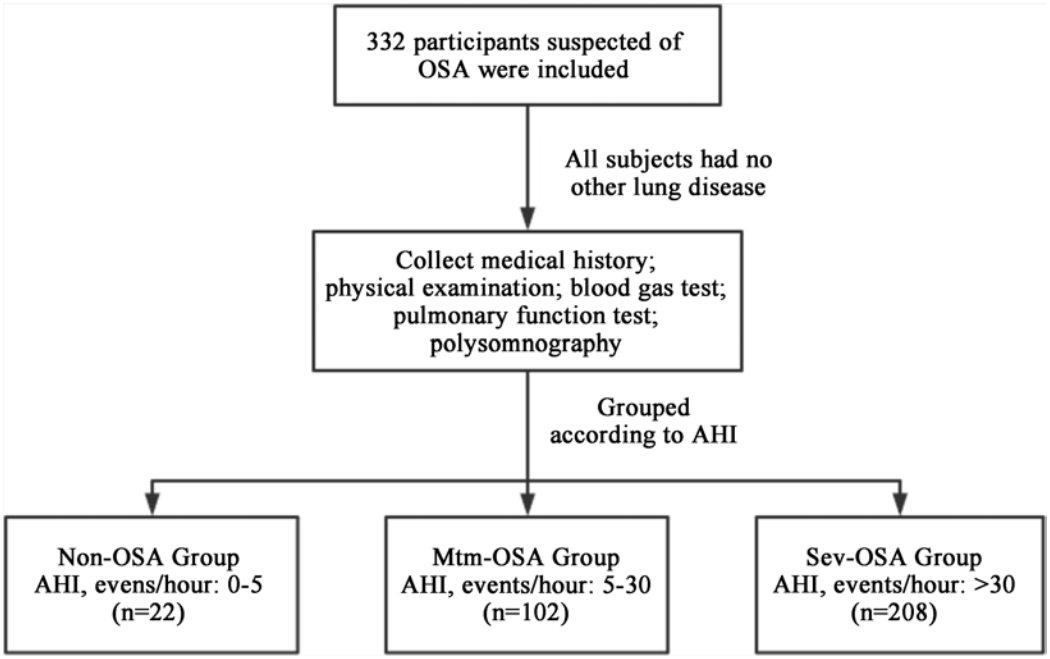
The protocol was approved by the Research Ethics Committee of the General Hospital of Tianjin Medical University under the number IRB2022-WZ-209, and it complied with the current national and international standards. All individuals signed informed consent when they were admitted to the hospital.

2.2. Overnight Polysomnography

All subjects received nocturnal polysomnography (Alice 5 Diagnostic Sleep System; Philips Respironics, Bend, OR, USA), consisting of at-least seven hour monitoring period of electroencephalogram (central and occipital), electromyogram, electrocardiogram (lead II), right and left extra-ocular eye movement, thoracic and abdominal wall movement, air flow, O_2 saturation, end-tidal CO_2 levels, snore volume, bilateral leg movement, and sleep position. All acquired PSG data were digitized and evaluated by the respiratory doctor of the Sleep Medical Center of the General Hospital of Tianjin Medical University. The ratio of the total number of apnea and hypopneas to the total sleep time in hours were calculated to obtain AHI scores. An AHI < 5 was considered as normal or simple snoring, 5 to 15 as mild OSA, 15 to 30 as moderate OSA, and >30 as severe OSA. [14] T90 was defined as the proportion of cumulative sleep time with oxygen saturation below 90% in total sleep time. According to the nocturnal polysomnography, the subjects were distributed into mild to moderate OSA group (Mtm-OSA Group), severe OSA group (Sev-OSA Group) and non-OSA group (**Figure 1**).

2.3. Pulmonary Function Testing

All of the subjects were asked to not use bronchodilators within 24 h prior to spirometric testing. The pulmonary function testing (PFT) (Master screen PFT, Jaeger crop, Hoechberg, Germany) performed were spirometry, body plethysmography, and diffusion capacity for carbon monoxide (DLCO). Participants were examined according to the standards set forth by the American Thoracic



Abbreviations: AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

Figure 1. Flow chart of the identification of the study population.

Society (ATS). [8] Guide the subjects to inhale or exhale deeply using the strength of their chest and abdomen to avoid respiratory muscle fatigue. At least three flow volume curves were measured, two of which were reproducible, meeting the recommended quality control criteria. The best curve was chosen on the basis of the sum of the best FVC (forced vital capacity) and the best FEV1 (forced expiratory volume in 1 second). The Chinese reference value was used, and the results are presented in terms of the measured value and expressed as percentages of the predicted values. [15] For the inspiratory parameters, at least 5 adequate values were obtained after a slow and maximal expiration. Inspiratory values were calculated using the curve that obtained the best inspiratory effort, *i.e.*, the greatest FIF50%. The best derived inspiratory parameters were further analyzed. All of the measurements were performed by the same person, who also explained the inhalation technique in detail before the test and monitored the technique carefully.

2.4. Demographic Characteristics and Laboratory Indicators

At admission, all participants underwent detailed physical examination and medical history collection, including sex, age, height, weight, waist circumference, neck circumference, medical history, and family medical history, etc. Prior to the test, all of the subjects were evaluated for pharyngeal obstruction on the use of the Friedman staging system. Daytime sleepiness was assessed based on the Epworth sleepiness scale (ESS) score. We collected and recorded the arterial blood gas of subjects (pH, arterial oxygen pressure (PaO_2), arterial carbon dioxide pressure ($PaCO_2$), bicarbonate [HCO_3^-], etc.)

3. Statistical Analysis

All parameters are expressed in mean differences ± standard deviation (x ± s), or median with interquartile range (IQR), or number (percentage), according to the normality test; Comparison of the clinical variables, PFTs, and PSG between subjects without OSA and subjects with sleep apnea in different groups was performed using one-way ANOVA or Kruskal Wallis test; Pearson's chi square test was used to compare the ratios of numerical variables. Calculate the correlation coefficient between pulmonary function parameters and AHI. The receiver operating characteristic (ROC) curve was constructed to study the predictive value of the baseline change percentage of each indicator to reach the diagnostic OSA.

SPSS for Windows (SPSS Inc., Chicago, IL, USA), version 20, was used for the statistical analyses, and GraphPad Prism 8.0 (GraphPad, San Diego, CA, USA) was used to construct the figures. P-value < 0.05 (two-sided) was considered statistically significant.

4. Result

A total of 332 subjects were finally included in the study analysis and grouped according to the AHI index. Baseline data of Clinical characteristics, pulmonary function, and PSG results for all subjects are given in Tables 1-3 respectively.

Table 1. General physiological characteristics and blood gas results of subjects in each group.

Variables	Non-OSA group (n = 22)	Mtm-OSA group (n = 102)	Sev-OSA group (n = 208)	F/X^2	P-Value
Gender, n (male/female)	22 (10/12)	102 (66/36)	208 (170/38)	20.405	0.000*
Age, years	43.64 ± 16.91	48.62 ± 15.13	47.61 ± 13.68	1.091	0.337
Height, cm	170.77 ± 6.72	169.67 ± 8.33	172.07 ± 8.65	2.795	0.063
Weight, kg	80.43 ± 22.09	83.20 ± 14.84	96.55 ± 26.71[ab]	13.718	0.000*
BMI, kg/m^2	27.45 ± 6.98	28.94 ± 4.98	32.51 ± 8.14[ab]	11.305	0.000*
SBP, mmHg	121.45 ± 15.29	125.39 ± 15.50	129.53 ± 18.88	3.309	0.038*
DBP, mmHg	76.96 ± 8.48	84.01 ± 11.81	85.88 ± 13.59	5.054	0.007*
Waist circumference, cm	94.00 ± 25.74	99.81 ± 18.25	108.09 ± 20.78	8.826	0.000*
Neck circumference, cm	39.19 ± 4.53	40.38 ± 4.03	42.90 ± 4.43[ab]	15.845	0.000*
Frideman position (I-II/III-IV)	9/13	36/66	65/143	1.148	0.563
Blood Gas Analysis					
PH	7.40 ± 0.03	7.41 ± 0.02	7.38 ± 0.36	0.241	0.786
PO_2, mmHg	76.88 ± 9.28	78.98 ± 10.95	71.63 ± 10.46[b]	13.171	0.000*
PCO_2, mmHg	39.18 ± 3.31	40.31 ± 6.63	41.19 ± 4.72	1.560	0.212
HCO_3^-, mmol/L	23.44 ± 1.66	24.73 ± 3.01	25.65 ± 4.37[a]	3.385	0.035*
SAO_2, %	97.1 (95.7 - 97.85)	96.9 (96.25 - 97.65)	96.2 (94.6 - 96.95)[b]	20.985	0.004**

Definition of abbreviations: BMI, body mass index; SBP, arterial systolic pressure; DBP, arterial diastolic pressure; Notes: a indicates P < 0.05 compared with non-OSA group; b indicates P < 0.05 compared with mild-moderate OSA group.

Table 2. Flow volume curve of pulmonary function parameters of all participants.

Pulmonary Function Parameters	Non-OSA group (n = 22)	Mtm-OSA group (n = 102)	Sev-OSA group (n = 208)	F	P-Value
Expiratory parameters of flow volume curve					
FVC, L	3.53 ± 1.24	3.33 ± 1.60	3.53 ± 1.33	0.613	0.542
FVC %predicted	97.91 ± 13.42	95.94 ± 20.29	91.67 ± 17.01	2.041	0.132
FEV1, L	2.73 ± 1.29	2.96 ± 1.12	2.97 ± 0.94	0.469	0.626
FEV1 %predicted	94.46 ± 18.29	92.42 ± 22.56	93.54 ± 64.02	0.061	0.984
FEV1/FVC	80.83 ± 9.14	78.52 ± 13.32	80.01 ± 6.82	0.794	0.453
PEF, L/s	11.98 ± 19.66	7.96 ± 2.37	8.47 ± 5.72	2.350	0.097
PEF %predicted, %	94.29 ± 19.58	101.00 ± 22.97	98.55 ± 21.48	0.723	0.487
FEF50, L/s	3.48 ± 1.85	3.30 ± 2.18	3.43 ± 1.71	0.166	0.847
FEF50, %	80.73 ± 31.19	80.95 ± 35.74	78.82 ± 29.62	0.128	0.880
Inspiratory parameters of flow volume curve					
FIV1, L	3.27 ± 1.01	3.24 ± 0.98	3.35 ± 1.07	0.414	0.661
FIV1/FVC	90.74 ± 13.45	91.86 ± 11.15	91.87 ± 11.08	0.103	0.902
PIF, L/s	4.87 ± 1.87	4.41 ± 1.53	4.49 ± 1.74	0.619	0.539
PEF/PIF, %	0.67 (0.54 - 1.13)	0.76 (0.44 - 0.99)	0.85 (0.58 - 1.14)	4.650	0.098
FIF75, L/s	3.81 ± 1.71	3.46 ± 1.46	3.57 ± 1.53	0.537	0.585
FIF50, L/s	4.50 ± 1.87	4.13 ± 1.55	4.19 ± 1.69	0.437	0.647
FIF25, L/s	4.30 ± 1.79	3.93 ± 1.42	4.02 ± 1.59	0.492	0.612
FEF50/FIF50, %	0.80 ± 0.48	0.80 ± 0.61	0.90 ± 0.49	1.261	0.285
In Area, L^2/s	13.95 ± 7.68	12.89 ± 7.62	13.70 ± 8.28	0.391	0.677
Ex Area/In Area, %	1.07 ± 0.45	1.18 ± 0.56	1.19 ± 0.45	0.658	0.519
Pulmonary diffusion function					
DLCO, mmol/min/kPa	7.13 ± 2.04	7.45 ± 2.08	7.74 ± 1.85	1.125	0.326
DLCO% predicted	74.33 ± 14.25	76.27 ± 16.70	80.85 ± 13.86	1.544	0.216

Definition of abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; FEF50: forced expiratory flow at 50% of FVC; FIV1, forced inspiratory volume in 1 second; PIF, peak inspiratory flow; FIF75, forced inspiratory flow at 75% of FVC; FIF50, forced inspiratory flow at 50% of FVC; FIF25, forced inspiratory flow at 50% of FVC; FEF50/FIF50, ratio of FEF50 to FIF50; In Area, area of Inspiratory part of flow volume curve; Ex Area, area of expiratory part of flow volume curve; DLCO, diffusing capacity of the lungs for carbon monoxide.

There were more men in severe OSA group, with higher BMI and thicker waist circumference and neck circumference (Table 1). No difference between groups in evaluating the degree of pharyngeal stenosis according to the Frideman. The daily blood gas indicators of participants in each group showed that the oxygen saturation and partial pressure of OSA patients decreased compared with the normal group, and the severe OSA decreased more significantly ($p < 0.01$). The

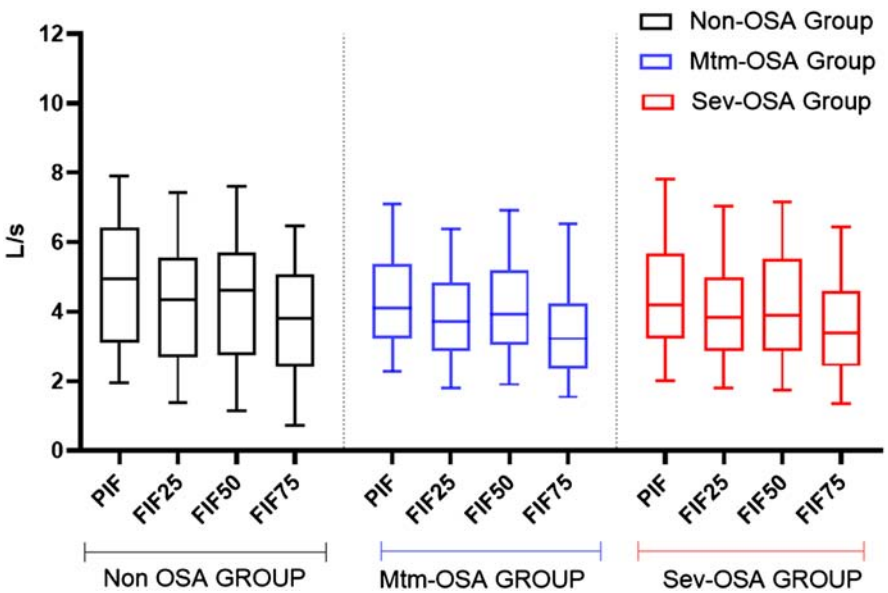
difference between the above groups was statistically significant, and HCO_3^- also changed to varying degrees ($p < 0.05$).

The data of pulmonary function flow volume curve are shown in Table 2 and Figure 2. The inspiratory flow velocity indexes in non-OSA group, including PIF, forced inspiratory flow at 75% of FVC (FIF75), FIF50, forced inspiratory flow at 25% of FVC (FIF25), and the area of inspiratory part of flow volume curve

Table 3. Polysomnographic characteristic of the study population.

Polysomnography	Non-OSA group (n = 22)	Mtm-OSA group (n = 102)	Sev-OSA group (n = 208)	F	P-Value
AHI, events/h	2.5 (1.45 - 3)	17.2 (10.1 - 23.8)[a]	67.5 (47.8 - 78.73)[a,b]	267.102	0.000**
ODI, events/h	1.7 (0.8 - 2.85)	14 (7.40 - 19.7)[a]	62.2 (43.03 - 89.65)[a,b]	178.747	0.000**
AI, events/h	0.3 (0 - 0.8)	1.9 (0.4 - 5.78)[a]	37.2 (12.33 - 64.33)[a,b]	153.664	0.000**
HI, events/h	1.65 (0.9 - 2.9)	12.55 (7.88 - 18.28)[a]	19.95 (6.5 - 34.7)[a,b]	30.152	0.000**
SpO_2mean, %	96.00 (95.00 - 97.00)	95.00 (94.00 - 96.00)	92.00 (89.00 - 94.00)[a,b]	106.023	0.000**
SpO_2min, %	91.00 (89.00 - 92.00)	85.00 (81.00 - 87.25)[a]	69.00 (57.00 - 78.00)[a,b]	160.015	0.000**
Arl, events/h	5.55 (3.68 - 9.55)	13.8 (8.1 - 18.2)[a]	37.7 (22.3 - 55.25)[a,b]	15.190	0.000**

Definition of abbreviations:: AHI, apnea-hypopnea index; ODI, oxygen desaturation index; AI, apnea index; HI, hypopnea index; SpO_2mean, mean percutaneous oxygen saturation; SpO_2min, minimum percutaneous oxygen saturation; Arl, arousal index. Notes: a indicates $P < 0.05$ compared with non-OSA group; b indicates $P < 0.05$ compared with mild-moderate OSA group; *, a statistical difference between representative groups ($P < 0.05$); *, a statistical difference between representative groups ($P < 0.01$).



Abbreviations: PIF, peak inspiratory flow; FIF75, forced inspiratory flow at 75% of FVC; FIF50, forced inspiratory flow at 50% of FVC; FIF25, forced inspiratory flow at 50% of FVC.

Figure 2. Inspiratory flow rate at different stages of each group. The inspiratory flow velocity indexes in non-OSA group, including PIF, FIF75, FIF50, FIF25, and In Area were higher than those in OSA patients, but there was no statistical difference.

(In Area), were higher than those in OSA patients, but there was no statistical difference. The ratio of peak expiratory flow to peak expiratory flow (PEF/PIF) and ratio of forced expiratory flow at 50% of FVC to forced inspiratory flow at 50% of FVC (FEF50/FIF50) increased in sev-OSA Group, which also indicated that the inspiratory flow rate was limited.

The study data showed that the inspiratory parameters of pulmonary function had no positive effect on the severity grading of OSA (**Figure 3**). We tried to analyze other factors that affect pulmonary function indicators, and found that age, gender, weight and inspiratory parameters are all related. The results showed that PIF was negatively correlated with the age ($r = -0.059$, $P < 0.001$) and neck circumference ($r = 0.044$, $P < 0.032$), and positively correlated with the body weight ($r = 0.012$, $P < 0.0013$).

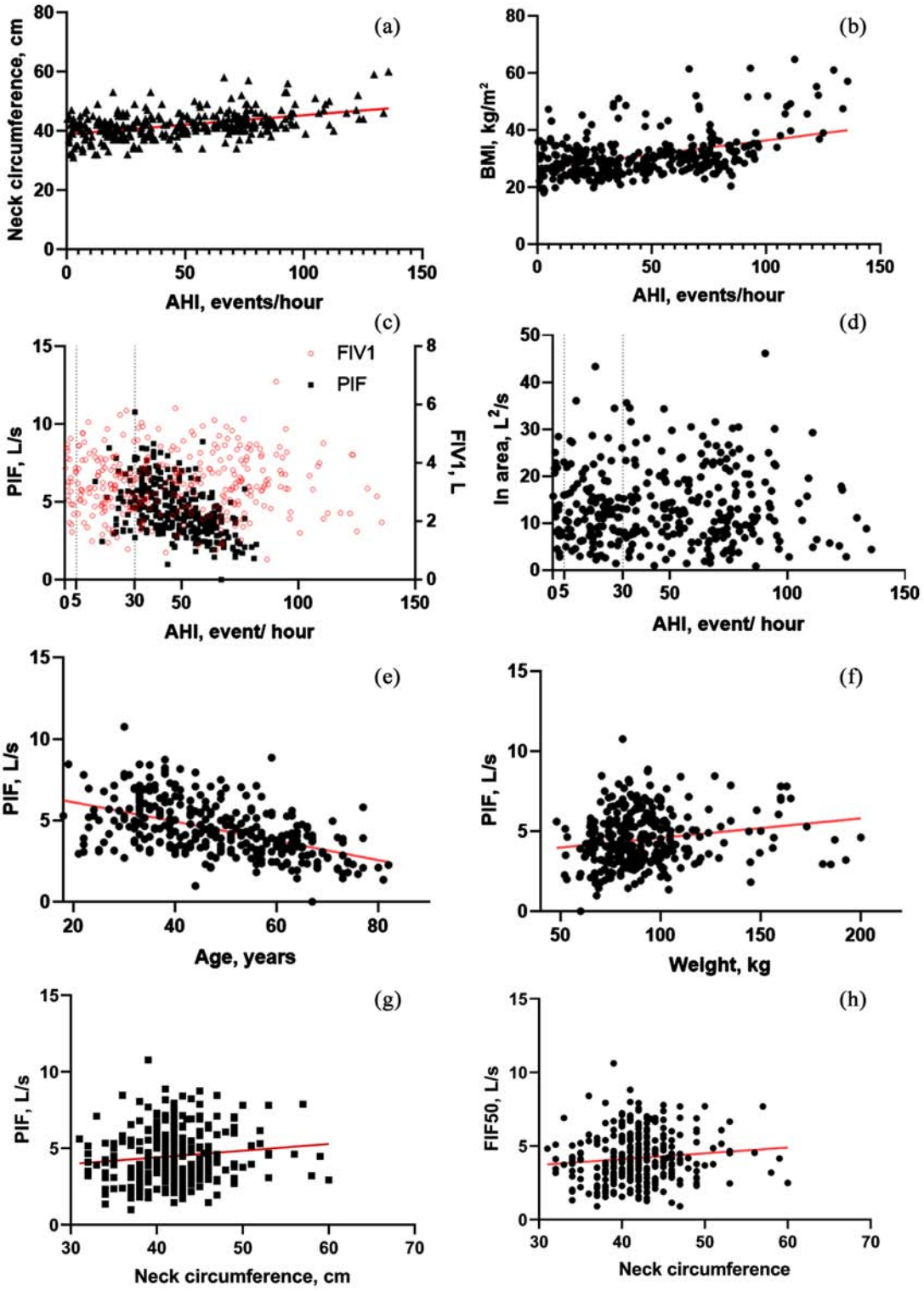
According to the neck circumference, arterial partial pressure of oxygen and BMI, the ROC curve was drawn to diagnose OSA. The results showed that the combined diagnostic ability of the three indicators was better than that of the single indicator (**Figure 4**).

PSG showed that the data of the overall participants were reliable. According to different AHI groups, the minimum percutaneous oxygen saturation (SpO_2min), mean percutaneous oxygen saturation (SpO_2mean), arousal index and oxygen desaturation index (ODI) of patients with severe OSA were more serious than those of the other two groups, and the difference was statistically significant. No positive results of pulmonary function parameters among the three groups (**Table 3**).

5. Discussion

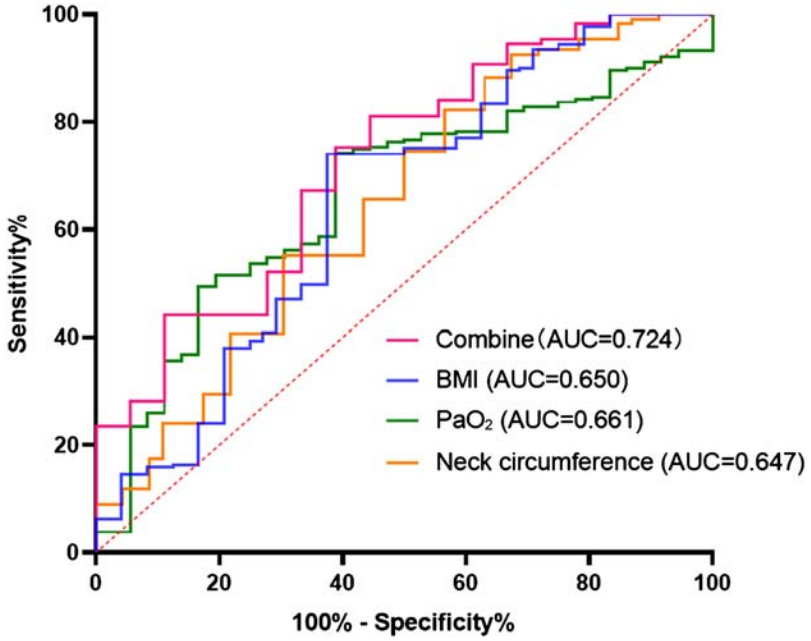
The study confirmed that the daytime pulmonary function test of OSA patients did not find the evidence of upper airway obstruction, even if the patients had severe apnea and hypoxia events during sleep. Stenosis of upper airway is an important factor in OSAHS. The increase of upper airway soft tissue with or without maxillofacial anatomical structure abnormality due to obesity, upper airway anatomy abnormality and other reasons can make the airway cross-section of OSAHS patients smaller, their airways are narrower and longer, and they are more likely to collapse than those without apnea. Among them, the stenosis of pharyngeal cavity anatomical structure is involved in airflow limitation during sleep. They rely heavily on the compensatory activation of the airway expander to maintain smooth airflow when awake. [1] [16] Liliana's research shows that the quantitative standard of flow curve has high sensitivity and specificity in detecting upper airway obstruction. [17] There are different views on the value of sawtooth wave as a screening test for OSA. [18]

In OSA patients, we have investigated the influence of the preceding expiratory, no significant difference was found among the groups. The inspiratory parameters of pulmonary function in OSA patients were not significantly different from those in simple snoring, and were not significantly related to the AHI and



Abbreviations: FIV1, forced inspiratory volume in 1 second; PIF, peak inspiratory flow; In Area, area of Inspiratory part of flow volume curve.

Figure 3. Linear relationship among variables. AHI was positively correlated with neck circumference and BMI (a) and (b); PIF, FIV1, In Area and AHI have no linear correlation (c) and (d); Negative correlation between PIF and age (e); Negative correlation between PIF and body weight (f); Neck circumference is positively correlated with PIF and FIF50 (g) and (h).



Abbreviations: PaO_2, arterial partial pressure of oxygen; BMI, body mass index; OSA, obstructive sleep apnea.

Figure 4. Receiver operating characteristic (ROC) curve analysis of BMI, neck circumference, PaO_2 to recognize OSA patients. The combination of three indicators has more advantages for OSA diagnosis.

the lowest oxygen saturation obtained from PSG. Because there is no clear standard for the predicted value of the inspiratory parameters at present, it is impossible to compare the percentage of the estimated value of people of different ages, genders, heights and weights, so the specificity of various indicators of the inspiratory curve for disease diagnosis is reduced. As the gold standard of diagnosis, PSG is an indispensable means of OSA examination.

Although there is no significant difference in inspiratory flow rate among patients with OSA of different degrees, we still have some interesting findings. The neck circumference of OSA patients is consistent with the inspiratory parameters, which is consistent with our hypothesis. The increase of neck circumference to some extent indicates the accumulation of neck fat, which further blocks the opening of the upper airway. When the subjects inhaled with great force, PIF, FIF50, and other indicators decreased to varying degrees. The result of our data is that each index of inspiratory flow is related to sex, age and weight. The study indicated that BMI was a clinical predictor of the AHI. The correlation between BMI and OSA was complex. Most of the literature in the past demonstrated that an increase in BMI was related to an increase in AHI. [19] [20] The result of our data is that the severity of OSA patients is closely related to BMI, and each index of inspiratory flow is related to gender, age and weight. It may be more important to use predicted values to predict upper airway obstruction in OSA.

Most individuals who are severely obese can maintain blood gas homeostasis through augmentation of alveolar ventilation and carbon dioxide (CO_2) output.

[21] [22] Our study found that the decrease of daytime arterial partial pressure of oxygen and the low level of oxygen saturation were related to the severity of OSA.

On the other hand, it has been reported that the degree of severity of OSAS was thought to be mostly associated with the sleep time spent in the supine position. Rissanen *et al.* showed that supine position is related to the duration of hypoventilation and apnea in different sleep periods, and it is a risk factor for aggravating OSA. [23] [24] Upper airway collapsibility was greater in supine position compared to lateral position. Suzuk *et al.* treated OSA by correcting sleep state in supine position. In supine position, the tongue base narrowed the upper airway by the effect of gravity. Therefore, respiratory events were seen less in side position. The standard pulmonary function test requires the patient to take the upper body upright position for forced inspiration and breathing, which is very different from the position during sleep at night. [8] It cannot be ruled out that the position has an impact on the pharyngeal anatomy. We did not find any abnormality of the inspiratory ring in OSA patients, including the reasons for posture. Compared with normal subjects, OSA patients have greater muscle tension in the upper airway, which is considered necessary to maintain the smooth airway with OSA stenosis. [4] [25] With the loss of upper airway expander activity at the beginning of sleep, the anatomical stenosis of OSA makes the upper airway particularly vulnerable to this loss of expander activity during sleep. [26] [27] This is consistent with the assumption that the increase in the degree of upper airway stenosis during sleep is sufficient to cause abnormal flow volume curves. These mechanisms may explain why flow restriction occurs during sleep, but not during waking. [28] But forced vital capacity was done while the participants were awake.

The limitations of this research are pointed out. Firstly, this is a cross sectional study, therefore, we cannot make any certain conclusion about the correlation between these factors and AHI. In addition, the patients studied were from only one sleep disorder center, which could have resulted in sampling bias. Larger, multicenter studies are required to further investigate the risk factors for OSA.

6. Conclusion

In this study, we tried to assess airflow limitation by means of physical examination during the awake period and PSG, and assumed that the abnormal parameters of the F-V curve of the spirometer in most patients could be attributed to the upper airway structure and airway expansion muscle response. Unfortunately, we have not found any effective parameters that can predict the occurrence of OSA from the pulmonary function test. The inspiratory parameters of lung function are closely related to many factors. It is hoped that more studies will be conducted in the future to propose reference standards for inspiratory predictive values of normal people, which will play a more effective role in evaluating clinical diseases. Positive results may be found as a percentage of expected values.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Ethics Statement

The study protocol was approved by the Medical Ethics Committee of Tianjin Medical University General Hospital (No. IRB2022-WZ-209), and the procedures followed were in accordance with the Helsinki Declaration in 1995, as revised in 2013. The information of the included subjects was extracted from the electronic medical records of the sleep center, and their personal identities were kept anonymous.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Jie Cao is co-correspondent.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Visual Outcomes and Risk of Rhegmatogenous Retinal Detachment Following Posterior Capsule Rupture during Cataract Surgery: With vs without Dropped Nuclear Lens Fragments

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Abstract

Background: Cataract surgery is the most frequently performed surgery worldwide. Posterior capsule rupture (PCR) remains one of the most common complications of cataract surgery and a major risk factor for poor visual outcomes. Cataract surgeries complicated by PCR and vitreous loss are managed with anterior vitrectomy at the time of surgery. However, the situation can be further complicated by dropping lens particles into the vitreous cavity necessitating a secondary pars plana vitrectomy (PPV). **Purpose:** To compare the visual outcomes and risk of rhegmatogenous retinal detachment (RRD) between eyes that required anterior vitrectomy (AV) alone for the management of vitreous loss and eyes that required AV and subsequent PPV for the management of dropped nuclear lens fragments (DNLF) following cataract surgery complicated by PCR in a tertiary care teaching hospital in Saudi Arabia. **Methods:** Medical records of patients in whom PCR occurred during phacoemulsification cataract surgery requiring AV or subsequent PPV for DNLF were retrospectively reviewed over a 6-year period from January 2016 to December 2021. **Results:** PCR occurred in 183 (2.3%) of 7757 consecutive eyes that underwent phacoemulsification cataract surgery during the study period. Seven eyes were excluded from analysis for missing data or short follow-up. Of the 176 eyes, 147 eyes (83.5%) were managed with AV alone, and the remaining 29 eyes (16.5%) underwent a secondary PPV for DNLF. After excluding eyes with pre-existing ocular pathology, final best-corrected visual acuity (BCVA) was similar in both groups with a mean of 0.32 logMAR (P = 0.99). Two of 147 eyes (1.4%) in the AV group developed RRD with poor final BCVA whereas none of the eyes in DNLF group developed RRD. **Con-**

clusion: The risk of RRD is lower in eyes that required PPV for DNLF than in eyes that were managed with AV alone following PCR during cataract surgery. The poor visual outcomes in eyes that suffered RRD underscore the importance of postoperative retinal examination and early detection of retinal breaks.

Keywords

Cataract Surgery, Posterior Capsule Rupture, Anterior Vitrectomy, Retinal Detachment, Dropped Nucleus

1. Introduction

Cataract surgery is the most frequently performed surgery worldwide, with an estimated 20 million cataract surgeries performed annually [1] [2]. Despite current advances in cataract surgery, posterior capsule rupture (PCR) remains one of the most common complications of cataract surgery and a major risk factor for poor visual outcomes [3]. The incidence of PCR varies in the literature, ranging from 0.98% to 4.7% of cataract surgery cases [4]-[9]. Cataract surgeries complicated by PCR and vitreous loss are managed with anterior vitrectomy at the time of surgery. However, the situation can be further complicated by dropping lens particles into the vitreous cavity necessitating a secondary pars plana vitrectomy (PPV). The reported incidence of dropped nuclear lens fragments (DNLF) ranges from 0.1% to 1.5% of cataract surgery cases [10] [11] [12].

Cataract surgery cases complicated by PCR are at higher risk of developing several potentially serious post-operative complications such as cystoid macular edema, retinal detachment, glaucoma, and endophthalmitis [13]. Retinal detachment is among the most common causes of severe visual loss following complicated cataract surgery, leading to poor visual outcomes in most cases [14]. Retinal detachment occurs in 0.5% - 1% of eyes undergoing phacoemulsification cataract surgery, while it is more prevalent in PCR cases [15]. The risk of developing retinal detachment is 13 - 16 times higher following PCR and vitreous loss compared to cases with intact capsule [16].

The purpose of this study was to compare the visual outcomes and risk of rhegmatogenous retinal detachment (RRD) between eyes that required anterior vitrectomy alone for the management of vitreous loss and eyes that required anterior vitrectomy and subsequent pars plana vitrectomy (PPV) for the management of dropped nuclear lens fragments (DNLF) following PCR during cataract surgery in a tertiary care teaching hospital in Saudi Arabia.

2. Methods

As part of a clinical audit program at our institution, all surgeons are required to report the occurrence of PCR at the conclusion of cataract surgery. Medical records of patients in whom PCR occurred during phacoemulsification cataract

surgery were retrospectively reviewed over a 6-year period from January 2016 to December 2021 at Department of Ophthalmology, King Saud University Medical City, Riyadh, Saudi Arabia. All patients who underwent anterior vitrectomy for PCR and vitreous loss with/without a secondary PPV for DNLF were included in the study regardless of pre-existing ocular pathology. However, eyes with pre-existing ocular pathology such as maculopathy (secondary to diabetes mellitus, myopia, or other vascular diseases), advanced glaucoma, neuropathies, amblyopia, significant corneal pathology, and previous ocular surgeries that would limit the visual potential were excluded from visual outcome analysis. Data collected included patient demographics, preoperative and final postoperative best-corrected visual acuity (BCVA) in logMAR, pre-existing ocular pathology, time interval between cataract surgery and PPV for the management of DNLF, and time interval between cataract surgery and development of RRD. Patients with less than one month of postoperative follow up were excluded from the study.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY). Descriptive statistics were presented as percentages and frequencies. Chi-square test was used to compare demographic variables between the two groups. A two-tailed *t* test was conducted to compare means between the two groups. A p-value < 0.05 was considered statistically significant.

The study was approved by the Institutional Review Board (IRB) at King Saud University Medical City, Riyadh, Saudi Arabia. This study adhered to the ethical principles outlined in the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

3. Results

One hundred eighty-three of 7757 consecutive eyes that underwent cataract surgery during the study period were reported to have PCR, giving an incidence of 2.3%. Of the 183 eyes, seven eyes were excluded from analysis for missing data or short follow-up. One hundred seventy-six cases had a minimum follow-up of 4 weeks and were included in analysis. Of the 176 eyes, 147 eyes (83.5%) were managed with anterior vitrectomy alone at the time of cataract surgery for vitreous loss, and the remaining 29 eyes (16.5%) underwent a secondary PPV for DNLF. Of the 176 eyes, 22 eyes with pre-existing ocular comorbidity were excluded from visual outcome analysis.

Table 1 summarizes the baseline characteristics and visual outcomes of the included eyes. There were no significant differences between the two groups. After excluding eyes with pre-existing ocular pathology, final BCVA was similar in both groups with a mean of 0.32 logMAR ($P = 0.99$). Final BCVA of 0.3 logMAR or better was achieved in 79.7% of eyes in the anterior vitrectomy group and 73.1% of eyes in the DNLF group ($P = 0.45$). In the DNLF group, the mean time for a secondary PPV for the removal of DNLF following the initial cataract

surgery was 19.45 days; 13/29 eyes had early PPV within 2 weeks following the initial cataract surgery and 16/29 eyes had late PPV after 2 weeks. After excluding eyes with pre-existing pathology, the final BCVA was similar in both groups with a mean of 0.36 logMAR in early PPV group and 0.28 logMAR in late PPV group (P = 0.60). Four of 29 eyes (13.7%) in the DNLF group were noted to have retinal tears during PPV and were treated accordingly. Almost 90% of patient in both groups had sulcus intra-ocular lens implantation.

Two of 147 eyes (1.4%) in the anterior vitrectomy group developed RRD with poor final BCVA. Table 2 shows the demographic and visual outcomes of the 2 eyes that developed RRD. None of the eyes in DNLF group developed RRD.

Table 1. Baseline characteristics and visual outcomes of the included eyes.

Variable	**Anterior vitrectomy (n = 147)**	**DNLF (n = 29)**	**Statistical significance**
Age, mean in years (range)	65.5 (30 - 92)	66.2 (51 - 93)	P = 0.76
Female gender, *n* (%)	88 (59.9)	18 (62.1)	P = 0.82
Mean preoperative logMAR BCVA (range)*	0.83 (0 - 2.30)	0.96 (0.18 - 2.30)	P = 0.32
Mean postoperative logMAR BCVA (range)*	0.32 (0 - 2.30)	0.32 (0 - 1.80)	P = 0.99
Percentage of patients with final logMAR BCVA of 0.3 or better*	79.7	73.1	P = 0.45
Mean time to PPV for DNLF removal, days (range)	Not Applicable	19.45 (0 - 175)	
The presence of retinal tears identified during PPV for DNLF removal, *n* (%)	Not Applicable	4 (13.7)	
Number progressing to RRD, *n* (%)	2 (1.4)	0	P = 0.52
Mean time to development of RRD, months (range)	8 (6 - 10)	Not Applicable	
Sulcus intraocular lens, *n* (%)	134 (91.2)	27 (93.1)	
Capsular bag intraocular lens, *n* (%)	6 (4.1)	0	
Anterior chamber intraocular lens, *n* (%)	0	0	
Scleral fixated intraocular lens, *n* (%)	4 (2.7)	1 (3.4)	
Aphakia, *n* (%)	3 (2)	1 (3.4)	

BCVA: Best-corrected visual acuity; DNLF: Dropped nuclear lens fragments; PPV: Pars plana vitrectomy; RRD: Rhegmatogenous retinal detachment; (*): 22 eyes with pre-existing ocular pathology were excluded from visual outcome analysis.

Table 2. Demographic and visual outcomes of the two eyes that were managed with anterior vitrectomy and progressed to develop RRD.

Age (years)	**Gender**	**Eye**	**Pre-existing ocular pathology**	**Pre-operative BCVA (logMAR)**	**IOL choice**	**Onset of RRD (months)**	**Macula status**	**Final BCVA (logMAR)**
61	Female	Left	None	0.70	Sulcus	6	OFF	2.30
72	Male	Left	None	1.00	Sulcus	10	OFF	1.80

BCVA: Best-corrected visual acuity; IOL: Intra-ocular lens; RRD: Rhegmatogenous retinal detachment.

4. Discussion

This study aimed to evaluate the visual outcomes and risk of RRD following cataract surgery complicated by PCR and managed with anterior vitrectomy for vitreous loss with/without subsequent PPV for DNLF in a tertiary care teaching hospital in Saudi Arabia.

The incidence of PCR during phacoemulsification cataract surgery is variable in the literature. Our PCR rate of 2.3% is comparable to the published rates. **Table 3** summarizes the rates of PCR in the recent literature.

Interestingly, the mean final BCVA was similar in eyes that were managed with anterior vitrectomy alone for vitreous loss and eyes that required a secondary PPV for DNLF, with a mean of 0.32 logMAR in both groups. Naderi *et al.* reported the same finding of comparable final BCVA between the two groups with a mean of 0.30 logMAR in the anterior vitrectomy group and 0.32 logMAR in the DNLF group [4]. Therefore, cataract surgeons should be reassured that even if the cataract surgery is complicated by DNLF, patients can achieve good visual outcomes.

Retinal tears following anterior vitrectomy for PCR occur secondary to the anterior movement of vitreous resulting from PCR that induces traction on the vitreous with a subsequent retinal tear. Jakobsson *et al.* showed that the risk of RRD increases by 10-fold in eyes with PCR, leading to poor visual outcomes in most cases [14]. Understanding that excessive pulling on the vitreous can result in retinal breaks in addition to mastering the skill of anterior vitrectomy are crucial for all cataract surgeons to decrease the risk of retinal tears or detachment and improve the visual outcomes. Also, meticulous postoperative examination of the retina is essential in complicated cataract surgery cases to detect retinal breaks and manage the condition in a timely manner. Our rate of 1.4% of RRD in the anterior vitrectomy group occurring within a median time of 8 months is lower than rates reported in the literature. Naderi *et al.* reported a RRD rate of 4.86% within a median time of 11 months [4]. Day *et al.* reported a RRD rate of 3.27% within a median time of 44 days [17]. Daniel *et al.* reported a high rate of RRDs of 6.39% within a median time of 8 months [18].

Table 3. Rates of posterior capsule rupture in recent literature.

Study	Country	Number of cases	PCR rate (%)
Ti, 2014 [9]	Singapore	55,567	1.9
Tsinopoulos, 2015 [5]	Greece	1335	4.7
Kahawita, 2015 [8]	Australia	3740	2.6
Kim, 2017 [7]	New Zealand	500	2.6
Akkach, 2019 [6]	Australia	13,124	1.0
Naderi, 2020 [4]	United Kingdom	20,235	0.98

PCR: posterior capsule rupture.

In our study, none of the eyes that required a secondary PPV for DNLF developed RRD, although 4/29 eyes (13.7%) were found to have retinal tears during PPV for the management of DNLF. Our findings are consistent with Naderi *et al.* where none of 55 eyes in the DNLF group progressed to develop RRD, in which 9/55 eyes (16.3%) were found to have retinal tears during the subsequent PPV [4]. Our findings are also comparable to Lashgari *et al.* where none of 36 eyes with DNLF went on to develop RRD, in which 4/36 eyes (11.1%) were found to have retinal tears during PPV [19]. Ryoo *et al.* also showed similar findings in which none of 32 eyes in the DNLF group developed RRD [20]. This finding of lack of progression to RRD in eyes with DNLF in addition to the comparable visual acuity outcomes to eyes without DNLF should be reassuring for cataract surgeons.

Timing between cataract surgery and PPV for the management of DNLF has been an area of debate [10] [11] [21]. The mean time between the initial cataract surgery and PPV for DNLF in our cohort was 19.45 days. In our study, eyes that underwent early PPV within 2 weeks following the initial cataract surgery had similar final BCVA to eyes that underwent late PPV after 2 weeks from the initial cataract surgery. Our finding is comparable to a retrospective study on 20 eyes with DNLF that showed no correlation between inter-surgery time and the final BCVA or retinal detachment rate [22]. On the other hand, a systemic review and meta-analysis on 43 studies showed better visual outcomes and lower risk of post-operative retinal detachment in eyes underwent early PPV for the management of DNLF [10].

There are some limitations to our study. Information about the type (co-axial vs bimanual), machine and settings of anterior vitrectomy were not documented in the operative report for most patients. Thus, this variable could not be analysed. The rate of RRD in our study could be underestimated as some patients might have presented to other hospitals. The data was collected retrospectively and was dependent on the quality of documentation.

5. Conclusion

In summary, our study showed that the risk of RRD is lower in eyes that required PPV for DNLF than in eyes that were managed with anterior vitrectomy alone for vitreous loss following PCR during cataract surgery. The poor visual outcomes in eyes that suffered RRD underscore the importance of postoperative retinal examination and early detection of retinal breaks following complicated cataract surgery.

Author Contribution

First Author: Literature review, data collection, data analysis and drafting the manuscript. Second and Third Authors: conception and design of the study, overall review and editing of the manuscript. All authors read and approved the final version of the manuscript.

Ethical Approval

The study was approved by the Institutional Review Board (IRB) at King Saud University, Riyadh, Saudi Arabia. This study adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013.

Consent

Patients signed an informed consent prior to enrollment in the study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Association between Fundus Atherosclerosis and Carotid Arterial Atherosclerosis

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Abstract

Objective: To investigate the correlation between fundus atherosclerosis and carotid arterial atherosclerosis. **Methods:** A total of 516 people undergoing physical examination in Deyang People's Hospital between June 2020 and December 2022 were randomly selected. Fundus atherosclerosis and carotid arterial atherosclerosis were evaluated by fundus photography and carotid artery ultrasonography, respectively. **Results:** Among the 516 physical examination patients, 198 (38.4%) had normal fundus examination, and 318 (61.6%) had fundus arteriosclerosis. Among them, 166 cases were of grade I (32.2%), 86 cases were of grade II (16.7%), and 66 cases were of grade III (12.8%). There were 286 cases (55.4%) without carotid atherosclerosis, 201 cases (38.9%) with carotid atherosclerotic plaque, and 33 cases (6.4%) with carotid stenosis. Fundus arteriosclerosis is independently associated with carotid artery intima-media thickness, vulnerable plaques, plaque scores, and carotid artery stenosis ($P < 0.05$). **Conclusion:** In summary, there is a close relationship between carotid artery disease and the degree of arteriosclerosis in the eyeground. Fundus photography is a simple, non-invasive, and easily acceptable method of inspection. The results obtained from it are useful in determining the severity of carotid atherosclerosis and guiding early detection and intervention in clinical cases. This can help reduce the incidence of cardiovascular and cerebrovascular diseases.

Keywords

Carotid Arterial Atherosclerosis, Fundus, Carotid Plaque, Carotid Stenosis, Ultrasonography

1. Introduction

Atherosclerosis, especially carotid atherosclerosis, is closely related to the occur-

rence, development and recurrence of cerebral infarction, and is the most important cause and risk factor of cerebral infarction [1]. Insufficient perfusion of the carotid artery will inevitably cause blood supply disorders to the retina, retrobulbar artery, and posterior ciliary artery, resulting in impaired circulation within the optic disc. The eyeground artery is the only artery that can be directly observed from the body surface through an ophthalmoscope or fundus camera. The degree of its atherosclerotic lesions can be used as a window to reflect systemic arteriosclerosis and is closely related to the onset of cardiovascular and cerebrovascular diseases [2] [3]. The carotid artery is an important branch of the human aorta, while the ophthalmic artery mostly originates from the internal carotid artery. Plaque-like lesions in the carotid artery can cause thickening of the intima-media, leading to arterial stenosis, hemodynamic changes, and blood microcirculation disorders, leading to ischemic eye diseases [4]. In addition, an increasing number of studies have confirmed that patients with carotid artery stenosis often have ischemic eye lesions, which often appear as the first symptom of internal carotid artery stenosis [5]. This study is intended to help clinical patients objectively evaluate the presence and severity of atherosclerosis in different individuals through non-invasive examinations such as ophthalmoscope or fundus camera by observing the correlation between eyeground arteriosclerosis and carotid atherosclerosis, and guide clinical patients to better prevent stroke at the first level.

2. Research Object and Method

2.1. Research Subjects

516 individuals aged ≥ 40 years who underwent neck vascular ultrasound and color fundus photography simultaneously at the physical examination center of Deyang People's Hospital in Sichuan Province from June 2020 to December 2022 using a random sampling method. Among them, there are 257 males and 259 females, aged 40 - 80 years, with an average age of 54.6 ± 16.3 years.

2.2. Method

1) Evaluate the traditional risk factors of the enrolled patients, including age, gender, hypertension, diabetes, coronary heart disease and other medical history; Fasting venous blood was collected to measure blood glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and homocysteine.

2) Fundus examination: Using the CR-2 fundus camera from CANON Company in Japan, the examination is completed in a dark room. According to Keith Wagner's classification of the presence and severity of retinal arteriosclerosis [6] [7]: 0 level: no retinal arteriosclerosis; Grade I: Mild extensive thinning of retinal arteries with enhanced reflective bands; Grade II: Retinal artery stenosis and widened reflective band, arteriovenous compression; Level III: On the basis of the above level II, accompanied by retinal hemorrhage or exudation; Grade IV: On

the basis of Grade III retinal fundus changes, optic nerve papillary edema appears. The above examinations and results are determined by two qualified clinical physicians. If the grading of the fundus examination of both eyes is inconsistent, the one with higher grading will be counted.

3) Carotid artery examination method and observation indicators: The Philips EPIQ7 color ultrasound diagnostic instrument and 7.5 MHz linear array probe were used to detect the bilateral carotid arteries of the subject. Sampling location: Common carotid artery (1.0 - 1.5 cm from the bifurcation); the bifurcation of the common carotid artery and the internal carotid artery (1.0 to 1.5 cm from the bifurcation). Observation indicators: a) Intima media thickness (IMT) of the common carotid artery, defined as IMT thickening when IMT ≥ 1.0 mm; b) presence or absence of carotid plaques, whether carotid plaques are vulnerable or stable. Carotid artery plaques are defined as those with IMT ≥ 1.5 mm. For patients with carotid artery plaques, the plaques can be further divided into: (i) hypoechoic lipid soft plaques; (ii) Fibrous flat plaques with moderate echogenicity and rich collagen tissue; (iii) Ulcerative mixed type plaques with varying echogenicity; (iv) A calcified hard plaque with strong echoes and echogenic shadows. Define types (i), (ii), and (iii) of plaques as vulnerable plaques, and type (iv) of plaques as stable plaques. The plaque score method was used to score the plaque [8], that is, without calculating the length of each plaque, only the maximum thickness (mm) of each isolated carotid atherosclerotic plaque on the same side was added to obtain the carotid plaque score on that side, and the sum of the carotid plaque scores on both sides was the total plaque score of the patient. The total plaque score of 1.1 - 5.0 is mild carotid atherosclerosis; 5.1 - 10.0 are moderate carotid atherosclerosis 10.0 is severe carotid atherosclerosis; c) The presence and severity of carotid artery stenosis: The location of the largest plaque is evaluated based on the ultrasound blood velocity of the carotid artery and the cross-sectional area of the residual cavity to determine the presence and severity of carotid artery stenosis. Based on this, the research subjects were divided into: normal or carotid artery stenosis group (vascular stenosis degree < 50%), moderate carotid artery stenosis group (stenosis degree 50% - 69%), and severe carotid artery stenosis group (stenosis degree 70% - 99%) [8] [9].

2.3. Statistical Analysis

Statistical analysis was conducted using SPSS 23.0 statistical software. Counting data is expressed in terms of rate, and inter group comparisons are made using X^2. The measurement data are expressed as mean ± standard deviation. The comparison of measurement data of normal distribution is performed by analysis of variance or t-test, otherwise, the rank sum test is used. Spearman rank correlation analysis of the correlation between fundus arteriosclerosis and age. Use logistic regression to analyze the risk factors of fundus arteriosclerosis and carotid arteriosclerosis. $P < 0.05$ indicates a statistically significant difference.

3. Results

3.1. Comparison of General Conditions and Risk Factors among Different Grades of Fundus Arteriosclerosis

Among the 516 physical examination patients, 198 (38.4%) had normal fundus examination, and 318 (61.6%) had fundus arteriosclerosis. Among them, 166 cases were of grade I (32.2%), 86 cases were of grade II (16.7%), and 66 cases were of grade III (12.8%). No grade IV lesions were found in this group of data. Compared with those with normal fundus examination, those with grade II and III fundus arteriosclerosis were older, had a history of hypertension and diabetes, and other general conditions and risk factors were not statistically significant between the two groups (see Table 1). Spearman correlation analysis found a correlation between the degree of fundus arteriosclerosis and age ($r = 0.422$).

3.2. Single Factor Analysis of the Correlation between the Grading of Eyeground Arteriosclerosis and Carotid Atherosclerosis

Among 516 physical examinees, 286 (55.4%) had no carotid atherosclerotic plaque, 201 (38.9%) had carotid atherosclerotic plaque, of which 58 (11.2%) were vulnerable plaque, 172 (33.3%) were stable plaque; There were 33 cases (6.4%) with carotid artery stenosis, including 23 cases (4.5%) with <50% stenosis and 10 cases (1.9%) with 50% - 69% stenosis. No stenosis ≥ 70% was found in this group of data. The IMT thickness of bilateral common carotid arteries, the incidence of carotid plaques and vulnerable plaques, the score of carotid plaques, and the presence of carotid stenosis in patients with fundus arteriosclerosis were significantly higher than those with normal fundus examination, with statistical significance ($P < 0.05$, see Table 1). Vascular elastic function is related to the degree of arteriolar wall sclerosis, expandability and lumen size, which are all affected by atherosclerosis. The first affected part of arteriosclerosis is the intima

Table 1. Correlation factors of different grades of eyeground arteriosclerosis and their relationship with carotid atherosclerosis.

	normal (198)	Grade I (166)	Class II (86)	Level III (66)	P-value
Age (years)	48.9 ± 13.6	53.3 ± 14.5	61.8 ± 20.6	62.2 ± 19.2	<0.001
Male [number of cases (%)]	96 (48.5)	83 (50.0)	44 (51.2)	34 (51.5)	0.996
Diabetes [cases (%)]	8 (4.0)	10 (6.6)	13 (15.1)	12 (18.2)	<0.001
Hypertension [cases (%)]	17 (8.6)	26 (15.7)	35 (40.7)	35 (53.0)	<0.001
Coronary heart disease [number of cases (%)]	3 (1.5)	3 (1.8)	3 (3.5)	2 (3.0)	0.958
Hyperlipidemia [% of cases]	76 (38.4)	82 (49.4)	53 (61.6)	44 (66.7)	<0.001
Bilateral common carotid artery IMT and (mm)	1.28 ± 0.33	1.46 ± 0.36	1.98 ± 0.38	2.01 ± 0.37	<0.001
Carotid artery plaques [% of cases]	40 (20.2)	65 (39.2)	51 (59.3)	45 (68.2)	<0.001
Vulnerable plaques [% of cases]	10 (5.1)	11 (6.6)	19 (22.1)	18 (27.3)	<0.001
Carotid artery plaque score (points)	1.77 ± 0.54	2.11 ± 0.62	3.98 ± 0.72	4.02 ± 0.81	<0.001
Carotid artery stenosis [% of cases]	4 (2.0)	6 (3.6)	12 (13.9)	11 (16.7)	<0.001

and media, and vascular elastic function is mainly maintained by the elastic fibers of the media. When hardening occurs, the media is damaged, and then the arterial elastic function decreases, thereby affecting the vascular volume, resulting in hemodynamic changes [10].

3.3. Multifactor Analysis of the Correlation between the Grading of Eyeground Arteriosclerosis and Carotid atherosclerosis

With eyeground arteriosclerosis II and III as dependent variables, the parameters with statistical significance between different grades of eyeground arteriosclerosis in the above univariate analysis as independent variables, including age, hypertension, diabetes, carotid atherosclerotic plaque, vulnerable carotid atherosclerotic plaque, carotid stenosis, bilateral common carotid artery IMT thickness and carotid plaque score, etc., Fundus arteriosclerosis was independently correlated with age, hypertension, vulnerable plaque of carotid atherosclerosis, carotid stenosis, IMT of common carotid artery, and carotid plaque score, with statistical significance ($P < 0.05$, see Table 2). Evidence-based medicine confirms that the occurrence of arteriosclerosis is influenced by age, blood pressure, blood lipids, diabetes, uric acid, obesity, smoking and diet habits, and the influence of various risk factors such as genetics. Fundus arteriosclerosis is a type of slow Sexual vascular disease that is one of the indications for target organ and peripheral arterial sclerosis, which is Aging manifestations of the vascular system around the body; Fundus artery microvascular abnormalities and heart. The occurrence, development, and prognosis of cerebrovascular diseases are closely related; Vascular lesions. It is systemic and can predict systemic arterial stiffness simultaneously with an increase in pulse pressure [11].

4. Discussion

Atherosclerosis is a chronic and progressive systemic arterial disease, which is characterized by the accumulation of lipids and complex sugars, bleeding and

Table 2. Multiple analyses of the main risk factors for vulnerable plaques.

risk factor	*OR*	95%CI	*P value*
Age	1.13	1.01-3.86	0.036
Hypertension	2.01	1.13-5.36	0.007
diabetes	0.91	0.78-1.36	0.523
carotid atherosclerotic plaque	0.93	0.71-1.68	0.327
Vulnerable plaque of carotid atherosclerosis	1.96	1.09-4.11	0.032
Carotid Stenosis	1.98	1.21-4.87	0.016
Bilateral common carotid artery IMT	1.85	1.16-3.98	0.029
Carotid artery plaque score	1.96	1.23-4.46	0.013

OR: Odds ratio; CI: Confidence interval.

thrombosis, followed by fibrous tissue hyperplasia and calcification, and the gradual degeneration and calcification of the middle layer of the artery, leading to thickening and hardening of the arterial wall and narrowing of the vascular lumen, which are the main reasons for clinical cardiovascular and cerebrovascular events [2] [8] [12]. Carotid atherosclerosis is closely related to the occurrence, development and recurrence of cerebral infarction, and is the most important cause and risk factor of cerebral infarction [1]. Atherosclerosis screening is beneficial for early detection of atherosclerosis patients and early intervention of atherosclerosis, which is of great significance in preventing cardiovascular and cerebrovascular diseases [13].

Carotid atherosclerosis inspection methods include carotid color Doppler ultrasound, CT angiography (CTA), magnetic resonance angiography (MRA) and cerebral angiography [14], but these inspection methods are expensive, some are invasive inspection methods, which is not conducive to carotid atherosclerosis screening. The retinal artery of the fundus is a branch of the internal carotid artery and is one of the few small arteries in clinical practice that can be directly observed in morphology in vivo. With the popularization of digital technology, fundus digital photography technology can provide objective and standardized manifestations of retinal arteriole abnormalities [6] [7], which is a simple, easy-to-implement, low-cost, non-invasive, and easily accepted examination method for patients. Multiple studies have found that the degree of fundus arteriosclerosis is related to cerebral small vessel disease, suggesting that fundus arteriosclerosis can serve as a clinical observation window for cerebral small vessel disease [15]. The correlation between fundus retinal angiopathy and cervical atherosclerosis has been confirmed by some studies. Studies have found that carotid artery IMT is associated with retinal arteriovenous diameter and arterial/venous ratio [16]. In addition, the severity of retinal microvascular lesions is related to the degree of extracranial carotid artery stenosis and the area of carotid artery plaques [17]. The results of this study found that eyeground arteriosclerosis was independently related to vulnerable carotid atherosclerotic plaque, carotid stenosis, common carotid artery IMT, and carotid plaque score, which was consistent with the above results. The results suggest that eyeground atherosclerosis can be used as one of the indicators to judge the presence and severity of carotid atherosclerosis.

This study found that eyeground arteriosclerosis is related to age, hypertension and diabetes, and age and hypertension are independently related to the severity of eyeground arteriosclerosis, which is consistent with previous research results [2] [7]. Therefore, for patients with these risk factors, timely change of bad lifestyle and active intervention of hypertension and diabetes may reduce the incidence of atherosclerosis, and thus reduce the incidence of cardiovascular and cerebrovascular diseases.

To sum up, carotid artery disease is closely related to the degree of eyeground arteriosclerosis. Fundus photography is a simple, easy, non-invasive and easy-to-accept inspection method. Its results are helpful to judge whether carotid athe-

rosclerosis is present and serious, guide clinical early detection and intervention of atherosclerosis, and reduce the incidence of cardiovascular and cerebrovascular diseases.

5. Limitations and Future Directions

This study is a cross-sectional study and cannot explain the sequence of occurrence of fundus arteriosclerosis and carotid arteriosclerosis. However, existing studies have shown that carotid arteriosclerosis occurs earlier than fundus arteriosclerosis. In the future, further experiments on improving arteriosclerosis can be conducted to improve the accuracy of predicting changes in the carotid artery in the fundus arteries.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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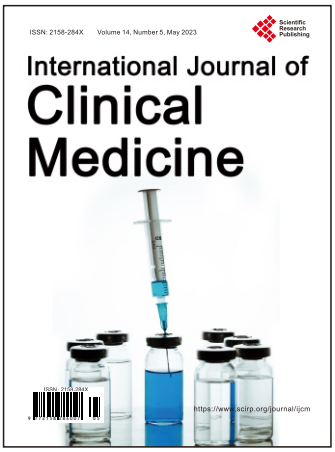

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