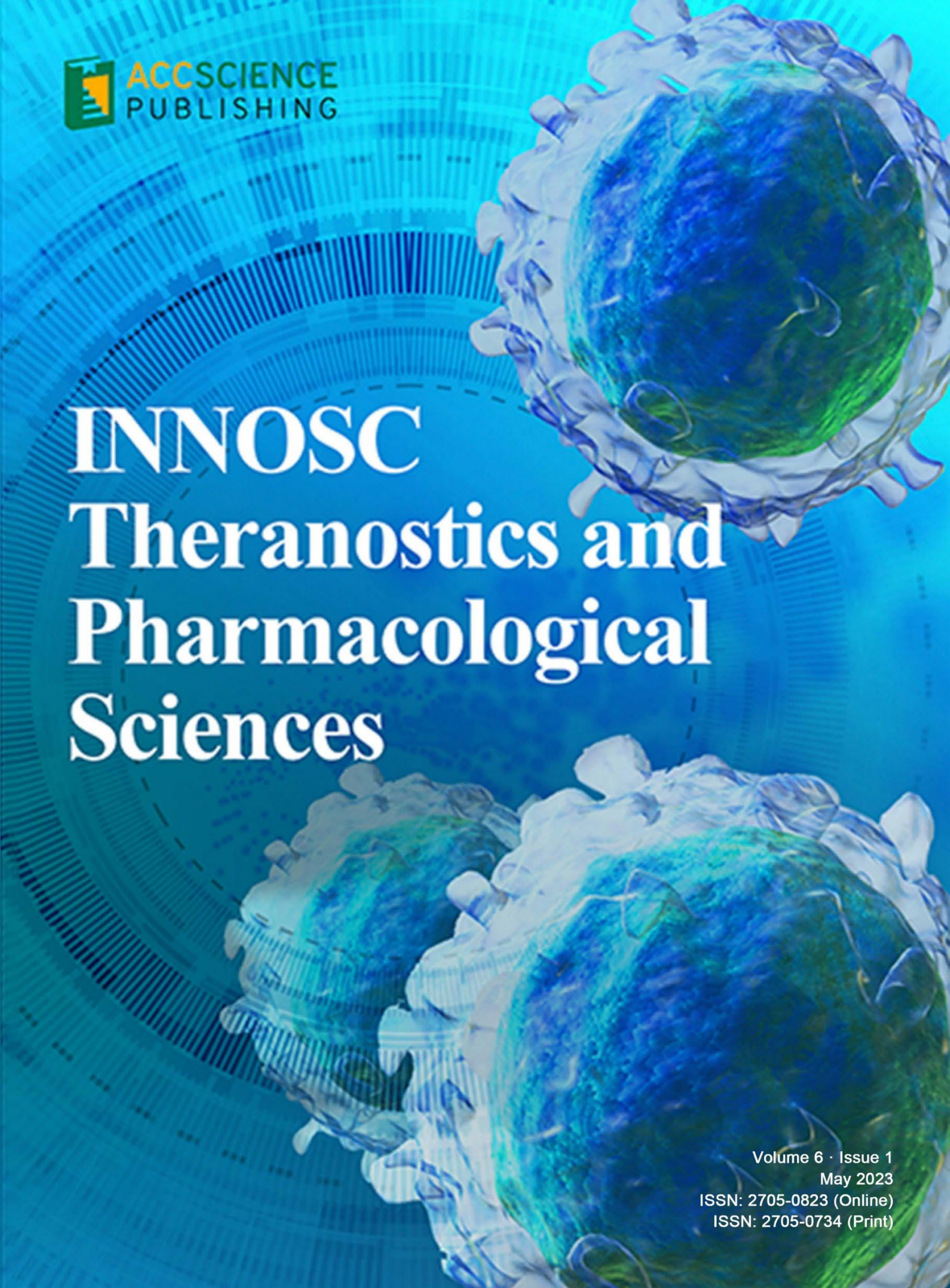

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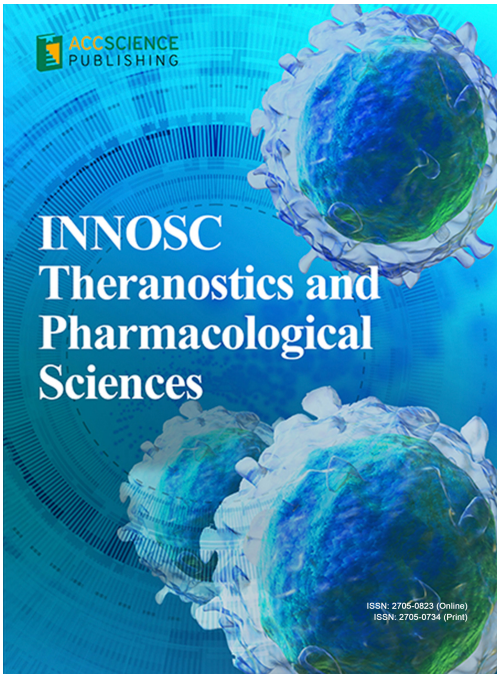

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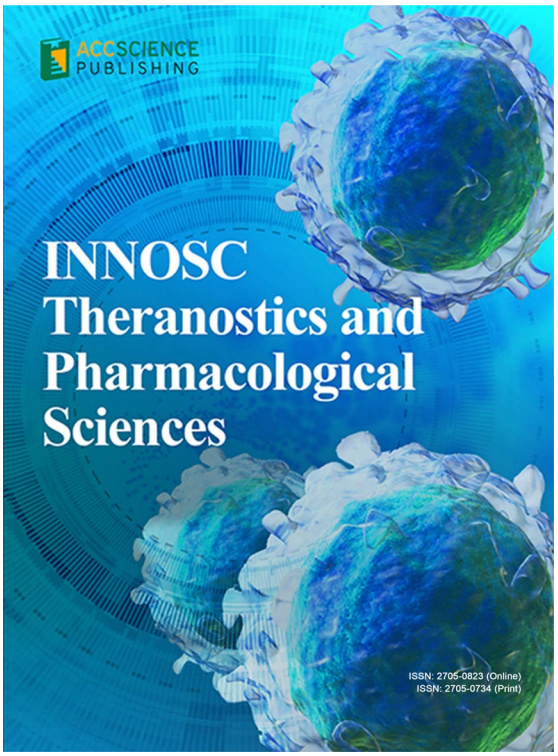

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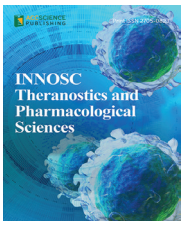

RESEARCH ARTICLE

Orally Administered Aqueous Extract of *Pleurotus ostreatus* Ameliorates Hyperglycemia in Streptozotocin-Induced Diabetic Rats

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Abstract:

Pleurotus ostreatus (Jacq.) P. Kumm. (Family: Pleurotaceae), commonly known as oyster mushroom, has been widely used to treat various ailments from simple headache to serious ones like diabetes. The mushroom has been shown to exert anti-inflammatory and antioxidant activities. In the present study, aqueous extract of *P. ostreatus* (AEPO) was examined for its antidiabetic activity in streptozotocin (STZ)-induced diabetic rats. STZ was administered to rats at 50 mg/kg body weight (i.p.), AEPO was orally administered at 100 and 200 mg/kg body weight, and metformin (500 mg/kg) was administered as positive control. The hypoglycemic effects of the AEPO were analyzed by assessing the blood glucose levels (oral glucose tolerance test, acute and postprandial antihyperglycemic activity), lipid parameters, and other hematological studies in comparison to standard drug (metformin). Results showed that AEPO caused a 26% reduction in blood glucose during fasting while 45% reduction in blood glucose during postprandial antihyperglycemic test in STZ-diabetic rats. It also helped in the normalizations of various complications associated with diabetes mellitus in rats. Observations from the current experiments indicate that *P. ostreatus* help in reduction of blood glucose level, thus confirming its antidiabetic activity in STZ-induced diabetes in rats. This study further advocates that supplementation of edible mushroom *P. ostreatus* could be a preventive approach in diabetes as well as in obesity management.

Keywords: Antidiabetic, *Pleurotus ostreatus*, Streptozotocin, Metformin

1. Introduction

Diabetes mellitus is known since ages as it has been mentioned in Ayurveda by Sushruta [1]. Diabetes mellitus is a chronic metabolic disease characterized by elevated plasma glucose concentration in fasting or postprandial state, or insulin resistance [2]. The World Health Organization and International Diabetes Federation reported an estimate of 10.5% (536.6 million people) global prevalence of diabetes, which is projected to rise to 643 million by 2030 and 783 million by 2045. An estimated 6.7 million deaths due to diabetes were reported in 2021. The incidences of diabetes are higher (3 in 4 adults) in low- and middle-income countries. Diabetes is characterized as a state of imbalance toward the factors that generate reactive oxygen radicals such as superoxide or hydroxyl radicals, and the level of antioxidant enzymes such as superoxide dismutases, catalase, and glutathione

peroxidases. The factors that generate reactive oxygen species (ROS) are both from the products of normal cellular physiology as well as from various exogenous sources. The excessive production of ROS and reactive nitrogen species (RNS) in or around the pancreatic beta cells is the major physiological reason that causes beta cells death and deficiency in insulin [3]. The development of insulin-dependent diabetes mellitus type 1 can be triggered by several risk factors, such as genetic, developmental, environmental and dietary factors. However, the ROS/RNS play central role in pancreatic β-cell death and disease progression, and both of the radical species play critical roles in cellular autoimmune-inflammatory responses [4]. Therefore, specific treatments with antioxidants and inflammatory drugs may inhibit the hyperglycemic response.

At present, treatments of diabetes mellitus include exercise, diet therapy, insulin therapy and oral antidiabetic agents such as sulfonylureas, biquanides, thiazolidinediones, and alpha glucosidase inhibitor. Despite of their effectiveness in reducing hyperglycemia, the use of these drugs is associated with non-desirable side effects [5]. Hence, herbal medicine can be used as an alternative therapy for treatment of diabetes. These herbal medicines help to reduce the complications associated with drugs and thus help in maintaining normal glucose level without triggering any complications [6]. Mushrooms are important food sources and represent a vast, untapped source of natural pharmaceutical products [7]. Mushrooms have low glycemic index which makes them low-calorie food, and contain high nutrients such as protein; therefore, they can be recommended for diabetics [7]. *Pleurotus* spp. or oyster mushrooms are rich in medicinal values such as effectiveness in reducing the total plasma cholesterol and triglyceride level and thus may reduce the chance of atherosclerosis and other cardiovascular and artery-related disorders [8]. These medicinal properties might be due to the presence of some important substance in dietary mushrooms [8]. *Pleurotus ostreatus* possessed potent antioxidant effects in the supplementation of corncobs with different herbs [9]. The antioxidant activity of *P. ostreatus* was found to be mechanistically associated with tyrosinase inhibitory effects tested in several antioxidant assays such as β-carotene-linoleic acid reduction, 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity, and ferrous chelating ability. It was further established that *P. ostreatus* has antioxidant properties by virtue of its phenolic composition and being enriched with selenium and zinc which serve as antioxidants [10]. Thus, this study aimed to utilize the antioxidant potential of *P. ostreatus* in an experimental model of diabetes. Streptozotocin (STZ), chemically an N-nitroso derivative of glucosamine, is a vast-spectrum antibiotic derived from *Streptomyces chromogens*. It acts as a pancreatic beta cell toxoid that stimulates and accelerates irreversible necrosis of pancreatic beta cells, making it an extensively used chemical inducer of diabetes in experimental animal models [11]. Thus, the present study determined the antidiabetic activity of an aqueous extract of *P. ostreatus* (AEPO) in an experimental model of diabetes induced by STZ in rats.

2. Materials and methods

2.1. Collection and preparation of AEPO

P. ostreatus was collected from Gorakhpur district, Uttar Pradesh, India. The sample was identified by relevant literature [12] and the sample was submitted with voucher number DDUNPL250 to the institutional repository. For extraction purpose, the fruiting bodies were dried under shade and ground to fine powder with the help of a grinder and stored in opaque screw top jar at room temperature. Aqueous extract of the macrofungal samples was prepared by the method of infusion. One gram of macrofungal sample as powder was mixed in 40 mL of boiling distilled water and allowed to infuse for 15 min. Then, it was filtered by Whatman no. 1 filter paper, and the volume was readjusted to 40 mL [13]. The final preparation named as AEPO was stored at 4°C until utilization.

2.2. Evaluation of antidiabetic potential in experimental model of diabetes in rats

In vivo experiment was designed according to method adopted by Kim *et al.* [14] with few modifications. The protocols for these experiments were approved by the Animal Ethical Committee of the Institute (IAEC/DDU/2021-22). Healthy adult male albino rats weighing approximately 60–160 g

were obtained and were kept at room temperature 25±5°C in large cage with polypropylene-coated wire gauze on all sides. Rats were exposed to a photoperiod of 12 h/day. The cages were cleaned regularly to avoid rat smell and to maintain proper hygienic conditions. The rats were acclimatized to laboratory conditions for 10 days and fed on rat pellets and water *ad libitum*. Each rat was weighed and assigned a number for convenience before the onset of experiment. Experimental animals were divided into five groups with three rats in each (n=3); the categorization plan is as follows:

(i) Group 1: Vehicle control (received 0.1 M citrate buffer, i.p.)
(ii) Group 2: Diabetic rat (received STZ 50 mg/kg b.w. in 0.1 M citrate buffer, i.p., single dose)
(iii) Group 3: Diabetic rat received metformin (500 mg/kg b.w. aqueous solution, p.o., per day, for 4 weeks)
(iv) Group 4: Diabetic rat received AEPO (100 mg/kg b.w., p.o., per day, for 4 weeks)
(v) Group 5: Diabetic rat received AEPO (200 mg/kg b.w., p.o., per day, for 4 weeks)

Studies have utilized a dose range of 100–500 mg/kg for investigating the biomedicinal effects of *P. ostreatus* against several disease models in rats [15-17]. Based on above observations and our previous studies with 100–300 mg/kg mushroom extracts [18-22] with no notable toxicity, we used 100 and 200 mg/kg AEPO in this study. STZ was administered as a single dose while metformin and AEPO per day for 4 weeks.

2.3. Induction of diabetes in rats

Diabetes mellitus in rats was induced by single intraperitoneal (i.p.) administration of freshly prepared solution of STZ (HiMedia, CMS 1758) dissolved in 0.1 M citrate buffer, pH = 4.5 (vehicle control). For diabetes induction, each test animal was injected with 50 mg/kg volume of freshly prepared STZ. At the same time, normal rats received the same volume of vehicle control through the same route. The animals were returned to their cages after injection and allowed for free access to food and water. After 3–4 days, the fasting blood glucose level was measured from the tail vein using glucometer (mylife Pura™ blood glucose monitoring system). Animals with blood glucose level higher than 180 mg/dL were considered diabetic and used for the experiment.

2.4. Assessment of body weight

Rats were weighed initially and after the experiment. The relative change in body weight (b.w.) of rat was determined in percentage using following equation:

$$\text{Percent relative change in b.w.} = \frac{\text{Pre-treatment b.w.} - \text{Post-treatment b.w.}}{\text{Pre-treatment b.w.}} \times 100$$

2.5. Oral glucose tolerance test (OGTT)

The experimental animals were fasted overnight (about 12 h) before commencing the experiment. Rats of all the groups were given D-glucose (500 mg/mL) solution after half an hour after metformin and AEPO administration. Blood samples were withdrawn from tail vein before and after the metformin and AEPO administration at 30, 60, 90, and 120 min.

2.6. Determination of serum glucose

Blood glucose level was measured in two steps; first, fasting blood glucose level was measured, and second, postprandial antihyperglycemic was tested.

2.6.1. Fasting blood glucose level

Experimental animals were deprived of food for about 16 h with free access to drinking water before the commencement of experiment. Experimental animals were tested for their blood glucose level at 0, 24, 48, and 72 h of treatment of AEPO. Blood samples were collected from the tail vein for glucose analysis.

2.6.2. Postprandial antihyperglycemic test

This study was done in two steps, that is, acute and chronic. For acute study, rats were fasted for 1 h before test. After the fasting period, rats were given either metformin or AEPO orally using intragastric gavage. Blood samples were collected from the tail vein just before (0 h) and after 2, 4, 6, and 24 h administration of metformin or AEPO. In chronic study, glucose level in blood was measured at 0 day and 5, 10, 15, and 30 days after treatment.

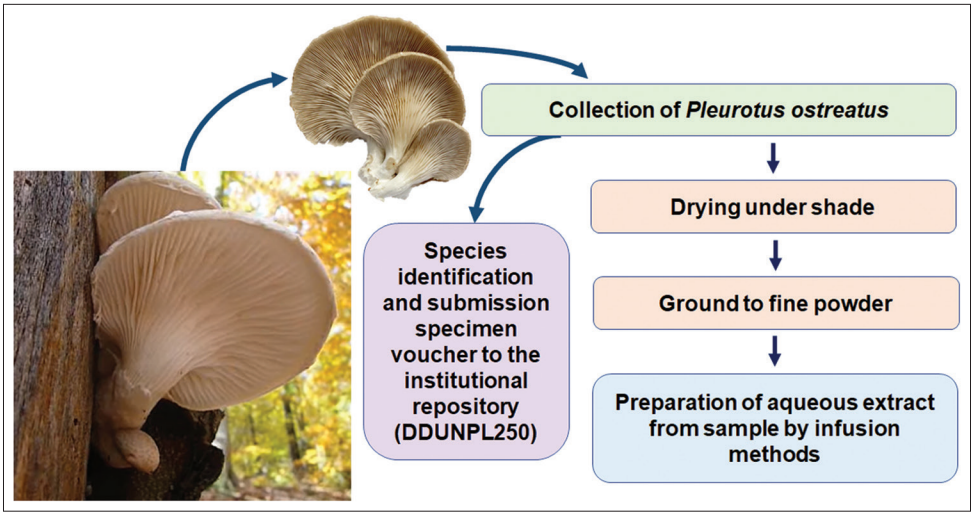

Figure 1. Schematic diagram for collection and preparation of the aqueous extract of *Pleurotus ostreatus*.

Metformin and AEPO were given to experimental rats every day.

2.7. Hematological assessment

Hematological analysis was performed from whole blood sample using the Hematological Analyzer Sysmex (KX 21, Japan). Erythrocyte count (red blood cell [RBC]), hemoglobin concentration (Hb), leukocyte count (white blood cell [WBC]), neutrophil percentage, and lymphocyte percentage in WBC were measured in control and treated rats. Biochemical Analyzer (Transasia ERA CHEM-5 PLUS, India) was used for analyzing blood biochemical parameters.

2.8. Statistical analysis

Data are presented as mean ± standard deviation (SD) or standard error of mean (SEM) from minimum three experimental repeats. The data were statistically analyzed by Students *t*-test and analysis of variance to compare parameters among groups. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of *P. ostreatus* on body weight of test animals

Body weight and behavioral change of the experimental animals were monitored as physiological markers of the health. Data showed that oral administration of AEPO caused no changes in gross behavior, and none of the animals died during the course of experiment. There were no harmful effects observed in rats due to treatment with AEPO, showing that it caused no changes in gross behavior of animals. Data presented in **Figure 2** demonstrated that control rats were more stable in their body weight. STZ-treated diabetic rats showed significant reduction in weight (39%) as compared to vehicle control ($P < 0.05$). Metformin-treated diabetic rats showed a greater effect on body weight with 17.3% reduction in body weight ($P < 0.05$). AEPO treatment to diabetic rats caused a dose-dependent increase in body weight by 16.3% and 20.2% increase in body weight at 100 and 200 mg/kg dosage, respectively. Diabetic rats treated with AEPO (200 mg/kg) showed a notable effect that helped to increase the body weight of experimental diabetic rat with a similar response to metformin (**Figure 1**). These results showed a preliminary protective effect of AEPO in diabetic rats as physiological marker of health.

3.2. Effect of *P. ostreatus* on fasting blood glucose level in STZ-induced diabetic rats

Reduction in blood glucose level is considered the biochemical marker of antidiabetic effect of a candidate drug agent. As it is evident from **Table 1**, fasting blood glucose level was elevated to a notable level (190 ± 1.38 mg/dL) in diabetic rats in comparison to vehicle control group (99 ± 2.32 mg/dL) at the time of starting the experiment (before treatment stage). STZ-induced diabetic rats showed a narrow range of blood glucose level (182 – 193 mg/dL) at the time of starting the experiment. Metformin treatment to

STZ-diabetic rats showed a reducing trend in the level of blood glucose by 170, 159, and 130 mg/dL at 24, 48, and 72 h, respectively. These reductions in the blood glucose levels accounted for 12%, 17%, and 32% at 24, 48, and 72 h, respectively. The data were significantly lowered ($P < 0.05$) as compared to vehicle control at different time points. AEPO at each concentration tested showed substantial results in lowering the blood glucose levels. Oral administration of AEPO to STZ-induced diabetic rats showed a dose- and time-dependent decrease in the blood glucose levels. AEPO (100 mg/kg) treatment to STZ-diabetic rats showed that blood glucose levels were reduced to 177, 165, and 145 mg/dL at 24, 48, and 72 h, respectively, which were about 3 – 20% reductions, whereas AEPO at 200 mg/kg dose led to a reduction oft blood glucose levels to 175, 161, and 139 mg/dL at 24, 48, and 72 h, respectively, with about 7 – 26% reductions. AEPO at 200 mg/kg dose showed a blood glucose-lowering effect in STZ-diabetic rats similar to that of metformin (500 mg/kg). Thus, these results showed potent antihyperglycemic effects of *P. ostreatus* in diabetic rats.

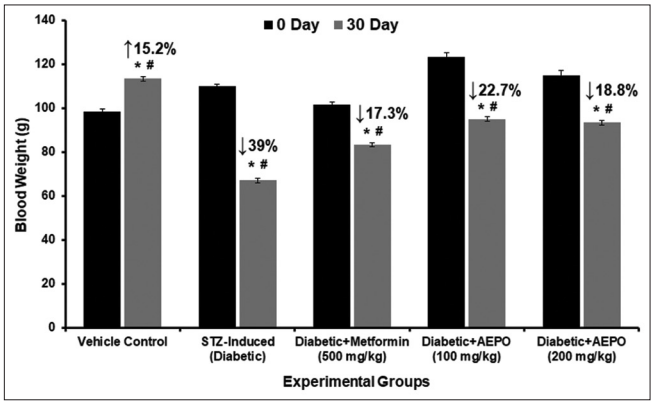

Figure 2. Effect of aqueous extract of *Pleurotus ostreatus* and metformin on body weight of diabetic rats. Values are mean ± standard error of mean for groups of 3 observations with their standard errors. ↓ decrease; ↑ increase in body weight. **P*<0.05 vs vehicle control 30 days; #*P*<0.05 vs. within group 30 min.

3.3. Postprandial antihyperglycemic effects of *P. ostreatus* on STZ-induced diabetic rats: acute and chronic assessment

Postprandial blood sugar levels are important indicator for diabetes and hyperglycemia, which is tested along with fasting blood sugar. Postprandial blood sugar measurements can give a clue about the metabolic health in a metabolically altered state of diabetes [23]. For postprandial antihyperglycemic test, two different criteria were used; first as acute study performed at different short intervals of 0, 2, 4, 6, and 24 h, and second as chronic study performed at 0, 5, 10, 15 and 30 days. In the acute study (**Table 2**), rats in vehicle control group showed a normal course of decline in postprandial blood glucose levels from 0 h to 24 h with total about 25 mg/dL reduction in 24 h, whereas STZ-induced diabetic rats showed an increasing trend in postprandial blood glucose levels from 0 h (270 ± 1.65 mg/dL) to 24 h (310 ± 2.92 mg/dL) with total about 40 mg/dL (14.8%) increment in 24 h. Treatment of STZ-induced diabetic rats with metformin (500 mg/kg) caused a time-dependent

Table 1. Effect of AEPO and metformin on fasting glucose level in STZ- induced diabetic rats

Experimental groups	Blood glucose level (mg/dL)			
	Before treatment	24 h after treatment	48 h after treatment	72 h after treatment
Vehicle control	99±2.32	95±1.95	98±2.77	98±2.98
STZ-induced (diabetic)	190±1.38*	193±2.84*	195±2.37*	195±2.85*
Diabetic+metformin (500 mg/kg)	193±2.33*	170±2.37# ^11.92%	159±1.19# ^17.61%	130±3.65# ^32.64%
Diabetic+AEPO (100 mg/kg)	182±2.72*	177±1.39# ^2.74%	165±0.99# ^9.34%	145±3.75# ^20.33%
Diabetic + AEPO (200 mg/kg)	188±2.84*	175±1.33# ^6.91%	161±1.37# ^14.36%	139±1.72# ^26.06%

Values are mean±SEM for groups of three observations with their standard errors. AEPO: Aqueous extract of *Pleurotus ostreatus*; STZ: Streptozotocin. ^Values in percent indicate reductions in the blood glucose levels relative to 0 h (before treatment) of the respective treatment groups. **P*<0.05 versus control; #*P*<0.05 versus STZ group

reduction in postprandial blood glucose levels from 0 h (275 ± 0.99 mg/dL) to 24 h (220 ± 1.08 mg/dL). Metformin showed a total 20% reduction in the postprandial blood glucose level as compared to STZ-induced diabetes. Oral administration of AEPO showed a dose- and time-dependent decrease in postprandial blood glucose level in STZ-diabetic rats. AEPO showed a reduction of 8.7 and 14.5% postprandial blood glucose level at 100 and 200 mg/kg dosage.

In the chronic study (**Table 3**), rats in vehicle control group showed an almost constant level of postprandial blood glucose from day 0 to day 30. STZ-induced diabetic rats showed a gradual increase in postprandial blood glucose levels from day 5 to day 15 (about 22%), and a total of 69 mg/dL (25%) increase in postprandial blood glucose at day 30. Metformin (500 mg/kg) treatment to STZ-induced diabetic rats caused a time-dependent reduction in postprandial blood glucose levels from day 0 (275 ± 2.87 mg/dL) to day 30 (135 ± 2.38 mg/dL) with total 140 mg/dL (about 51%) reduction in postprandial blood glucose at day 30 which denotes a potent therapeutic reduction in hyperglycemia. Furthermore, oral administration of AEPO to STZ-induced diabetic rats showed a dose- and time-dependent decrease in postprandial blood glucose levels from day 0 to day 30. AEPO (100 mg/kg) treated diabetic rats showed about 80 mg/dL (about 30%) reduction in postprandial blood

Table 2. Effect of AEPO and metformin on postprandial blood glucose levels in STZ-induced diabetic rats (acute study within 24 h of treatment)

Experimental groups	Blood glucose level (mg/dL)				
	0	2 h	4 h	6 h	24 h
Vehicle control	115±2.99	110±1.98	106±2.55	102±2.32	90±1.03
STZ-induced (Diabetic)	270±1.65*	275±3.20* ^1.85%	280±2.74* ^3.70%	295±1.33* ^9.25%	310±2.92* ^14.8%
Diabetic+metformin (500 mg/kg)	275±0.99*	262±3.65 ^4.73%	257±2.39# ^6.54%	237±1.91# ^13.81%	220±1.08# ^20.0%
Diabetic+AEPO (100 mg/kg)	285±3.32*	276±2.39 ^3.16%	270±0.99 ^5.26%	269±2.87#,$ ^5.61%	260±2.61#,$ ^8.77%
Diabetic + AEPO (200 mg/kg)	275±0.98*	255±3.20# ^7.27%	247±1.87# ^10.18%	241±3.33# ^12.36%	235±1.87# ^14.54%

Values are mean±SEM for groups of three observations with their standard errors at different time points within 24 h. AEPO: Aqueous extract of *Pleurotus ostreatus*; STZ: Streptozotocin. ^Values in percent indicate the change in the blood glucose levels relative to 0 h (before treatment) of the respective treatment groups. *P<0.05 versus control; #P<0.05 versus STZ group; $$P$<0.05 versus metformin group

Table 3. Effect of AEPO and metformin on postprandial blood glucose levels in STZ-induced diabetic rats (chronic study up to 30 days of treatment)

Experimental groups	Blood glucose level (mg/dL)				
	0 day	5 day	10 day	15 day	30 day
Vehicle control	90±2.33	93±3.20	95±0.99	95±2.75	96±1.53
STZ-induced (diabetic)	270±2.54*	328±2.39* ^21.48%	330±1.54* ^22.22%	333±1.05* ^23.33%	339±0.99* ^25.55%
Diabetic+metformin (500 mg/kg)	275±2.87*	208±1.98# ^24.36%	195±1.85# ^29.09%	175±1.99# ^36.66%	135±2.38# ^50.90%
Diabetic+AEPO (100 mg/kg)	270±2.23*	235±1.32#,$ ^12.96%	226±2.45#,$ ^16.30%	220±1.56#,$ ^18.51%	190±1.89#,$ ^29.62%
Diabetic + AEPO (200 mg/kg)	275±0.98*	228±1.28#,$ ^17.09%	215±1.57#,$ ^29.81%	190±2.21# ^30.90%	150±2.63# ^45.45%

Values are mean±SEM for groups of three observations with their standard errors at different time points within 24 h. AEPO: Aqueous extract of *Pleurotus ostreatus*; STZ: Streptozotocin. ^Values in percent indicate the change in the blood glucose levels relative to 0 h (before treatment) of the respective treatment groups. *P<0.05 versus control; #P<0.05 versus STZ group; $$P$<0.05 versus metformin group.

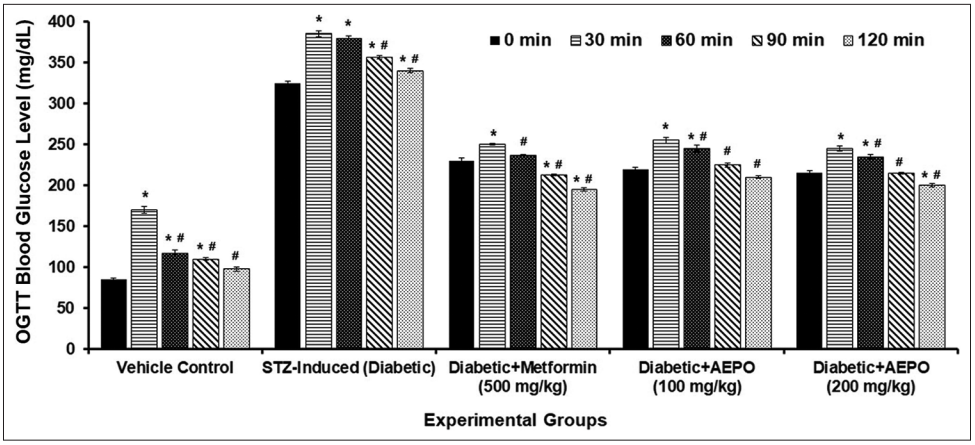

Figure 3. Effect of aqueous extract of *Pleurotus ostreatus* and metformin on oral glucose tolerance in diabetic rats. Values are mean ± standard error of mean for groups of three observations with their standard errors. *$P < 0.05$ versus 0-min within group; $^{\#}P < 0.05$ versus 30-min within group.

glucose, whereas diabetic rats treated with AEPO (200 mg/kg) showed about 125 mg/dL (about 45%) reduction in postprandial blood glucose.

Thus, results showed that AEPO act as potent antihyperglycemic agent and caused an active reduction in postprandial blood glucose in both acute and chronic studies. The antihyperglycemic effect of AEPO at 200 mg/kg was comparatively similar to that of metformin (500 mg/kg) in diabetic rats, suggesting its potent use in diabetes management.

3.4. Effect of *P. ostreatus* on oral glucose tolerance in STZ-induced diabetic rats

The OGTT is a vital preclinical test for characterizing the metabolic syndrome from prediabetes stage to type 2 diabetes. The oral glucose tolerance in both humans and animals acts as an indicator of the relative roles of insulin secretion and insulin resistance in the progression of glucose intolerance [24]. The OGTT was conducted at 0, 30, 60, 90, and 120 min, and results are presented in **Figure 3**. Results indicated interesting finding in observations from different treatment groups. Vehicle control group rats showed a response of OGTT as shown by a significant increase in blood glucose at 30 min that gradually reduced and retained a similar level to 0 min after 2 h ($P < 0.05$). STZ-induced diabetic rats showed a hyperglycemic response in OGTT with a significant increase in blood glucose at 30 min that remained similarly increased till 60 min ($P > 0.05$). The blood glucose level was moderately reduced at 90- and 120-min time intervals in STZ-diabetic rats that was significant as compared to 0-min ($P < 0.05$) as well as 30-min intervals ($P < 0.05$). This indicated that STZ-diabetic rats mimicked type 2 diabetes and that they serve as a suitable model for preclinical assessment of antihyperglycemic agents. Metformin treatment was very effective in controlling the blood glucose level and helped to reduce the OGTT glucose levels in very effective manner. STZ-diabetic rats treated with metformin (500 mg/kg) showed a promising therapeutic response in OGTT glucose levels. Metformin-treated diabetic rats showed that blood glucose level was significantly increased in first 30 min ($P < 0.05$) and that was gradually and significantly reduced at 120 min as compared to 0-min ($P < 0.05$) as well as 30-min ($P < 0.05$). Treatment of STZ-diabetic rats with AEPO showed a dose- and time-dependent reduction in blood glucose levels in OGTT with a response comparable to metformin. AEPO (100 mg/kg) group showed a significant increase in blood glucose at first 30 min ($P < 0.05$) and a gradual decrease that was significant as compared to 30-min ($P < 0.05$) and similar to 0-min ($P > 0.05$). AEPO at 200 mg/kg showed similar yet more potent response on blood glucose levels in OGTT with notable decrease at 120 min ($P > 0.05$). These observations suggested that AEPO has a potent antidiabetic effect as it could effectively regulate glucose tolerance in rats.

3.5. Effect of *P. ostreatus* on hematological parameters in STZ-induced diabetic rats

Diabetes causes elevated blood glucose level, which contributes to disturbed profile of blood cells and its

indices. Early normalization of glycemia has been suggested to inhibit pathological processes, which are meticulously associated with hyperglycemia such as increased oxidative stress and glycation of cellular proteins and lipids [25]. Thus, a good glycemic control remedy is recommended that could exert preventive effects on the blood profile as well. Results of the hematological analysis for hemoglobin levels are depicted in **Figure 4A**. Results indicated that hemoglobin level was significantly decreased in STZ-induced diabetic rats (13.9 ± 0.27 g/dL) as compared to vehicle control (15.7 ± 0.58 g/dL) with $P < 0.05$. Metformin (500 mg/kg) treatment to diabetic rats caused a notable increase in hemoglobin level (14.8 ± 0.75 g/dL) that was comparatively close to vehicle control ($P > 0.05$). Administration of AEPO to diabetic rats caused a dose-dependent restoration of hemoglobin toward normal range. Diabetic rats treated with AEPO at 100 mg/kg showed hemoglobin level 14 ± 0.55 g/dL, while AEPO at 200 mg/kg showed hemoglobin level 14.5 ± 0.81 g/dL with statistically similar values as compared to vehicle control. Total WBC count was estimated in experimental groups as another hematological parameter and the results are presented in **Figure 4B**. Results indicated that total WBC count was significantly increased in STZ-induced diabetic rats (5100/cc^3) as compared to vehicle control (4100/cc^3) with statistical significance ($P < 0.05$). Metformin (500 mg/kg) treatment to diabetic rats caused reduction in WBC count to a level (4200/cc^3) closely similar to vehicle control and significant to STZ-diabetic group ($P < 0.05$). AEPO treatment to diabetic rats showed a restorative effect on WBC count with 4500 and 4400/cc^3 at 100 and 200 mg/kg, respectively. WBC count restoration was significant as compared to STZ-diabetic group ($P < 0.05$) yet statistically similar as compared to vehicle control.

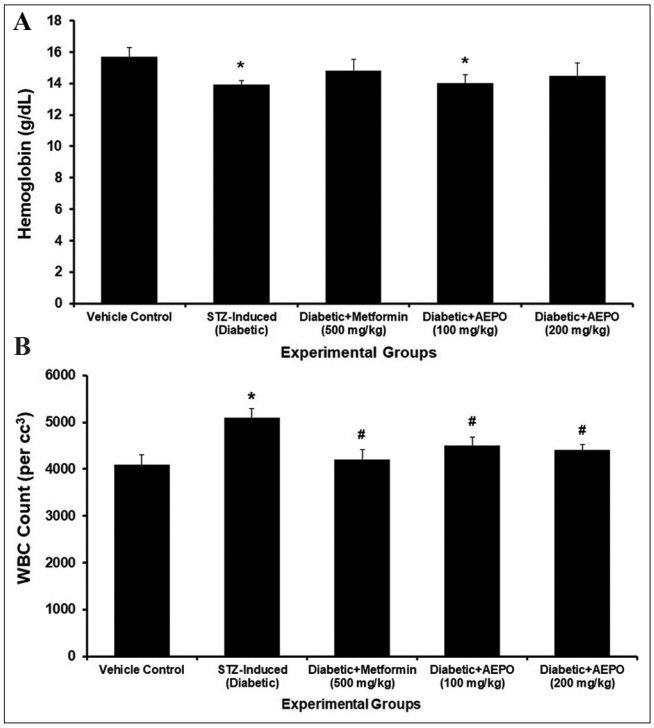

Figure 4. Effect of aqueous extract of *Pleurotus ostreatus* and metformin on hemoglobin and white blood cell (WBC) levels in diabetic rats. (A) Hemoglobin levels and (B) WBC count are presented as mean ± standard error of mean for groups of three observations with their standard errors. *$P < 0.05$ versus vehicle control; $^{\#}P < 0.05$ versus Streptozotocin-diabetic group.

The further analyzed hematological parameter was different leukocytes count (DLC) from different experimental groups (**Table 4**). Results showed notable variations in the DLC parameter in different experimental groups. The level of neutrophils was drastically increased (40%) in STZ-diabetic rats (84%) as compared to vehicle control (60%). Diabetic rats treated with metformin (500 mg/kg) showed 65% neutrophils which were comparatively close to vehicle control. Administration of AEPO caused a dose-dependent restoration in the neutrophils level in diabetic rats with 77% and 69% neutrophils at 100 and 200 mg/kg dosage, respectively. The level of lymphocytes was decreased by 35% in STZ-diabetic rats (26%) as compared to vehicle control (40%). Metformin (500 mg/kg) treatment could elevate the level of lymphocytes (33%) in diabetic rats yet not significant when compared with STZ-diabetic or vehicle control groups. Treatment of diabetic rats with AEPO caused a limited restoration of lymphocytes to 29% and 30% at 100 and 200 mg/kg, respectively. Estimation of RBC count showed that its level was reduced in STZ-diabetic rats to 4.25 million/mm^3 as compared to vehicle control (5.50 million/mm^3). Diabetic rats treated with metformin (500 mg/kg) showed RBC level of 5.22 million/mm^3, which was comparatively close to vehicle control ($P > 0.05$) and significantly elevated as compared to STZ-diabetic group ($P < 0.05$).

Table 4. Effect of AEPO and metformin on different leukocyte count (DLC) of experimental rats

Experimental groups	Neutrophils (%)	Lymphocytes (%)	Eosinophils (%)	Monocytes (%)	Basophils (%)	Total RBC count (million/mm^3)	Platelet count (lac/mm^3)	Hematocrit (%)
Vehicle control	60±1.09	40±0.65	0	0	0	5.50±0.58	1.53±0.32	42.9±0.37
STZ-induced (diabetic)	84±1.22* ↑40%	26±0.8* ↓35%	1	2	0	4.25±0.27* ↓22.73%	2.1±0.25* ↑37.25%	47.1±1.38* ↑9.80%
Diabetic+metformin (500 mg/kg)	65±0.95$^{\#}$ ↑8.33%	33±1.9*$^{\#}$ ↓17.5%	0	0	0	5.22±0.36$^{\#}$ ↓5.10%	1.59±0.82$^{\#}$ ↑3.92%	44.2±1.12*$^{\#}$ ↑3.03%
Diabetic+AEPO (100 mg/kg)	77±1.32* ↑22.18%	29±0.3* ↓27.5%	0	0	0	4.82±0.72*$^{\#\$}$ ↓12.36%	1.85±0.35*$^{\#\$}$ ↑20.92%	45.3±1.33*$^{\#}$ ↑5.60%
Diabetic + AEPO (200 mg/kg)	69±1.94$^{\#}$ ↑15%	30±0.8* ↓25%	0	0	0	5.18±0.89*$^{\#}$ ↓5.82%	1.73±0.21*$^{\#}$ ↑13.07%	44.4±1.87*$^{\#}$ ↑4.66%

Values are mean±SEM for groups of three observations with their standard errors. Values in percent indicate increase (↑) or decrease (↓) in parameters. RBC: Red blood cell, erythrocyte count; AEPO: Aqueous extract of *Pleurotus ostreatus*; STZ: Streptozotocin. *P<0.05 versus control; $^{\#}P$<0.05 versus STZ group; $^{\$}P$<0.05 versus metformin group

Administration of AEPO to diabetic rats caused a dose-dependent restoration in the RBC levels with 4.82 and 5.18 million/mm^3 RBCs at 100 and 200 mg/kg dosages, respectively. Measurement of platelet count showed similar observations as RBC count. STZ-diabetic rats showed 2.1 lac/mm^3 as compared to vehicle control (1.53 lac/mm^3). Metformin (500 mg/kg) treatment to diabetic rats showed notable restoration in the platelet count (1.59 lac/mm^3) which was comparatively close to vehicle control (P > 0.05) and significantly elevated in comparison to STZ-diabetic group (P < 0.05). AEPO administration to diabetic rats caused a dose-dependent restoration in the platelet count by 1.85 and 1.73 lac/mm^3 at 100 and 200 mg/kg, respectively. Estimation of hematocrit levels showed that it was by about 10% in STZ-diabetic rats (47.1%) as compared to vehicle control (42.9%). Metformin (500 mg/kg) treatment to diabetic rats restored the level of hematocrit to 44.2% which was comparatively close to vehicle control (P > 0.05) and statistically significant as compared STZ-diabetic group (P < 0.05). AEPO administration to diabetic rats caused a dose-dependent restoration in the hematocrit level by 45.3 and 44.4% at 100 and 200 mg/kg, respectively. The change in hematocrit by AEPO (200 mg/kg) was statistically close to the level of vehicle control. The DLC profile of experimental groups showed that there was not much notable difference in the levels of eosinophils, monocytes, and basophils (**Table 4**).

The assessment of the liver function test (LFT) parameters was analyzed in different experimental groups and presented in **Table 5**. In a nutshell, results showed that the levels of total cholesterol, triglyceride, low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), total cholesterol/high-density lipoprotein (HDL) ratio, and cholesterol/HDL ratio were elevated multifold in STZ-diabetic rats with statistical significance. Treatment with metformin (500 mg/kg) to diabetic rats was preventive in nature to larger extent yet statistically not closer to vehicle control or STZ-diabetic group. Administration of AEPO to diabetic rats showed a dose-dependent restoration of LFT parameters yet statistically not closer to vehicle control or STZ-diabetic group. The levels of HDL were reduced in STZ-diabetic rats as compared

Table 5. Effect of AEPO and metformin on lipid profile of experimental rats

Experimental groups	Total cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL Ch. (mg/dL)	LDL Ch. (mg/dL)	VLDL Ch. (mg/dL)	Total Ch./HDL Ch. ratio (mg/dL)	LDL Ch./HDL Ch. ratio (mg/dL)
Vehicle control	58.5±1.02	24.1±1.54	42.1±1.05	17.76±1.22	4.82±0.86	1.73±0.09	0.45±0.02
STZ-induced (diabetic)	138.63±1.98*	134.7±1.22*	31.9±1.22*	45.16±2.01*	26.94±1.25*	2.84±0.27*	1.42±0.05*
Diabetic+metformin (500 mg/kg)	73.9±1.81*$^{\#}$	40.23±1.87*$^{\#}$	39.7±1.51*$^{\#}$	19.78±1.85*$^{\#}$	13.64±0.92*$^{\#}$	1.86±0.04*$^{\#}$	0.58±0.07*$^{\#}$
Diabetic+AEPO (100 mg/kg)	90.7±0.99*$^{\#\$}$	89.91±1.54*$^{\#\$}$	32.1±1.62*$^{\$}$	28.77±1.51*$^{\#\$}$	17.50±0.88*$^{\#\$}$	2.46±0.08*$^{\#\$}$	0.70±0.06*$^{\#\$}$
Diabetic + AEPO (200 mg/kg)	78.52±1.58*$^{\#\$}$	68.2±0.98*$^{\#\$}$	33.5±1.25*	26.75±1.85*$^{\#\$}$	16.44±0.42*$^{\#\$}$	2.31±0.09*$^{\#\$}$	0.67±0.02*$^{\#\$}$

Values are mean±SEM for groups of three observations with their standard errors. HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very-low-density lipoprotein; Ch.: Cholesterol; AEPO: Aqueous extract of *Pleurotus ostreatus*; STZ: Streptozotocin. *$P<0.05$ versus control; $^{\#}P<0.05$ versus STZ group; $^{\$}P<0.05$ versus metformin group

to vehicle control that was largely restored by metformin (500 mg/kg) treatment yet statistically reduced compared to vehicle control. Exceptionally AEPO was unable to show statistical alterations in the HDL level as compared to STZ-diabetic rats.

We further assessed the kidney function profile of different experimental groups and data are presented in **Table 6**. Results clearly indicate that all the diabetic rats showed altered levels of kidney function parameters. In a nutshell, results showed that the levels of serum creatinine, serum uric acid, serum urea, and serum blood urea nitrogen (BUN) were elevated multifold in STZ-diabetic rats with statistical significance. Treatment with metformin (500 mg/kg) to diabetic rats was preventive in nature to larger extent yet statistically not closer to vehicle control or STZ-diabetic group. Likewise, administration of diabetic rats with AEPO showed a dose-dependent restoration of kidney function parameters yet statistically not closer to vehicle control or STZ-diabetic group.

4. Discussion

Diabetes mellitus is one of the most common chronic diseases associated with carbohydrate metabolism. It is also an indication of co-morbidities such as obesity, hypertension, and hyperlipidemia, which are metabolic complications of both clinical and experimental diabetes [26]. At present, drug therapy either alone or in combination cannot restore normal blood glucose homeostasis, and many limitations exist in their use. While external insulin is necessary for control of type 1 diabetes mellitus, the use of drug therapy in type 2 diabetes is initiated only after dietary and lifestyle modifications [13]. Oyster mushroom (*Pleurotus* spp.) is known in the Indian traditional system of medicine for its antihyperglycemic and antihyperlipidemic potential. *P. ostreatus* is reported to contain several bioactive molecules that are attributed to its therapeutic effects. The major bioactive molecules are phenolics, flavonoids, polysaccharides, lectins, terpenoids, steroids, lipids, and glycoproteins. These phytochemical compounds act as exogenous antioxidants that can regulate oxidative stress, suppress inflammation, and regulate glycemic and lipidemic alterations in the human body [27]. By virtues of the benefits of oyster mushrooms, we attempted to explore the effects of an AEPO on

Table 6. Effect of AEPO and metformin on liver and function of experimental rats

Experimental groups	Serum creatinine (mg/dL)	Serum uric acid (mg/dL)	Serum urea (mg/dL)	Serum BUN (mg/dL)
Vehicle control	0.69±0.01	2.98±0.09	32.7±0.98	15.28±0.74
STZ-induced (diabetic)	1.11±0.07*	5.23±0.52*	85.5±0.81*	49.86±1.12*
Diabetic+metformin (500 mg/kg)	0.78±0.02*#	3.86±0.32*#	42.9±0.68*#	29.44±1.09*#
Diabetic+AEPO (100 mg/kg)	0.93±0.02*#$	4.88±0.55*#$	72.1±0.94*#$	40.22±0.98*#$
Diabetic + AEPO (200 mg/kg)	0.81±0.04*#	3.90±0.87*#	63.0±0.84*#$	32.52±0.85*#$

Values are mean±SEM for groups of three observations with their standard errors. BUN: Blood urea nitrogen; AEPO: Aqueous extract of *Pleurotus ostreatus*; STZ: Streptozotocin. *$P<0.05$ versus control; #$P<0.05$ versus STZ group; $$P<0.05$ versus metformin group

STZ-induced diabetes in rats through assessment of the antihyperglycemic mechanism.

The OGTT measures the body's ability to use a type of sugar, called glucose, that is the body's main source of energy. OGTT, a test of immense value and sentiment, in favor of using fasting plasma glucose concentration alone was seen as a practical attempt to simplify and facilitate the diagnosis of diabetes [28]. Badole and Bodhankar [29] reported that the combination treatment of aqueous extract of *P. pulmonarius* with acarbose produced a more synergistic antihyperglycemic effect than either drug alone. They explained that in the OGTT, administration of glucose load (2.5 g/kg) increased serum glucose levels significantly after 30 min in alloxan-treated diabetic mice. In OGTT of the present study, blood glucose concentration increases rapidly at 30 min. In the case of normal set, blood glucose returned to normal after 120 min. *P. ostreatus* was found to be effective in controlling blood glucose level in OGTT study, and after 120 min of study, blood glucose level was found to be 200 mg/dL at higher concentration (200 mg/kg) when compared to glucose at 0 h which was 215 mg/dL. Lower concentration (100 mg/kg) of *P. ostreatus* extract was also effective in reducing blood glucose. Similar result was also reported by Cha *et al.* [30] for *Fomitopsis pinicola* that showed a significant fall in fasting blood sugar and HbA1c, which may be attributed to the hypoglycemic potential of the oyster mushroom supplementation [31]. The previous studies on diabetes revealed that oral administration of macrofungal extracellular polysaccharides (EPS) or crude extract exhibits an excellent hypoglycemic effect, lowering the average plasma glucose level in EPS-fed rats to 55.1% with enhanced glucose tolerance [32]. In the present study, AEPO helped in the reduction of blood glucose when compared to diabetic control and metformin-treated animals. Significant fall in fasting blood sugar may be attributed to the hypoglycemic potential of the oyster mushroom supplement [31]. It was reported that macrofungi significantly reduced blood glucose level in diabetic subjects. It helps in the reduction of plasma glucose concentrations up to 24.7% in diabetic animal tested [33]. Badole and Bodhankar [29] stated that a single administration of aqueous extract of *Pleurotus pulmonarius* (500 mg/kg) significantly reduced serum glucose level at 2, 4, 6, and 24 h after administration. The macrofungi was reported to significantly reduce the blood glucose level in diabetic subjects [33]. *Agaricus bisporus* (white button mushroom) contains high levels of dietary fibers and antioxidants including Vitamins C, D, and B12, as well as folate and polyphenols that provide beneficial effects on cardiovascular and diabetic diseases. It helps in the reduction of plasma glucose concentrations up to 24.7% in diabetic animal tested [33].

Body weight was measured to confirm the effect of STZ on experimental animals. Rats of vehicle control were shown to be stable in their body weight. Diabetic rats (STZ-induced) showed decrease in body weight after 30 days of treatment. STZ-mediated decrease (39%) in body weight was significantly reversed by the AEPO administration in a dose-dependent manner. AEPO at 100 and 200 mg/kg dosage showed 22.7% and 18.8% decrease in body weight when compared against STZ-diabetic rats. On the other hand, there was 16.3% and 20.2% increment in body weight at 100 and 200 mg/kg AEPO as compared to STZ-diabetic rats. *P. ostreatus* was effective in maintaining body weight of STZ-induced diabetic mice and mimic the activity of metformin. Badole and Bodhankar [29] reported that the combination

treatment of *P. pulmonarius* with acarbose prevented a decrease in the body weight of the diabetic mice in a very effective manner. The ability to prevent body weight loss seems to be due to its ability to suppress hyperglycemia. STZ-induced diabetes was characterized by a severe loss in body weight and this reduction in body weight is due to the loss or degradation of structural proteins since structural proteins are known to contribute to the body weight. The previous reports showed that protein synthesis is decreased in all tissues due to decreased production of ATP and absolute or relative deficiency of insulin [34].

Diabetes mellitus has been found to be associated with neutrophilic dysfunction and lymphocyte function impairments. Leukocyte such as neutrophils, monocytes, and eosinophils as well as hematocrit was found to be significantly increased in the diabetic animals when compared to the normal animals, and this condition on treatment with the infusion of the mushroom was significantly reverted to the near normal level [35]. STZ-induced diabetic rats were treated with AEPO, and results obtained were compared with normal rats, diabetic rats (without treatment) and metformin-treated rats. The results from the present study showed the significant changes in biochemical parameters during the experimentally inducted diabetes. Blood glucose, hemoglobin, total WBC, leukocyte count, lipid profile, creatinine level, serum uric acid, serum urea, and serum BUN levels were determined in control and aqueous extract- and metformin-treated rats. The present study clearly showed that *P. ostreatus* lowers blood lipid levels by reducing the levels of total serum cholesterol, VLDL, LDL and serum triglyceride, and it increased serum HDL level, in keeping with work done by Agrawal *et al.* [31] on oyster mushroom (*Pleurotus* spp). According to Yang *et al.* [36], *Collybia confluens* mycelial powder (CCMP) lowered the plasma total cholesterol, triglyceride, and LDL by 22.9%, 19.9%, and 37.3%, respectively. In summary, the study presented the potential beneficial effects of an AEPO that were exerted through an antihyperglycemic mechanism in diabetic animal model.

5. Conclusions

While many plants that are known to be able to treat ailments in humans are emerging nowadays, mushrooms are becoming increasingly known for its potential in treating diseases. In diabetes, some herbal alternatives are proven to provide symptomatic relief and assist in the prevention of secondary complications of the disease. Alternative therapies for diabetes treatment are needed because of inability of current therapies to contribute to normoglycemia and prevent diabetic complications. Despite of their effectiveness in reducing hyperglycemia, the use of these drugs is associated with non-desirable side effects. Mushrooms are exemplary sources of natural medicines with antidiabetic potential. They serve as an ideal choice for diabetic patients due to their high content of fiber and protein along with low fat content. *P. ostreatus* has immense potential and can be developed as effective and safe antidiabetic drug. However, a further study is needed to identify the active fractions responsible for antidiabetic activity and to clarify the mechanism of the effect.

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Conflict of interest

The authors declare no conflict of interest related to this publication.

Author contributions

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Ethics approval and consent to participate

The protocols for these experiments were approved by the Animal Ethical Committee of the Institute (IAEC/DDU/2021-22).

Consent for publication

Not applicable.

Availability of data

Data used in this work can be made available to the readers.

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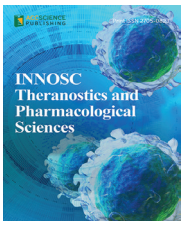

REVIEW ARTICLE

Impact of COVID-19 Pandemic on Cancer Patients with Pulmonary Fibrosis on Chemosurveillance

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Abstract:

COVID-19 infection and multiplication can be regulated with the aid of vaccines, immunosurveillance, and antiviral medications, such interferon and nucleoside analogs. The main concern with COVID-19 infection is the proliferation of the virus. However, there is no medication to treat pulmonary fibrosis, a life-threatening condition, once it has manifested. To treat critically ill patients with cancer and pulmonary fibrosis, it is imperative to develop cell differentiation agent (CDA) formulations that can kill cancer stem cells. Chemosurveillance for cancer patients no longer functions as intended. As a result, people with cancer are more likely to experience severe symptoms of pulmonary fibrosis. The harm to chemosurveillance caused by cancer treatments that focus on cell death, such as cytotoxic drugs, radiation, and immunotherapy, may gravely accelerate the development of fatal pulmonary fibrosis. To prevent the development of fatal pulmonary fibrosis symptoms, cancer patients should be advised against contracting COVID-19, but, if they do, targeted therapy should be their first choice. The purpose of this study was to highlight the significance of chemosurveillance in determining when fatal pulmonary fibrosis manifests after COVID-19 infection in cancer patients and to conceptualize CDA formulations that can be used to treat both pulmonary fibrosis and cancer. COVID-19 infection causes biological and immunological reactions that are similar to those of a wound, leading to the production of prostaglandins and tumor necrosis factor, which cause respiratory illness symptoms, such as fever and cough, and cachexia symptoms, respectively. This results in the breakdown of chemosurveillance, a natural defense mechanism that ensures optimal wound healing, thus further promoting the development of cancer and pulmonary fibrosis.

Keywords: Cancer, COVID-19, Cell differentiation agent formulations, Chemosurveillance, Pulmonary fibrosis, Wound healing

1. Introduction

In December 2019, the COVID-19 pandemic began in China and swiftly spread to other nations, resulting in 6.34 million confirmed deaths and 571 million confirmed cases worldwide as of August 2022 [1,2]. Most individuals suffered either directly from infection or indirectly as a result of restrictions on public gatherings. The COVID-19 infection may result in deadly pulmonary fibrosis and severe acute respiratory syndrome [3]. The development of vaccinations significantly slowed the spread of the pandemic. However, the rapid development of viral variations has led to the COVID-19 pandemic's incessant spread in successive waves [2].

Immunosurveillance, vaccinations and antiviral medications such as interferon and nucleoside analogues can all slow the growth of COVID-19. Lung fibrosis, as the primary cause of death from COVID-19 infection, is not yet treatable with medication. If pulmonary fibrosis can be successfully treated, COVID-19 might not

impose as much socially disruptive restrictions on patients [4,5]. Our goals were to investigate the causes of pulmonary fibrosis and conceptualize the cell differentiation agent (CDA) formulations that can be used as efficient treatments for the disease.

The repair of lung damage brought on by COVID-19 infection is crucial to restoring lung function. However, the healing process is not going as it should be as evident in the formation of pulmonary fibrosis [6,7]. Another outcome of improper wound healing is the development of cancer [8]. COVID-19 infection must, therefore, have a significant impact on cancer, and vice versa. Chemosurveillance is a built-in process that controls how well wounds heal [8-10]. A careful investigation of how COVID-19 infection affects cancer patients is conducted.

A reported risk factor for the emergence of severe events was receiving cancer therapy within 14 days of receiving a COVID-19 diagnosis [11]. Septic shock, acute myocardial infarction, and acute respiratory distress syndrome are a few of the reported serious complications in the study group. Millions of people worldwide are affected by the deadly illness of cancer. Patients with cancer must attend medical institutions more frequently than individuals with other diseases because of the nature of the disease and its treatment [12]. Multidisciplinary teams must be fully involved in the treatment of cancer patients at all stages of the disease, from diagnosis to survivorship or end-of-life care. Patients need numerous hospital visits over the course of the disease for evaluation by various clinicians, as well as numerous imaging or laboratory tests for diagnosis, staging, or monitoring the effects of treatment, in addition to various types of surgeries and interventions [13].

Patients with cancer require assistance from a wide range of professionals in addition to medical professionals, including social workers, psychologists, educators, and other support services. Patients who have been diagnosed with cancer require ongoing care and support both during and after treatment [14]. Because any unjustified divergence from the well-established standards may result in fragmented and subpar care and a worse patient outcome, these services should be operating in harmony and a timely manner with strong commitment and compliance from the patients [15-17]. The COVID-19 global pandemic had a wide-ranging impact on health care services, interfering with the flow of patients to medical facilities as usual, taxing, and overwhelming the system's resources, and forcing the adoption of additional protective measures and social segregation with increased telehealth and remote treatments use.

2. Viewpoints and conversations

The concept of chemotherapy surveillance was introduced as a built-in protection against cancer. Later, it was altered as a natural system to guarantee optimal wound healing as the main goal of preventing the development of diseases as a result of improper wound healing. Cancer, dementia, and tissue fibrosis are some of the illnesses linked to poor wound healing [18,19]. The idea behind chemosurveillance was inspired by the discovery that while cancer patients frequently displayed deficiencies of these metabolites due to excessive urinary excretion, healthy individuals were able to maintain a steady level of metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs) [20]. DIs are compounds that can remove telomerase from aberrant methylation enzymes (MEs), while DHIs are ME inhibitors [21].

Methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolases (SAHH) are the building blocks of MEs. Since the hypomethylation of nucleic acids is a crucial mechanism for achieving terminal differentiation, the connection of telomerase with MEs renders MEs to be highly persistent and active [22]. Normal stem cells, also known as progenitor stem cells (PSCs), produce telomerase, which causes MEs to become aberrant cancer cells (CCs). The cells responsible for wound healing are the PSCs, which require DIs and DHIs to promote terminal differentiation for effective wound healing [23]. CDA is the moniker given to the concoction of DIs and DHIs. CDAs are metabolites that aid in wound healing and are actively involved in chemo-surveillance. Depending on the extent of cancer, patients have varying degrees of CDA insufficiency [24].

Low molecular weight metabolites include DIs and DHIs. Major DIs include acidic peptides and organic acids. Uroerythrin and pregnenolone

have been identified as important DHIs, while arachidonic acid (AA) and its metabolites have been identified as organic acids of major DIs [21,22]. In general, MT and SAHH inhibitors are considered excellent DHIs [25]. The function of acidic peptides as surveillance DI is still a mystery. Acidic peptides, uroerythrin, and other products of erythrocyte breakdown make up a significant portion of CDAs [26]. Organs that are actively involved in steroid metabolism, such as the adrenal gland, liver, and reproductive system organs, provide pregnenolone and steroid metabolites.

Evidently, proper wound healing depends on the preservation of a constant amount of CDAs [27]. Since injuries tend to heal naturally without the need for effort, research on chemosurveillance and wound healing has received little attention [28]. For good reasons, the natural world includes chemosurveillance to prevent fatal conditions such as cancer, lung fibrosis, and Alzheimer's disease. Cancer is the leading cause of death in most countries, and pulmonary fibrosis is the primary cause of death from COVID-19 infection; meanwhile, Alzheimer's disease remains incurable [29]. If medical establishments continue to downplay the significance of wound healing and chemosurveillance, these diseases remain incurable [30-32].

3. Impact of COVID-19 pandemic on cancer patients

The lung damage brought on by COVID-19 infection triggers wound repair processes that result in the production of prostaglandins (PGs) and tumor necrosis factor (TNF) [33]. PGs help wounds heal faster by increasing the levels of CDA. TNF; however, hinders wound healing by lowering CDA levels. TNF is also known as cachectin due to the cachexia symptoms it causes. The increased excretion of low molecular weight metabolites as a result of TNF's capacity to cause vascular hyperpermeability is a sign of cachexia [16,34]. The breakdown of chemosurveillance is caused by the excretion of low molecular weight metabolites, including active CDAs. Pulmonary fibrosis results from a lack of adequate CDAs to trigger terminal differentiation of PSCs [35].

The failure of chemosurveillance to induce terminal differentiation of PSCs is another reason for the development of cancer [36]. The renowned German scientist Virchow first proposed the idea of cancer as a non-healing wound in the 19th century [37]. MacCarthy-Morrogh and Martin observed the link between cancer and wound healing [38]. The most crucial information on this subject is related to abnormal MEs to prevent differentiation [39]. The mechanism of wound healing; the hypomethylation of nucleic acids as the most important mechanism to achieve terminal differentiation of PSCs, cancer stem cells (CSCs), and CCs; the evolution of CSCs from PSCs as a result of chemosurveillance breakdown; and the DIs and DHIs as wound healing metabolites and active players in chemosurveillance are all discussed [40,41]. For a cancer symptom to manifest, the chemosurveillance functioning must be severely impaired. Therefore, cancer patients are particularly susceptible to developing life-threatening pulmonary fibrosis symptoms when infected with COVID-19. To prevent infection, immunization is indicated [42]. If patients become infected, a transition of treatment from cell-killing treatments, such as cytotoxic drugs, radiation, or immunotherapy, to targeted treatments, like growth factor inhibitors or signal transduction blockers, is encouraged [43]. The loss of chemosurveillance brought on by cell killing can exacerbate COVID-19 infection by causing harm similar to that brought on by viral infection. Targeted therapy drugs are excellent DIs or DHIs that can stop the progression of fatal pulmonary fibrosis.

Compared to the general population, some cancer patients have higher infection risks due to their immunosuppressed state, which can be brought on by the illness itself or treatment. Immune response may put cancer patients at risk for severe infection-related side effects, which could delay treatment and necessitate hospital stay. These could be harmful to the prognosis of such patients. When compared to patients without cancer, cancer patients have a roughly 3.5-fold higher chance of dying, needing mechanical ventilation, being admitted to the intensive care unit, and developing severe infections. Due to their immunosuppressed state from having cancer and receiving anticancer therapies such as chemotherapy or surgery, cancer patients are more vulnerable to serious COVID-19 complications. Studies have found that the risk of severe events was higher in patients who had

experienced surgery or chemotherapy within 30 days before presenting with COVID-19 than in patients who had not. In addition, it has been discovered that having a history of cancer increased the chance of serious complications and was associated with poor COVID-19 outcomes [42,43]. Compared to patients with other cancer types, patients with lung cancer did not show a greater likelihood of developing serious complications. When lung cancer patients receive immune checkpoint inhibitor therapy, medical professionals must be aware of the side effects that may occur with the medication (such as severe myocarditis and pneumonitis) as they may have a negative impact on patients' prognosis.

4. Conceptualization of CDA formulations to fight against COVID-19 and cancer

Since pulmonary fibrosis accounts for a significant portion of COVID-19 fatalities, this symptom causes the most concern. The accumulation of PSCs that are unable to undergo terminal differentiation due to chemosurveillance failure is what leads to pulmonary fibrosis. This scenario is rather reminiscent of myelodysplastic syndrome (MDS), which is brought on by an accumulation of CSCs that cannot differentiate further [44-46]. By silencing the ten-eleven translocation 1 (TET-1) enzyme with a single hit, PSCs can be converted into CSCs [47]. The problems in MDS and pulmonary fibrosis are identical. The only remedy is to stimulate the terminal differentiation of diseased cells, which transforms them into functioning cells and is a crucial component for wound healing [48-50]. The induction of terminal differentiation is, therefore, the most effective treatment for pulmonary fibrosis and MDS. Drug resistance and anti-apoptosis mechanisms guard PSCs and CSCs [48].

Radiation is likewise ineffectual and toxic substances are unable to reach these cells. They are partnered with metabolites that promote wound healing in their natural mission to heal wounds. Metabolites that promote wound healing can easily enter these cells and induce terminal differentiation. Hence, they are the best medication option for treating pulmonary fibrosis and MDS [37,44]. China Food and Drug Administration (FDA) has approved the use of CDA-2, a preparation of wound healing metabolites purified from recently collected urine, for the treatment of cancer and MDS [51,52]. If pulmonary fibrosis could be successfully treated, the virulence of COVID-19 can be subdued to that of an influenza virus.

Following the peak in COVID-19 infection in February 2020 across several cities in China, there was a decline in cases, indicating that preventive measures such as closing all public transportation and entertainment centers and prohibiting large public gatherings were effective in preventing hundreds of thousands of cases of infection. Since it is unlikely that the decline occurred due to a decrease in number of susceptible individuals, relaxing control measures could result in resurgence. The reductions in case incidence were correlated with the suspension of intracity public transportation, closure of entertainment venues, and outlawing of public meetings. The COVID-19 epidemic in China appeared to have slowed down and kept in check during the peak of infection due to its national emergency response.

In addition to the travel ban in Wuhan, as part of the national emergency response, suspected and confirmed cases were isolated, public transportation by bus and subway was suspended, schools and entertainment venues were closed, public gatherings were banned, health checks on migrants were performed, travelling within and outside of cities was prohibited, and information on COVID-19 was widely distributed. These control measures may be instructive to other countries across the globe. During the first week of the outbreak, fewer cases were reported in areas that immediately suspended intracity public transportation, closed their amusement parks, and/or restricted public gatherings. This study did not offer any evidence that the intercity travel restriction reduced the number of COVID-19 cases.

5. Conclusion

For almost 3 years, the COVID-19 pandemic has wreaked havoc across the world, killing 6.34 million people. The primary factor in fatalities is the onset of lung fibrosis brought on by chemo-surveillance failure, which also leads to the development of cancer. Cancer patients are susceptible to developing fatal pulmonary fibrosis when infected with COVID-19. Therefore, vaccination against COVID-19 infection is indicated for cancer

patients. The failure of chemosurveillance is a result of cancer treatments that focus on cell death, such as cytotoxic drugs, radiotherapy, and immunotherapy. To prevent the development of pulmonary fibrosis following COVID-19 infection, cancer patients are recommended to switch their medications to targeted therapies entailing DIs or DHIs that promote wound healing.

To end the threat posed by the COVID-19 pandemic, new treatments for pulmonary fibrosis must be developed. COVID-19 symptoms are varied from minor upper respiratory tract symptoms to serious acute respiratory distress syndrome. The main risk factors for serious COVID-19 are similar to those for idiopathic pulmonary fibrosis, including aging and having comorbid conditions such as diabetes and hypertension. Moreover, due to their immunosuppressed state brought due to their disease and anticancer therapies such as chemotherapy, cancer patients are more vulnerable to serious COVID-19 complications.

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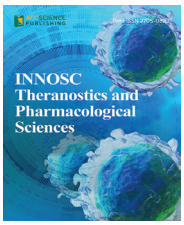

RESEARCH ARTICLE

Cardiovascular Evaluation in Patients with Systemic Sclerosis in the Turkish Population

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Abstract:

Cardiac involvement in systemic sclerosis (SSc) can lead to high morbidity and mortality. Therefore, early diagnosis and treatment are required. The aim of this study was to investigate the clinical, laboratory, and echocardiographic features of SSc, evaluate the proportion of patients with cardiovascular disease, and compare them with other population-based studies in the Turkish population. This study included 150 patients who were previously diagnosed and treated in the rheumatology clinic. Their age, sex, clinical signs and symptoms, laboratory and echocardiography findings, and concomitant diseases were evaluated. The results showed that the disease duration was <1 year and, at most, 11 years, with only one patient having elevated pulmonary artery pressure. In addition, patients with SSc in our region had similar demographic, clinical, laboratory, and echocardiographic features with those in other countries. This study demonstrated that hypertension is positively correlated with disease duration and the incidence of pulmonary hypertension is very low in patients with SSc.

Keywords: Systemic sclerosis, Cardiovascular disease, Scleroderma, Pulmonary hypertension, Hypertension

1. Introduction

Systemic sclerosis (SSc) is a chronic multisystemic autoimmune inflammatory disease characterized by fibrosis, vasculopathy, and extracellular matrix synthesis and accumulation in the skin and internal organs. Among its clinical manifestations, skin hardening and thickening are the most crucial determinants of skin fibrosis. This chronic multisystemic disease is characterized by changes in the skin, circulatory system, synovium, and musculoskeletal system due to connective tissue accumulation and fibrosis in the internal organs, especially the gastrointestinal system, heart, lungs, and kidneys [1]. SSc is generally seen in women between ages 30 and 55. Although it is accompanied by severe complications, it has a low incidence.

The exact prevalence of SSc in Turkey is unknown. In view of regional differences across the world, it is essential to evaluate patients with SSc in different regions. Differences in incidence are due to the diversity of genetic and ethnic composition, climatic conditions, and environmental exposures [2].

The presentation of SSc is complex and varies to a certain extent. Therefore, the classification criteria for SSc, published by the American College of Rheumatology (ACR) in 1980, have rendered a more straightforward approach to the diagnosis and treatment of the disease [3,4]. By focusing

on different clinical features as initial symptoms in its diagnosis, such as the presence of Raynaud phenomenon, the nail bed capillary pattern, proximal or distal cutaneous changes, and the presence of autoantibodies [5], SSc can be divided into two types: SSc with limited skin involvement and diffuse skin involvement. By referring to the European League Against Rheumatism (EULAR) records, Minier *et al*. stated that puffy fingers are the main findings in the initial assessment of SSc [6].

Hypertension (HT), diabetes mellitus (DM), and renal diseases are the major systemic vascular diseases in which differences can be observed in the disease progression, presentation, and prognosis. The previous studies have shown that the development of HT can be predicted in patients over 45 with high inflammatory markers and skin involvement [7]. HT causes vascular changes similar to those observed in SSc [8]. Perivascular inflammatory infiltrates, impaired angiogenesis, and endothelial apoptosis are all observed in the early stages of the disease. Data from animal models have shown that prolonged, uncontrolled overexpression of vascular endothelial growth factor may have paradoxical effects on the formation of new vessels, leading to capillary changes similar to those observed in SSc. In addition to impaired angiogenesis, defective vasculogenesis may contribute to the vascular symptoms in SSc [9]. Cardiovascular diseases are frequently observed in patients with rheumatoid joint diseases and individuals with SSc [10].

Although the relationship between SSc and pulmonary arterial hypertension (PAH) is known, idiopathic PAH and PAH associated with SSc (SSc-PAH) are histologically different [11]. SSc-PAH is the most common form of PAH associated with connective tissue disease. SSc-PAH is essential to all cases of PAH [12]. Approximately 12%–15% of patients with SSc are estimated to have a lifetime risk of developing PAH. Despite treatment with pulmonary vasodilators, patients with SSc-PAH have a high mortality rate [13].

Although the etiopathogenesis of scleroderma-like conditions in DM is associated with non-enzymatic glycation of collagen, it has not been established. High blood glucose levels can stimulate the proliferation of fibroblasts and the production of other extracellular matrix components, causing skin hardening. Scleroderma-like syndrome, especially diabetic sclerodactyly as the most common skin manifestation of type 1 DM, strongly correlates with the duration of the disease. In many cases, it may be challenging to distinguish the histopathological changes in diabetic scleroderma-like syndrome from those in the course of SSc [14].

Cardiac involvement in SSc may lead to high morbidity and mortality. Therefore, early diagnosis and treatment are required. For instance, the 10-year mortality of patients with cardiac involvement in SSc is around 20%. Both primary and secondary cardiac involvement may be present in SSc. While primary involvement occurs due to the direct effect of inflammation on cardiac tissue, secondary involvement is secondary to pulmonary hypertension.

SSc may cause myocardial fibrosis and right and left ventricular systolic and diastolic dysfunction, as well as pericardial and endocardial damages. Echocardiography is a contributory non-invasive test used to evaluate cardiac involvement. Through echocardiography, the left and right ventricular functions can be assessed, and pulmonary hypertension can be detected with high sensitivity [15].

In this study, we aimed to investigate the clinical, laboratory, and echocardiographic features of SSc patients in our center, evaluate the proportion of patients with cardiovascular disease ratio, and compare them with other population-based studies in the Turkish population.

2. Methods

2.1. Study participants

In this study, 150 patients who were previously diagnosed and treated in the rheumatology clinic were included in the study. Their age, sex, clinical signs and symptoms, laboratory and echocardiography findings, and concomitant diseases were evaluated. The determinants of the study were signs of excessive fibrosis (skin lesion and pulmonary fibrosis), vasculopathy (hypertension and proteinuria), and inflammation (arthritis and elevated C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], or rheumatoid factor [RF]). This study was approved by the Local Ethics Committee.

2.2. Observations

The diagnosis of SSc was based on the SSc criteria by EULAR and ACR [17]. Raynaud's phenomenon was defined clinically discoloration of the skin of the fingers in response to exposure to cold or emotional stress) and through nailfold videocapillaroscopy.

In echocardiography, the left and right ventricular dimensions and functions, wall thickness, systolic pulmonary artery pressure, and tricuspid gradient were evaluated. PAH was confirmed by the right heart catheterization with pulmonary artery pressure >40 mmHg.

Skin lesion was defined as any observation of focal swelling, stiffness, or atrophy, regardless of location. Arthritis was considered as swelling and tenderness in one or more joints. Chest radiography or computed tomography (CT) was used to evaluate the presence of pulmonary fibrosis. Local standards and the European Society of Cardiology (ESC) guidelines were used to diagnose and treat arterial hypertension. In cases of dysphagia accompanied by changes in gastroscopy or barium swallow, gastrointestinal involvement was considered. Proteinuria was detected in 24-h urine samples by microelectrophoresis, and spot urine was examined for cylindruria. Standard measurement methods were used for CRP (>10 mg/L) and RF (>14 IU/mL), and an ESR of 25 mm/h was determined as the limit value. Anemia was considered when hemoglobin (Hgb) levels were < 13 g/dL and 12 g/dL in men and women, respectively. Low-density lipoprotein of more than 160 mg/dL was accepted as the limit value for the diagnosis of hyperlipidemia.

We also evaluated the patient's history for coronary artery disease and antidiabetic and antihypertensive treatment.

2.3. Statistical analysis

The data obtained were evaluated using SPSS 22.0. Mean values and frequencies were used for statistical analysis. In general, descriptive statistics were used. Statistical significance was accepted as $P < 0.05$.

3. Results and Discussion

In our study, the mean age of the patients was 47.75, with the youngest being 19, and the oldest 78. The disease duration was <1 year and, at most, 11 years; the mean disease duration was 5.41 years. Hypertension was detected in 34.7% of patients (**Table 1**). RF values were low in 52.7% and high in 47.3% of patients (**Table 2**). We found the mean ejection fraction (EF) to be 60.21% through echocardiographic evaluation and the systolic pulmonary artery pressure to be 31 mmHg (**Table 3**). Hypertension was found to be positively correlated with disease duration ($r = 0.278$; $P = 0.001$) (**Table 4**).

The mean age of the patients in our study was similar to other community-based studies [5]. In addition, the proportion of female patients in our study at 87.3% was similar to EULAR records at 87.8%. The frequency of SSc-associated pulmonary hypertension in our study was 6%, whereas that in the previous prospective study was between 7.8% and 12% [16]. The proportion of patients with EF < 55% was 3.4% in our study and 5.4% in the EULAR-based study [17]. Comparing with the mean pulmonary artery pressure (31 mmHg) observed in our study, the mean pulmonary artery pressure in a similar study was observed to be 33.3 mmHg [18]. In the same study [18], the left ventricle end diastolic diameter, interventricular septum, posterior wall thickness, and EF values were similar with those observed in our study.

Table 1. Assessment in systemic sclerosis

Disease	Negative	Positive
Hypertension	98 (65.3%)	52 (34.7%)
Diabetes mellitus	142 (94.7%)	8 (5.3%)
Coronary artery disease	124 (82.7%)	26 (17.3%)
Hyperlipidemia	132 (88%)	18 (12%)
Anemia	124 (82.7%)	26 (17.3%)
Proteinuria	106 (70.7%)	44 (29.3%)
Cylindruria	139 (92.7%)	11 (7.3%)
Pulmonary hypertension	149 (99.3%)	1 (0.7%)

Table 2. Inflammatory markers in systemic sclerosis

Markers	Negative	Positive
CRP	141 (94%)	9 (6%)
ESR	116 (77.3%)	34 (22.7%)
RF	79 (52.7%)	71 (47.3%)

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor

Table 3. Evaluation results in systemic sclerosis

Parameters	Number	Minimum	Maximum	Mean	Standard deviation
Age	150	19	78	47.75	13.337
Disease duration (years)	150	0	11	5.41	2.774
Ejection fraction (%)	150	35	72	60.21	4.912
Left ventricular end-diastolic diameter (mm)	150	34	57	42.87	3.764
Right ventricle diameter (mm)	150	2	40	20.92	3.220
Pulmonary artery pressure (mmHg)	150	17	111	31.07	11.816
Tricuspic regurgitation velocity (m/sn)	150	12	96	25.82	10.647

Table 4. Relationship between hypertension and duration of systemic sclerosis

Variables	Hypertension	Disease duration
Hypertension		
Correlation	1	0.278**
Sig. (2-tailed)		0.001
Number	150	150
Disease duration		
Correlation	0.278**	1
Sig. (2-tailed)	0.001	
Number	150	150

Statistical significance at $p<0.05$

Similar to our study, the decrease in myocardial contractility was lower than predicted in many studies, which is contentious given the presence of myocardial depression in SSc [19-21].

In most of our patients, the ESR and CRP levels were low. A study has reported that high ESR values are strongly associated with pulmonary hypertension in such patients [22]. High CRP levels were observed in 6% of our patients, whereas one-fourth of patients in a study of inflammatory indicators had high CRP levels [23]. In another study, high CRP levels were observed in 48% of patients, rising to 80% in patients with finger ulcers [24]. Low ESR and CRP levels were attributed to the disease activities. Compared with a regional study in Central Ukraine [5], anemia and CRP results were lower, while ESR was higher; however, cylindruria and proteinuria values were similar.

Hyperlipidemia was observed in 12% of patients who participated in our study. Similar to the previous studies, we found that impaired lipid profile is associated with increased macrovascular diseases in patients with SSc [25,26].

Unlike previous studies [14], we could not detect a significant relationship between DM and SSc. This can be explained by the low number of DM patients and the short duration of DM.

HT was observed in 34.7% of patients who participated in our study. We found a significant relationship between age and HT in SSc. In addition, there was also a significant correlation between HT and disease duration. HT at the onset of SSc was found to be associated with skin lesion, arthritis, pulmonary fibrosis, abnormal platelet and ESR levels, and a higher incidence of cylindruria. Moreover, the incidence of gastrointestinal complications was observed to be higher in hypertensive patients. The absence of HT was associated with a higher incidence of anemia. In hypertensive patients, the mean pulmonary artery pressure was slightly higher, and the mean glomerular filtration rate was significantly lower; these results were similar with those observed in the Central Ukraine population [5].

The limitations of our study were the small geographical area constituting the patients included in our study, the omission of evaluating the age of onset of SSc and the initial symptoms, and the inability to perform diastolic evaluation on all patients.

4. Conclusions

As seen in our study, patients with SSc in our region had similar demographic, clinical, laboratory, and echocardiographic features with those in other countries. The results are comparable with those in the UK registry, Pittsburg Scleroderma Databank, PHAROS registry, CRRG registry, and Brazilian registry (GEPRO). Our study was based on the fact that there may be regional differences especially

in scleroderma patients. The study provides an overview of cardiovascular disease risk factors in scleroderma patients in the Turkish population. Our study is a pioneer for more complex studies to be done in the scleroderma patient group.

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Conflict of interest

The authors declare no conflicts of interests.

Author contribution

Conceptualization: Suleyman Serdar Koca
Formal analysis: Mehdi Karasu
Investigation: Mehdi Karasu, Ozkan Karaca
Writing – original draft: Tarik Kivrak
Writing – review & editing: Tarik Kivrak

Ethics approval and consent to participate

This study was approved by the Local Ethics Committee (218714).

Consent for publication

Consent for publication was obtained from all the participants.

Availability of data

The data can be obtained following request from the corresponding author.

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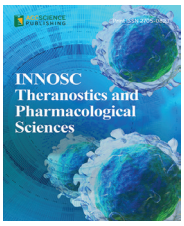

REVIEW ARTICLE

Adhesive Cementation of Ceramic Restorations: A Comprehensive Review

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Abstract:

The success and tendency of the indirect restorations were mainly affected by the patient and dental surgeon factors. The patient factors consist of their dietary, functional habits, and oral hygiene, while the surgeon factors consist of their management in tooth preparation, impression, and cementation. Among these factors, cementation is a very crucial step to ensure retention, durability, and marginal seal of indirect restoration. The field of dentistry has largely benefited from the various newer types of ceramic introduced. However, this cementation process can be either adhesive or non-adhesive. Adhesive cementation refers to the use of an agent that promotes the bonding of restorative material to substrate, whereas the non-adhesive cementation involves the use of luting agent for filling the gap between restoration and natural tooth. However, the indication for use of adhesive or non-adhesive cementation depends on various factors, such as resistance form, ceramic composition, available preparation retention, and field control during the cementation process. Hence, it is important for the clinicians and dental surgeons to understand these factors before selecting an appropriate cementation process for ceramic restorations. In this review, we provide an overview of adhesive cementation process for ceramic restorations and make appropriate recommendations for routine dental practice.

Keywords: Adhesive dentistry, Ceramic restorations, Cementation, Dental cements

1. Introduction

Dental restorations aim to restore lost tooth structure caused by factors such as decay or esthetic corrections. Indirect restorations, among various types of restorations, offer a more sustainable form and function, particularly when large decay is present. The success of these restorations depends on two factors: patient-related factors such as their dietary, functional habits, and oral hygiene, and clinician-related factors such as tooth preparation, impression, and cementation [1].

Contemporary ceramics have become popular among patients and clinicians for indirect restorations due to their optical properties, physical strength, and conservative preparation requirements [2,3]. However, the success of ceramic restorations depends on several factors, including fracture resistance, marginal fit, marginal accuracy, choice of cement, and cement thickness [4]. The choice of cement, in particular, plays a significant role in the retention and marginal seal of indirect ceramic restorations as they do not have secondary retentive features [4,5].

The cementation process can be either adhesive or non-adhesive [4,5]. Adhesive systems have significantly improved the longevity of indirect restorations due to their added benefit of chemical and micromechanical bonding [6]. Correctly,

applied adhesive cements have higher bond strength and low solubility compared to non-adhesive cements [7,8]. However, sustaining scrupulous isolation becomes crucial for the success of restoration in the case of adhesive cements.

It is important for dental surgeons to understand these factors to decide on the appropriate cementation process for ceramic restorations. This review will focus on the adhesive cementation process for ceramic restorations, its interaction with different ceramic compositions, and appropriate recommendations for routine dental practice.

2. Cementation procedure

The choice of cement depends on various factors such as resistance form, ceramic composition, cavity preparation, and isolation technique used during the cementation process [9,10]. Adhesive cement forms a hybrid layer between the ceramic and tooth interface. It binds micromechanically and chemically with ceramic and the tooth structure [6].

At the tooth interface, etching followed by priming and bonding is done. Resin cement binds with etched enamel and dentin, forming a hybrid layer resulting in resin tags. It was found that bond strength of ceramic-cement-tooth complex was higher than that of the individual bond strength of cement and tooth or cement and ceramic interface [7]. Short and tapered preparations benefit from the cementation process using the adhesive techniques. This is due to the hybrid layer formed that helps in improving the mechanical retention of restoration [8].

Based on their ability to etch, these cements can be total etch/etch and wash type where etchant is applied and rinsed off, or self-etch that does not require washing as the cement is incorporated with monomer and adhesive. However, self-etch cements were found to have a weaker bond strength to the enamel than that of the total etching system [2,9]. Hence, total etching 3-step adhesive system has been considered the gold standard process. The bonded layer should be prevented from contamination as it jeopardizes the cement adhesion to tooth structure. This requires good isolation which sometimes becomes a challenge in a normal dental setup [1]. In addition, the clinicians and dental surgeons must ensure that the technicians use certain precise methods for achieving proper adaptation, as the adhesive cement use might not compensate for its poor fit.

3. Surface treatment for the etchable ceramic restorations

Pretreatment of the ceramic interface improves adhesion of cement and the restoration. This is achieved by techniques such as air abrasion, sand blasting with aluminum oxide particles, or application of etchant. Studies have proven that among all the techniques, acid etching has yielded maximum bond strength and ceramic composition has played not much significant role in it [8]. Etching results in formation of microporosities that increase the surface area of the interface, enhancing wettability of the cement. This aids in micromechanical interlocking of cement at the ceramic interface and thus is a crucial step in the process of cementation. Different etch patterns are formed in successful adhesion process depending on the adequate cleaning of internal surfaces of the ceramic restorations. The resultant hexafluorosilicate formed after etching is rinsed off with water spray [11]. This etched surface is then salinized. The bifunctional molecule of silanes chemically bonds with inorganic part of ceramic and copolymerizes with the cement resin through organofunctional radical [12-15]. Efficacious action of the silane depends mainly on the hydrolysis by a weaker acid. The single-bottle system of the silane was pre-hydrolyzed and was found to have a shorter shelf-life with reduced effectiveness over a period of time. Hence, the double-bottle forms are mostly preferred [16].

4. Composition of ceramic and its bond strength at cement interface

The durability and strength of the bond at cement and ceramic interface depends on the mode of treatment selected. This in turn is governed by microstructure of the ceramic composition. Conventional ceramic has silica and potash feldspar and/or soda feldspar as their basic components. They are also rich in glass phase and have been found to have higher strength of bonding to resin cement [11-13].

When the surface treatments commonly used for the feldspathic ceramics are applied to the

ceramics with a higher content of alumina (Al_2O_3), the results were found to be poor [17]. Scarcity of glass phase has promoted neither the crystal exposure at ceramic structure nor the chemical reaction with silane, resulting in weaker bond with resin cement [17]. Hence, composition of particular ceramics system must be considered before surface treatment is chosen. However, this does not significantly affect the bond strength as compared to etching [8]. Depending on glass phase content of ceramic, it might be sensitive to the acid-etching or might be resistant to the acid [18]. Sandblasting procedure is an effective alternative procedure for conditioning of the aluminum oxide ceramic with little or no glass content. Given the greater amount of resistance to fracture of these ceramics, they could be cemented to the dentin using zinc phosphate or glass-ionomer cement [18]. Silicoating procedure is another effective alternative, which promotes durable bond with higher content of zirconium ceramics or alumina [17,18].

5. Types of ceramics and its interaction with adhesive system

While the clinicians and dental surgeons select the cementation procedure for the process of ceramic restorations, it is essential for them to know the structure, composition, and resistance form of the ceramics selected for fabricating the restoration process.

Based on their reaction to acid, ceramics are classified as acid-sensitive or acid-resistant. This yields useful information on the bond strength of the cement adhesive with restoration. Acid-sensitive ceramics such as leucite, feldspar, and lithium disilicate bases are readily etched by acids and form different etch patterns. The high crystalline ceramic or acid-resistant ceramic does not result in formation of microporosities and hence require other methods to improve bonding of cement and ceramic. These types of ceramic include densely sintered alumina ceramics, glass infiltrated alumina and zirconia, and Y-TZP ceramics [19].

The dental ceramic is also stratified based on the fillers, dopants, and matrix material. Based on these parameters, dental ceramics are classified into three major categories: predominantly glass ceramic, particle-filled glass ceramic, and polycrystalline (non-glass) ceramic [2,3]. We will look into the properties and surface treatment process for each of these ceramic type as follows:

5.1. Predominantly glass ceramic

This form of ceramic has been predominantly derived from the silicon oxide, feldspar minerals, and aluminum oxide. It has been used as the covering material over the metal or the ceramic coping and framework [3,20]. In addition, it has been used to construct the jacket crowns, on lays, porcelain veneers, and inlays. This form of ceramic is also highly esthetic, abrasion-resistant, and biocompatible, characterized by lesser mechanical strength as compared to other forms of ceramic. With a good cavity preparation and appropriate adhesive cement, it exhibits increased fracture resistance [21]. For the same reason, non-adhesive cementation process has not been indicated for the feldspathic ceramic [22].

5.1.1. Methods in conducting the adhesive cementation process using predominantly glass ceramic

Clinicians need to pretreat the "predominantly glass feldspathic ceramics" before doing the adhesive cementation process. They need to etch the intaglio surface of the ceramics with hydrofluoric acid solution (within 5 – 10% concentration), for about 1 min approximately. Doing this increases the surface area, cleans the surface and aids in micromechanical retention of the adhesive cements [23]. Application of silanes on etched surface increases the wettability of the cement and enables chemical interaction with the surface of hydroxylated porcelain and the resin matrix [24,25].

5.1.1.1. Silanation

Both silanation and etching processes are recommended in the routine practice, as few researchers have reported that there are higher rates of veneer failure when the ceramic has been silanated and air-abraded but has not been etched with the hydrofluoric acid [26,27]. For the process of silanation, two forms of silanes are available: Hydrolyzed and unhydrolyzed silanes. Hydrolyzed silanes are one-bottle systems with a shorter shelf life. However, if the contents in the bottle were

utilized after the date of expiry, it adversely affects the bond strength [27]. Unhydrolyzed form of silanes or inactive silanes was two-bottle systems utilized by the clinicians. Mixing of the ingredients is done before application, ensuring a more active form with a longer shelf life [28,29].

5.1.1.2. Etching system

Adhesive cementation process for dentin or the enamel necessitates the adhesive system use, followed by the resin cement application [4]. The adhesive systems can be either a self-etching system or a total etching system. Among these two-adhesive systems, self-etching system is the popular one among the dental surgeons as it is easier to use.

5.1.1.3. Resin cement

It is also vital to strictly follow the instructions provided by the manufacturers during the adhesive cementation process, including the use of the resin cement and adhesive combination of the manufacturers, as the researchers found certain incompatibilities between the simplified adhesive system and dual cure resin cement [30,31].

Resin cements are usually polymerized through chemicals, light or a process combining both light and chemicals. Light-polymerized resin is recommended when a thin and translucent ceramic is available. This is because it allows the light transmission through itself for reaching resin cement. In contrast to light-polymerized resin, dual-polymerized resin cement is indicated whenever the ceramic has been too opaque or too thick to enable light transmission through it [17]. Finally, polymerized resin cement with chemicals does not offer selection in terms of translucency or shade. Hence, the dual-polymerized resin cement is considered to be the most beneficial. In addition, the accessible areas might benefit from the use of light polymerization along with the dual-polymerized resin cement [32].

A self-adhesive resin cement has been introduced to reduce the steps in bonding and also enhance the ease of use. Such approach helps in combining the cement and adhesive in a single step. Using a self-etching primer before the application of cement is another approach developed. Dental surgeons might end up choosing these cements due to their simplicity and lower potential in application error. However, *in vitro* investigation of these cements showed that they bond to the dentin and enamel lesser than the effect demonstrated by the adhesive system and resin cement [33,34].

5.2. Particle-filled glass ceramic

This form of ceramic consists of several amounts, particle types, and glassy matrix. The particles inclusion has helped in improving the physical strength of ceramic. Reduction in the amount of glass and increase in the number of particles leads to increase in the strength of material. However, some esthetic and translucent properties are diminished due to this process. Based on its strength, several materials in the category can be utilized as the copings or veneering material [2].

5.2.1. Low-filled material

Low-filled material such as ordinary Portland cement (OPC) ("Jeneric Pentron, Wallingford, Conn") and IPS Empress Esthetic ("Ivoclar Vivadent") has been filled with the leucite. The physical strength of these materials has been relatively lower when compared to other filled glass material. This is one of the major reasons why these materials were indicated mainly for the veneers, outlays, and inlays and lower stress situations [3]. These forms of ceramics should be adhesively cemented for improving their strength [20]. The procedure of cementation is almost similar to the procedure described for predominantly glass ceramic.

5.2.2. Intermediate-filled material

Intermediate-filled material such as OPC 3G ("Jeneric Pentron") and IPS e-max Press ("Ivoclar Vivadent") has been reinforced with the lithium disilicate, and it has enough strength and good esthetic properties, which are sufficient to allow the use of this material for the single crown, veneers, and copings. These materials can be cemented either adhesively or non-adhesively, when it is utilized for the full-coverage restorations. Research studies have been reporting that there have been no significant differences between both types of cementations [35,36].

5.2.3. Methods in conducting the adhesive cementation process using particle-filled glass ceramic

Partial-coverage restoration such as the onlay, inlay, and porcelain veneer restoration requires adhesive cementation process for increasing the amount of fracture resistance and its retention. Full-coverage crown can be cemented either adhesively or conventionally based on their preparation design. Conventional method of cementation has been done with the conventional luting agent like resin-modified glass-ionomer cement, without requiring the intermediate agents. However, shorter, clinically non-retentive preparations must be adhesively cemented.

Another major area of consideration is the field control, as it is important for the clinicians to achieve an effective isolation in order to preserve the field free from saliva and any other contaminants while using the adhesive cements. The adhesive cementation technique for particle-filled glass ceramic is similar to procedure used for the predominantly glass ceramic. Nonetheless, the clinicians must modify the conditioning process of the intaglio surface of restoration for achieving the optimal adhesion. Manufacturers have been recommending to etch the intaglio surface of leucite-reinforced restoration with 10% hydrofluoric acid solution for 60 s approximately before the cementation process. Ceramic reinforced with lithium disilicate need to be etched with 5% hydrofluoric acid solution for about 20 s approximately. The dentists should then apply the silane, followed by a resin cement and an adhesive system, similar to procedure used for the predominantly glass ceramic.

More types of particle-filled glass have been made up of sintered core of the aluminum oxide infiltrated with the molten glass. These ceramics have a higher strength and fracture resistance with minimal content of glasses. They are also referred to as the glass-infiltrated aluminum-oxide ceramic. However, these materials are conventionally cemented rather than the adhesive cementation, because the etching glass with hydrofluoric acid does not increase the resin cement retention [37]. However, some investigators have been reporting that ceramic coating with the tribochemical silica and air-abrading the intaglio surface, followed by application of 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) (silane and phosphate monomer) before using the resin cement, might help in improving the bond to this ceramic type [38,39].

5.3. Polycrystalline ceramics

These forms of ceramics were densely sintered aluminum or zirconium oxide materials. They are characterized by the absence of glass in its composition [2,3]. These materials resist crack propagation as its atoms were packed into the regular arrays [40]. Polycrystalline ceramics have higher level of strength and toughness, and it can be utilized for framework and coping.

5.3.1. Methods in conducting the adhesive cementation process using polycrystalline ceramic

These ceramics were most commonly conventionally cemented but, in some circumstances, it might benefit from the adhesive cementation process. It is reported that air abrasion along with application of tribochemical silica or aluminium oxide followed by application of adhesive agents increases bond strength of resin cements [41]. The air abrasion process increases the surface area available for the bonding and also introduces the quasi-plasticity, microcracks or potential sites for fracture initiation. Hence, the utilization of the post-sintering surface treatment still remains controversial, although the low-pressure abrasion has been recommended [42].

Recent *in vitro* studies shows that treatment of zirconium oxide restorations with combination of 10- MDP (MDP Monomer) and tribochemical silica or using primer based on the carboxylate and phosphate functional monomer or a combination of metal primer and MDP, improves the bonding of resin based luting cements [43-45]. In addition, using primer containing MDP without the air abrasion improves the *in vitro* long-term adhesive property when compared to the conventional cementation procedure [42,46]. It has also been thought that such adhesion-promoting agent might produce the chemical bond to zirconium oxide [43-47]. Hence, the usage of air abrasion with the 50-μm powder of aluminum oxide powder at 7 pounds/square inch followed by the application of primer containing MDP before applying the resin cement

has been recommended whenever higher amount of retention is required.

6. Conclusions

Adhesive cementation is a complex technique for ceramic restorations that require a thorough understanding of adhesive principles and meticulous adherence to the clinical protocol to maximize bonding between the restorative material and tooth structure. The growing demand for esthetically pleasing restorations has led to the introduction and development of several dental ceramics. Dental surgeons should carefully consider not only the appropriate ceramic based on functional and esthetic demands but also the type of cement and cementation procedure for each system and clinical situation.

Furthermore, the success of adhesive cementation for ceramic restorations relies heavily on proper isolation, selection of appropriate adhesive systems and cements, and correct application techniques. Dental surgeons should continuously update their knowledge and skills to provide the best outcomes for their patients. In summary, adhesive cementation for ceramic restorations is an essential technique in modern restorative dentistry that can achieve highly esthetic and durable results. However, it requires careful consideration of multiple factors, including ceramic type, adhesive systems, and clinical protocol, to ensure long-term success.

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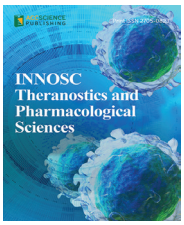

REVIEW ARTICLE

Pulmonary Hypertension among Children and Adolescents with Sickle Cell Anemia: A Systematic Review and Meta-analysis

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Abstract:

Pulmonary hypertension (PHT) is a major life-threatening complication associated with sickle cell anemia (SCA). However, there is scarcity of evidence in pooling the knowledge regarding the prevalence of PHT in the pediatric SCA patients. Hence, this systematic review was done to determine the pooled prevalence of PHT among SCA children and adolescents. Until January 2021, systematic searches were conducted in MEDLINE, SCOPUS, Web of Science, ScienceDirect, Cochrane library, and Google Scholar. The listed studies' caliber was evaluated using the Newcastle Ottawa scale. The results of a meta-analysis using a random-effects model included a pooled prevalence and 95% confidence intervals (CIs). In total, 31 studies with 3686 participants were included in the study. Majority of the included studies (26 out of 31 studies) had low risk of bias. The final pooled prevalence of PHT among children and adolescents with SCA was 22% (95% CI: 18 – 26%). Maximum burden of PHT among SCA children was reported in Europe (26%) and Eastern Mediterranean region, while the least burden was found in Africa (17%). There was a significant heterogeneity found between the studies in our analysis (I^2 = 87.8%; P < 0.001). The presence of publication bias indicated by an asymmetrical funnel plot was also found. About one in five children and adolescents with SCA suffer from PHTN. The burden is maximum in Europe followed by Eastern Mediterranean region. Diagnostic and intervention packages targeting these patients should be developed and implemented across the high-risk settings.

Keywords: Epidemiology, Meta-analysis, Pulmonary hypertension, Sickle cell anemia

1. Introduction

Sickle cell anemia (SCA) is one of the most common inherited genetic hematological condition affecting children and adolescents [1]. It can be characterized by the red cell sickling accompanied by end organ damage due to vaso-occlusion and hemolytic anemia [1]. Almost 5% of the world population were found to be healthy carriers of SCA or thalassemia gene [2]. About 300,000 children are born with severe form of these conditions, with majority occurring in low- and low middle-income countries [2]. SCA is associated with several different complications with varying severity.

Pulmonary hypertension (PHT) is a major life-threatening complication associated with SCA [3]. It is a hemodynamic illness characterized by increased vascular resistance of pulmonary circulation. The previous studies have shown that SCA is frequently associated with PHT among children and adolescents [3,4]. The occurrence of PHT in SCA patients is caused by hemolytic reaction and distorted nitric acid metabolism [5,6]. It may remain clinically silent for prolonged period and can be discovered late during illness. It has

also been reported to be a severe complication of SCA leading to an accelerated death [7]. Hence, PHT occurring secondary to SCA is classified as a separate condition as the mortality due to SCA-PHT can be 10 times higher than SCA patients without PHT [8,9].

A diagnosis of PHT can be established by the right ventricular catheterization with end systolic pressure value ≥25 mmHg. However, there are certain non-invasive methods available to diagnose PHT such as Doppler echocardiography. It can be used to assess the tricuspid valve regurgitant velocity (TRV). TRV ≥2.5 m/s among SCA patients has been established as a surrogate marker for PHT [10-12]. Several studies have made efforts to determine the burden of PHT using TRV among children and adolescents with SCA [13-16]. However, studies have reported wide variation in the prevalence of PHT among SCA children and adolescents. However, there is scarcity in pooling the knowledge regarding the prevalence of PHT in the pediatric SCA patients. Hence, this study was conducted to pool the evidence reporting the PHT among SCA children and adolescents and report a pooled estimate.

2. Materials and methods

2.1. Design

We conducted a systematic review and meta-analysis of observational studies. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist for reporting systematic reviews incorporating meta-analyses for reporting our review [17].

2.2. Eligibility criteria

2.2.1. Type of studies

For the present study, articles describing the prevalence of PHT among SCA patients were considered. There were no limitations based on the site or design of the study. Unpublished data and grey literature were discarded, but studies with complete texts or abstracts were included.

2.2.2. Type of participants

Studies conducted among children and adolescents (aged up to 19 years), irrespective of their ethnicity, comorbid status, or severity of the condition were included in the study.

2.2.3. Type of outcome measure

Studies reporting the prevalence of PHT and diagnosed it using either the right heart catheterization or transthoracic Doppler echocardiography were included in the study.

2.3. Search strategy

To find relevant information, we created a thorough search strategy and conducted thorough, methodical searches in databases and search engines such as MEDLINE, SCOPUS, Web of Science, ScienceDirect, Cochrane library, and Google Scholar. To conduct the search, we employed free-text headings and MeSH—selected medical subject headings. The phrases "SCA," "PHT," "Pulmonary Arterial Hypertension," "Children," "Adolescent," "Epidemiology," "Prevalence," and "Burden" were used in different combinations in PubMed and other search engines. Without regard to language, the search period was set from the database's establishment through January 2021. In addition, we manually searched for any articles meeting the inclusion criteria and cross-checked the bibliographies of the research we have retrieved.

2.4. Study selection

Title, keyword, and abstract screening — or primary screening — was carried out initially. The complete text of the articles that might meet the eligibility requirements was obtained. The retrieved full texts were then subjected to a further screening to determine their eligibility based on pre-established standards.

2.5. Data extraction

A pre-defined template was used as a data extraction form to obtain the following set of data: authors, title of study, year of publication, study period, study design, setting, country/region, total sample size, sampling criteria, diagnostic tool and measures, cutoff, statistical tests, outcome assessment details, average age, non-response rate, and burden of PHT.

2.6. Risk of bias (quality) assessment

The risk of bias evaluation was done using the Newcastle-Ottawa scale, which has been modified for cross-sectional studies [18]. Six domains and two criteria are used to evaluate the bias risk. The sample representativeness, sample size justification, rate of non-responses, information on non-responders, and use of validated measuring tools are the primary factors associated to participant selection. The second criterion relates to the participants' outcomes and comprises two subdomains: outcome assessment using a blinded, independent assessment and record linkage, and statistical tests used. Based on the degree of bias risk, each of these domains was rated as either high-risk (one point) or low-risk (zero point). Studies having three or more points were considered high risk.

2.7. Statistical analysis

With the final group of chosen studies, a meta-analysis was carried out using STATA 14.2's "metaprop" command package (StataCorp, College Station, TX, USA) [19]. To reduce the impact of extremely tiny or large values on the overall estimate and stabilize the variance, we employed the Freeman Tukey double arcsine transformation [19]. Because of the anticipated heterogeneity, a random effects model was used, and the final data were given as pooled prevalence with a 95% confidence interval (CI). Using a forest plot, these combined estimations were visually shown.

Using the I^2 statistic and the Chi-square of heterogeneity, heterogeneity was assessed. I^2 value was utilized to assess the heterogeneity, and $P < 0.05$ in the Chi-square test indicates significant heterogeneity [20]. Due to the significant heterogeneity in our research, we also conducted subgroup analysis and meta-regression. This strategy was used to investigate the cause of the high level of heterogeneity. A funnel plot was used to examine and depict publication bias. Using Egger's test, we also evaluated the asymmetry of the plot. Publication bias was deemed statistically significant when the *P*-value was 0.10 or higher [21].

3. Results

3.1. Study selection

In primary screening, 189 full-text studies were retrieved, which after removal of duplicates become 171 studies. These studies, in addition to the three articles retrieved from the bibliography of the screened articles, underwent secondary screening. Finally, we included data from 31 studies with 3686 participants satisfying the inclusion criteria (**Figure 1**) [13-16,22-48].

3.2. Study characteristics

Majority of the studies (11 out of 31) were prospective in nature, while 10 studies were retrospective and cross-sectional in nature. Most studies (19 out of 31) were conducted in United States of America (USA) followed by Nigeria (5) and India (2). The mean age of study participants ranged from 6.2 to 16.1 years. The sample sizes among the included studies varied from 20 to 630. All the studies have used transthoracic Doppler ultrasonography to measure tricuspid regurgitation velocity (TRV) for diagnosing PHT. Almost all the studies have used the cutoff 2.5 m/s to diagnose PHT except Nouraie *et al.* that used the cutoff of 2.7 m/s [38]. Regarding the quality assessment, five out of 31 studies were of poorer quality, while all other studies had good quality (**Table 1**).

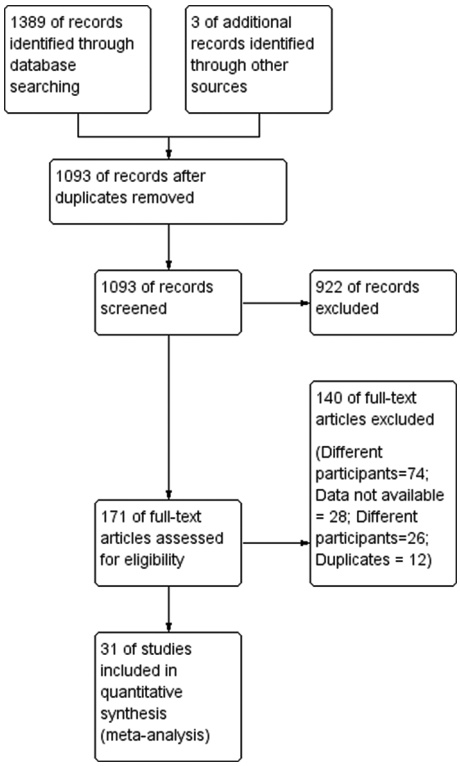

Figure 1. Flowchart showing the search strategy and selection of studies.

Table 1. Characteristics of the included studies (n = 31)

Study no.	First author and year	Region	Country	Study design	Sample size	Study participants	Criteria and cut - off	Mean age (in years)	Quality of evidence
1	Agha *et al*. 2014 [22]	Europe	Egypt	Cross - sectional	80	Children and younger population with SCA under basal conditions	TRJV and 2.5	12.7	High
2	Allen *et al*. 2019 [13]	America	USA	Retrospective	105	Children ≥10 years of age with SCA who underwent an outpatient transthoracic echocardiogram as part of a screening program.	TRJV and 2.5	15	High
3	Ambrusko *et al*. 2006 [14]	America	USA	Retrospective	44	Pediatric SCA patients	TRJV and 2.5	14.8	High
4	Chinawa *et al*. 2020 [15]	Africa	Nigeria	Cross - sectional	51	Children aged 3 years to 17 years, who attended the sickle cell clinics of the study hospitals and were in steady state	TRJV and 2.5	9.7	High
5	Colombatti *et al*. 2010 [16]	Europe	Italy	Prospective	37	SCA children >3 years old at steady state	TRJV and 2.5	6.2	High
6	Cox *et al*. 2014 [23]	Africa	Tanzania	Prospective	215	Children and adolescents aged 9–19 years, HbSS by hemoglobin electrophoresis and high - performance liquid chromatography for SCA	TRJV and 2.5	14.1	High
7	Dahoui *et al*. 2010 [24]	EMR	Lebanon	Prospective	85	All patients with hemoglobin SS, Sb0thal, or Sbþthal seen at the comprehensive sickle cell clinic at Children's Cancer Center of Lebanon	TRJV and 2.5	12.9	High
8	Eddine *et al*. 2012 [25]	America	USA	Retrospective	40	Children with SCA	TRJV and 2.5	14.2	High
9	Forrest *et al*. 2012 [26]	America	USA	Retrospective	85	Children with Hb SS and Hb Sb0 thalassemia older than 6 years of age	TRJV and 2.5	12.1	High

(*Cont'd...*)

Table 1. (*Continued*)

Study no.	First author and year	Region	Country	Study design	Sample size	Study participants	Criteria and cut - off	Mean age (in years)	Quality of evidence
10	Gordeuk *et al*. 2011 [27]	America	USA	Prospective	160	Participants with SCA who had clinical evaluation, echocardiography and 6 - min walk test performed at steady - state	TRJV and 2.5	13	High
11	Gore *et al*. 2018 [28]	SEAR	India	Cross - sectional	38	Children with SCA	TRJV and 2.5	NA	High
12	Hagar *et al*. 2007 [29]	America	USA	Retrospective	61	Children with SCA	TRJV and 2.5	12.7	High
13	Hebson *et al*. 2015 [30]	America	USA	Retrospective	630	Children with SCA	TRJV and 2.5	11.7	High
14	Jesus Rojas *et al*. 2018 [31]	America	USA	Prospective	29	Children with SCA	TRJV and 2.5	NA	High
15	Lamina *et al*. 2019 [32]	Africa	Nigeria	Cross - sectional	200	SCA children aged 1 to 12 years attending the sickle cell clinic who were in steady state	TRJV and 2.5	6.6	Low
16	Liem *et al*. 2007 [33]	America	USA	Prospective	51	Children with SCA	TRJV and 2.5	14	High
17	Liem *et al*. 2009 [34]	America	USA	Prospective	78	Children with SCA	TRJV and 2.5	14.3	High
18	Minniti *et al*. 2009 [35]	America	USA	Prospective	310	Children and adolescents with SCA	TRJV and 2.5	13	High
19	Molavi *et al*. 2014 [36]	EMR	Iran	Retrospective	70	Children with SCA	TRJV and 2.5	NA	High
20	Mondal *et al*. 2018 [37]	America	USA	Retrospective	20	Children with SCA	TRJV and 2.5	10.4	High
21	Nelson *et al*. 2007 [38]	America	USA	Prospective	53	SCA patients under the age of 10 years	TRJV and 2.5	12.4	High
22	Nouraie *et al*. 2020 [39]	America	USA	Prospective	469	Children and adolescents with SCA	TRJV and 2.7	12	High
23	Onalo *et al*. 2020 [40]	Africa	Nigeria	Cross - sectional	176	Children with SCA	TRJV and 2.5	10.4	Low
24	Onyekwere *et al*. 2008 [41]	America	USA	Cross - sectional	52	Children and adolescents with SCA	TRJV and 2.5	16.1	High
25	Pashankar *et al*. 2008 [42]	America	USA	Prospective	62	Children with SCA	TRJV and 2.5	13.5	High

(*Cont'd...*)

Table 1. (*Continued*)

Study no.	First author and year	Region	Country	Study design	Sample size	Study participants	Criteria and cut - off	Mean age (in years)	Quality of evidence
26	Patel *et al*. 2016 [43]	SEAR	India	Cross - sectional	50	All patients between the age group of 5 to 18 years diagnosed to have sickle cell syndromes	TRJV and 2.5	11.3	Low
27	Peter *et al*. 2019 [44]	Africa	Nigeria	Cross - sectional	100	SCA subjects 3–14 years of age in their steady state	TRJV and 2.5	7	Low
28	Qureshi *et al*. 2006 [45]	America	USA	Retrospective	32	Children with SCA	TRJV and 2.5	8.9	High
29	Sedak *et al*. 2009 [46]	America	USA	Cross - sectional	48	Children with SCA	TRJV and 2.5	12	High
30	Sokunbi *et al*. 2017 [47]	Africa	Nigeria	Cross - sectional	175	SCA subjects with haemoglobin genotype SS aged 5 – 18 years	TRJV and 2.5	8.8	Low
31	Suell *et al.* 2005 [48]	America	USA	Retrospective	80	Children with SCA	TRJV and 2.5	15.6	High

EMR: Eastern Mediterranean region; NA: not available; SCA: sickle cell anemia; SEAR: South East Asian region; TRJV: tricuspid valve jet velocity; USA: United States of America

3.3. Burden of PHT in SCA children and adolescents

The final pooled prevalence of PHT among children and adolescents with SCA was 22% (95%CI: 18 – 26%) **(Figure 2)**. Country-wise distribution of PHT is depicted in **Figure 3**. Maximum burden of PHT among SCA children was reported in Europe (26%) and Eastern Mediterranean region (EMR), while the least burden was found in Africa (17%). There was a significant heterogeneity found between the studies in our analysis (I^2 = 87.8%; P < 0.001). Meta-regression was done to find the source of heterogeneity.

3.4. Meta-regression

We included that the following potential covariates for meta-regression were study design, region, quality of evidence, mean age, and year of publication. All these factors had p-value < 0.20 in the univariable model, and they were included to perform multivariable meta-regression analysis. The adjusted model was able to explain 100% of the between-study variability and the model was statistically significant (P = 0.01). Quality of evidence, mean age, and study design were found to be the significant source of heterogeneity in the adjusted model with $P < 0.05$.

3.5. Publication bias

Egger's test was performed for the assessment of publication bias. There were significant small study effects with coefficient value (coefficient: 1.31; P = 0.002) which shows possibility of publication bias. Graphical representation of the test of publication bias is depicted using funnel plot in **Figure 4**. The funnel plot also shows asymmetric plot indicating the presence of publication bias.

4. Discussion

This review was conducted to obtain a comprehensive estimate for burden of PHT among children and adolescents with SCA. In total, we analyzed data from 31 studies with 3,686 participants. Most of the studies were conducted in USA followed by Nigeria and India. Majority of the included studies had lower risk of bias. Significant

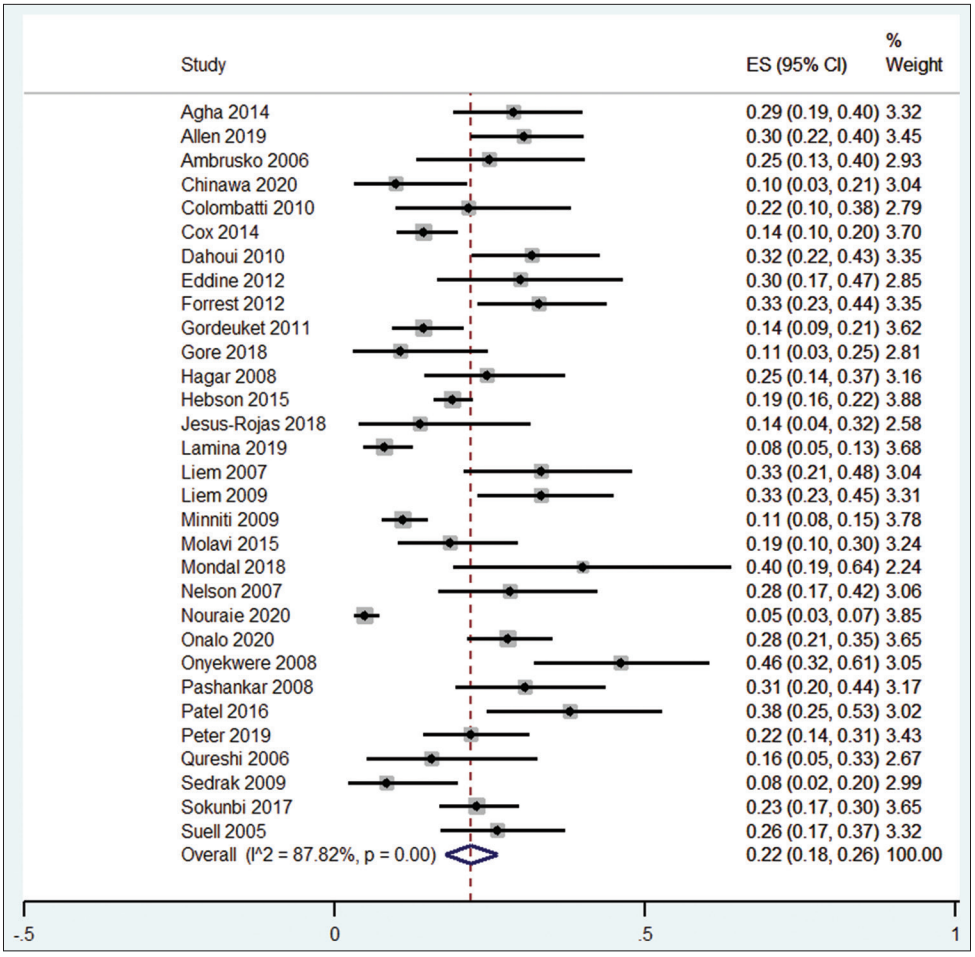

Figure 2. Forest plot showing the prevalence of pulmonary hypertension among sickle cell anemia children and adolescents (n = 31).

heterogeneity was found among the included studies. Hence, meta-regression was performed and found that quality of evidence, mean age, and study design are potential source of heterogeneity in this review. The presence of publication bias indicated by asymmetrical funnel plot was also found.

The prevalence of PHT among children and adolescents with SCA was 22% (95% CI: 18 – 26%). The previous reviews on PHT focused primarily on the participants with SCA irrespective of their age group or general population or special groups such as acquired immunodeficiency syndrome (AIDS) patients, end-stage renal disease patients, and systemic sclerosis patients [49-53]. Our findings were almost similar to the previous review reporting the prevalence of PHT among adult SCA patients [49]. This indicates that there is not much variation in the burden of PHT among SCA patients, irrespective of their age group. Hence, equal importance should be given to all the SCA patients as the risk of PHT is similar across the groups. In addition, we found the burden of PHT in SCA patients to be higher than those in general population or special groups suh as AIDS patients and systemic sclerosis patients [50,51,53]. However, it was significantly lower compared to patients with cardiac, respiratory, or renal comorbid conditions [51,52]. However, most of the studies included in the current review and previous reviews have used TRV to determine the burden of PHT. This tends to overestimate the prevalence as the definition of PHT with echocardiography is still a matter of continuous debate. This is because TRV of 2.5 m/s reflects a right ventricular systolic pressure of 27 mmHg plus right atrial pressure, a pressure far from being relevant for pulmonary vasculopathy. Hence, it is mandatory to use cardiac catheterization when defining PHT, and the future studies should focus on doing it to establish the burden of PHT. Still, the findings from this

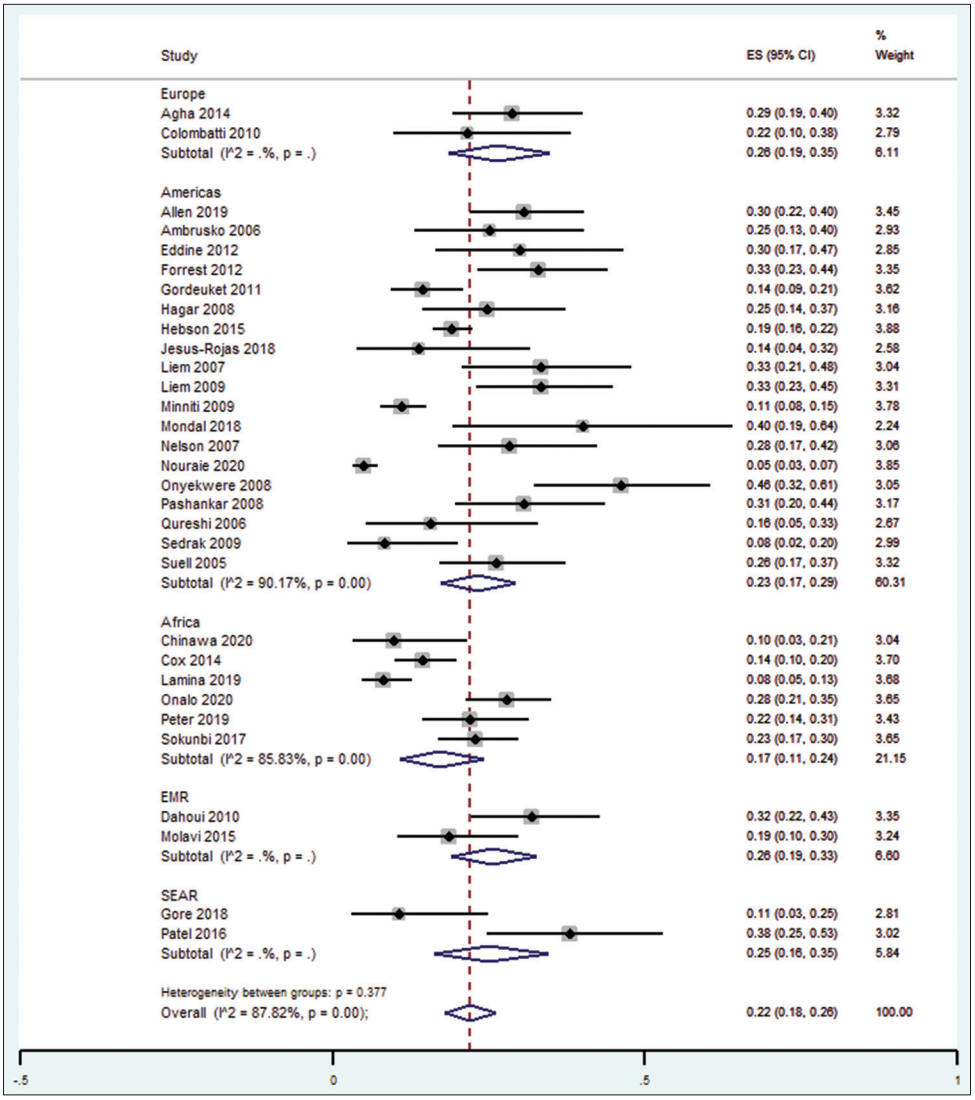

Figure 3. Forest plot showing the region-wise subgroup analysis of pulmonary hypertension burden among sickle cell anemia children and adolescents (n = 31).

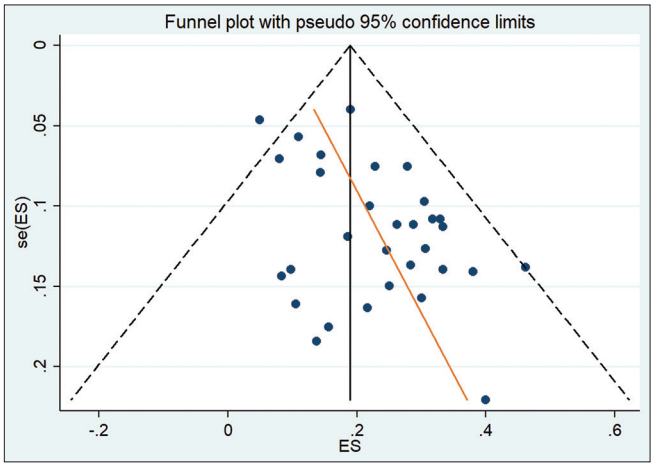

Figure 4. Funnel plot for checking the possibility of publication bias (n = 31).

systematic review highlight the need for screening all the children and adolescents with SCA using TRV as a screening procedure, and the children diagnosed to have PHT using TRV can undergo cardiac catheterization for further confirmation.

Subgroup analysis was performed to see whether there is any variation in the burden across the regions. We found that the SCA children and adolescents in Europe and EMR had the highest burden of PHT, while Africa had the least prevalence. The previous review has also found that the burden of PHT was higher in the European region and lesser in the African region [49]. Although the number of patients with SCA is higher among the people in African region, the burden of PHTN is lesser when compared to European region. This difference in the burden can be attributed to the better diagnostic tool availability in high-income region like Europe. It may also be due to lack of access to diagnostic

care in the African countries. Availability, accessibility, and affordability of the diagnostic and therapeutic care in Europe may improve the survival of the patients, thereby showing a comparatively higher prevalence in the region. Hence, there is a need to close the gap in providing care for the SCA patients between Europe and Africa. This calls for the development of simple, non-invasive, and cost-effective tools for screening the patients, as it ultimately leads to early diagnosis and adequate management of the condition. Using right heart catheterization as a screening tool is not practically possible due to lack of trained/skilled human resources in such low-income/high-SCA-burden countries in Africa. TRV screening can be considered a more pragmatic option for screening the SCA patients for PHT in such settings. There is also availability of many biomarkers that suggest the presence of PHT and can be used as an effective screening tool [54].

The major strength of the study is that this is so far the first comprehensive review on burden of PHT among the younger population with SCA globally. We have also included large number of studies to provide reasonable estimate on the burden. However, our review had certain limitations. All the included studies have used TRV to diagnose PHT. This can overestimate the prevalence as the right heart catheterization is the gold standard for diagnosing a case of PHT. The Chi-square test for heterogeneity also revealed significant variability across the included studies. This limitation was overcome in this work by conducting meta-regression to explain the between-study variability using meta-regression and identify the potential sources of heterogeneity. Significant publication bias was also found, indicating that the point estimate obtained in our review should be interpreted with caution.

5. Conclusions

Current review provides important baseline information on the epidemiology of PHT among children and adolescents with SCA in the world. The findings of this systematic review highlight that PHT is one of the important complications among SCA patients irrespective of their age. This review also highlights the fact that only fewer studies have investigated the extent of PHT among the SCA patients in lower- and lower middle-income regions. Diagnostic and intervention packages targeting these patients should be developed and implemented by clinicians across the high-risk settings. Further studies on exploring the factors responsible for high burden of PHT among SCA patients should be done as it will help the clinicians to understand the mechanism and take decisive actions and implement patient-specific interventions accordingly.

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Conflict of interest

The author declares no conflicts of interests.

Author contributions

This is single-authored manuscript.

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Availability of data

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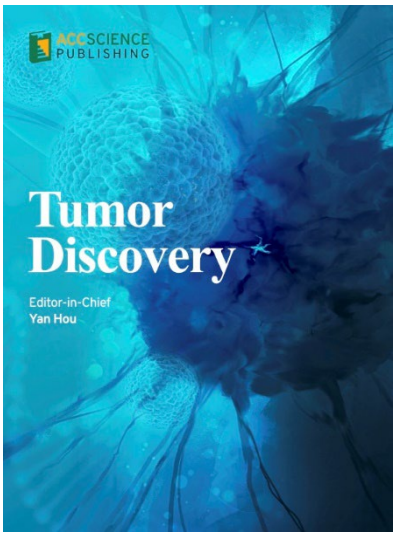

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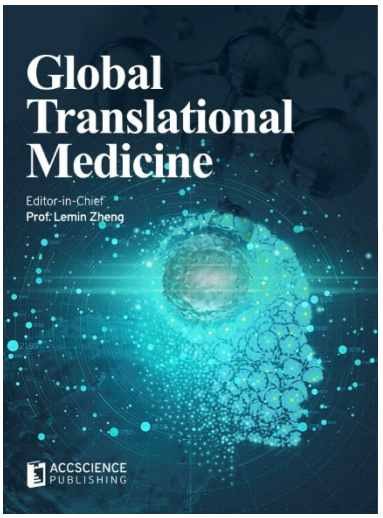

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