# Study of Variations in the Origin of Profunda Femoris Artery and Internal Diameter of Femoral Artery in Human Cadavers

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#### **Abstract**

Introduction: Profunda femoris artery is the largest deep branch of femoral artery, provides the principal supply to the extensor, adductor and flexor muscles of the thigh. This large artery arises from the posterolateral side of the femoral artery about 3.5-5cm from the mid-inguinal point. The study of the femoral artery and its branching pattern has been a great interest among the anatomists and the surgeons because of its major implication in the clinical as well as radiological interventions. Material and Methods: In the present study, hundred formaldehyde embalmed cadavers without malformations were dissected and site and level of origin of the profunda femoris artery in relation to the midpoint of the inguinal ligament from the femoral artery studied, also the internal diameter of femoral artery measured by dissection method. Results: Profunda Femoris Artery originated on right side in 46% cases and 44% on left side from the posterolateral aspect. The average distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament on right side was observed to be 4.45 cm while on left side was observed to be 4.69cm. The mean value of Internal Diameter of Femoral Artery was found to be 7.46 mm in males and 6.33 mm in females on right side and 7.43 mm in males and 6.29 mm in females on left side. Conclusion: Most common site of origin of profunda femoris artery was observed to be the posterolateral aspect of the femoral artery. Variations seen in the form of posterior and lateral origins. The average distance of origin of profunda femoris artery was observed between 4-5cm. In the present study 3 cases of high origin of profunda femoris artery observed. The advantage of such a high origin of profunda femoris artery is that it can be used for catheterisation and further investigation of any arterial system of the body. Gender wise comparison of mean value of internal diameter of femoral artery on both sides showed statistically highly significant difference.

Keywords: Femoral Artery; Inguinal Ligament; Profunda Femoris Artery.

#### Introduction

The big horizon of interventional radiology opens new avenues for the study of variations of the course of the profunda femoris artery [1]. In Homo sapiens, the main stem artery supplying arterial branches to deep structures of the proximal thigh and hip joint is the profunda femoris artery (deep femoral artery) [2].

It is the largest deep branch of femoral artery. It is the principal artery to supply to the extensor, adductor and flexor muscles of the thigh [3]. This large artery arises from the posterolateral side of the femoral artery about 4-5cm below the inguinal ligament [4].

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Femoral artery is the continuation of the external iliac artery and enters the femoral triangle behind the inguinal ligament midway between the Anterior Superior Iliac Spine and the symphysis pubis [5]. This is the point where its pulsations can be felt. This location is also used for the femoral catheterization [6].

The study of the femoral artery and its branching pattern has been a great interest among the anatomists and the surgeons because of its major implication in the clinical as well as radiological interventions [7].

It is used for investigation of any arterial system in the body and for various clinical procedures like coronary angioplasty. In addition to those the femoral artery at the femoral triangle is directly opened at the origin of the profunda femoris artery for femoral embolectomy in lower limb arterial thrombo embolism [8]. The profunda femoris artery is used for arteriography, ultrasound and Doppler imaging, digital subtraction angiography and magnetic resonance imaging [9].

Since the advent of interventional radiology, the methods of investigation of the cardiac patients have taken a big leap towards this end. Femoral arteriography is the main line for investigation in peripheral occlusive arterial diseases and in diagnosis of suspected congenital anomalies [1]. Femoral artery is also used for the procedure called embalming for the disinfection and preservation of cadavers by injecting the embalming fluid from femoral artery [10]. As the femoral arteries are commonly used for these procedures, the internal diameter and as well as the origin of the profunda femoris artery are of clinical significance in the procedures used for diagnosis [1].

Aims & Objectives

- 1. To determine site of origin of Profunda Femoris Artery.
- 2. To determine the distance of origin of Profunda Femoris Artery from the midpoint of the inguinal ligament.
- 3. To determine the internal diameter of Femoral Artery.
- To compare the obtained results with those of other studies.

#### Material and Methods

Source of Data

The present study was carried out on fifty (50) formalin embalmed cadavers allotted to the undergraduate students for dissection in the Department of Anatomy, at Government medical colleges. Among these there were thirty (30) males and twenty (20) females.

#### **Dissection Method**

A series of 100 femoral triangles in 50 human cadavers were dissected (30 males and 20 females). The femoral artery and the profunda femoris artery were identified, their origin and course studied. The mode of origin of profunda femoris from the femoral artery was studied. The distance of origin of the profunda from the midpoint of the inguinal ligament was measured in millimeters with digital vernier calliper (Figure 1).

A segment of 5 cm of the femoral artery (vessel) is cut just below the midpoint of the inguinal ligament. Then a vertical nick is given to the vessel and extended throughout the length vertically. This vessel is kept on an even surface and spread out.

Now, near the proximal end of the vessel horizontal length is measured from the inner side of the vessel by spreading a thread over that end horizontally (Figure 2). Two points were marked on the thread at the ends. Then this distance between the two points on the thread is measured by digital vernier caliper (Figure 3).

This gives the circumference (C) of the vessel.

 $C = 2\delta r$ 

r denotes radius and 2r = D

D denotes diameter of the vessel

As this distance is measured from inner side of vessel, this diameter D denotes the internal diameter of the vessel.

Now,  $C = \delta D$ 

Or internal diameter  $D = C \div \delta$ 

Where  $\delta = 3.14$ 

So D =  $C \div 3.14$ 

So by this method, internal diameter of the vessel is measured. The variations in the branching pattern were noted, photographs taken with a digital camera. The observations were tabulated and analyzed.

Study design

Observational study

Study setting

Dissection hall, Department of Anatomy

Study duration

January 2012 to December 2013.

Study sample size

100 femoral triangles.

Study subjects

Human cadave

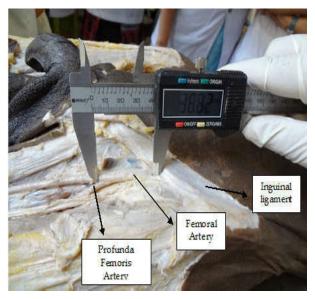
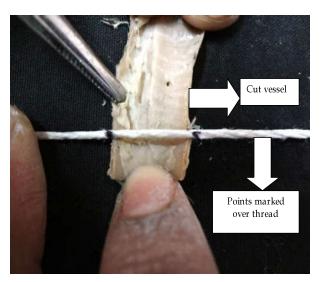


Fig. 1: Measurement of distance of origin of Profunda femoris artery from midpoint of inguinal ligament

Data Analysis

- 1. Data entry:- It was done using Microsoft excel 2007.
- 2. Statistical Analysis:
- a. Descriptive statistics (Percentage, Mean, Median and Standard deviation) was used to summarize baseline characteristics of the study subjects.
- b. Various data obtained from dissection of human cadavers and variations were noted.
- c. Data was analysed using STATA VERSION-10 statistical software.
- d. Chi square test, Unpaired t-test used to analyse data.



**Fig. 2:** Measurement of internal diameter of femoral artery: howing near the proximal end of the vessel horizontal length is measured from the inner side of the vessel by spreading a thread over that end horizontally and two points are marked on thread at the ends



**Fig. 3:** Measurement of internal diameter of femoral artery: Distance between the two points on the thread is measured by digital vernier caliper

#### **Observation and Results**

In most of the cases, site of origin of the Profunda Femoris Artery was from the posterolateral aspect of the Femoral Artery, in 46% on right side and 44% left side. The site of origin of Profunda Femoris Artery between the right and left sides, showed statistically non significant difference by chi square test

The site of origin of Profunda Femoris Artery between the right and left sides in males showed statistically non significant difference by chi square test. On both sides it arosed most commonly from posterolateral aspect in males i.e. 43.33% on right side and 36.67% on left side.

In females also it showed statistically non significant difference by chi square test. On both sides it arosed most commonly from posterolateral aspect i.e. 50% on right side and 55% on left side.

Distance of origin Profunda Femoris Artery from midpoint of inguinal ligament was recorded most commonly in the range of 4.1-5cm on both sides.

The average distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament on Right side was observed to be 4.45cm whereas on left side 4.69cm.

The comparison of mean of distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament on Right And Left side showed statistically non significant difference by unpaired t-test.

The internal diameter of Femoral Artery was recorded in the range of 7.1-8 cm in 70% cases on right side and 73.33% cases on the left side.

Whereas in females 70% of the cases on right side and 75% cases on the left side in the range of 6.1-7 cm.

The mean value of Internal Diameter of Femoral Artery was found to be 7.46 mm on right side and 7.43 mm on left side in males.

In females the mean value was found to be 6.33 mm on right side and 6.29 mm on left side.

The mean value of comparison of internal diameter of the male subjects between right and left legs showed statistically non significant difference by unpaired t-test.

Similarly in females too the mean value of comparison of internal diameter between right and left legs showed statistically non significant difference by unpaired t-test.

The mean value of Internal Diameter of Femoral Artery was found to be 7.46 mm in males and 6.33 mm in females on right side.

Table 1: Distribution of site of origin for Profunda Femoris Artery

	LA	PL	РО	P-Value	Chi. Sq.
Right Left	10(20%) 11(22%)	23(46%) 22(44%)	17(34%) 17(34%)	0.9657, NS	0.069 df=2

Table 2: Distribution of site of origin of Profunda Femoris Artery separately among males and females

	Male (30)		Female (20)		
	Right	Left	Right	Left	
LA	8 (26.67%)	9 (30%)	2 (10%)	2 (10%)	
PL	13 (43.33%)	11 (36.67%)	10(50%)	11(55%)	
PO	9 (30%)	10 (33.33%)	8 (40%)	7 (35%)	
P-VALUE	0.87, NS		0.94, NS		
Chi square	0.2781 df=2		re 0.2781 df=2 0.1143 df=2		3 df=2

Table 3: Showing Distribution of distance of origin of Profunda Femoris Artery from midpoint of inguinal ligament

Distance(cm)	Right	0/0	Left	0/0
0-1	2	4	1	2
1.1-2.0	1	2	2	4
2.1-3.0	2	4	2	4
3.1-4.0	6	12	6	12
4.1-5.0	23	46	21	42
5.1-6.0	11	22	13	26
6.1-7.0	5	10	5	10
Total	50	100	50	100

**Table 4:** Comparison of distance of origin of Profunda Femoris Artery Midpoint of Inguinal Ligament on Right and Left side

	Right	Left
Mean	4.45	4.69
SD	1.22	1.26
Median	4.3	4.8
SEM	0.1725	0.1796
T-Value	0.9799	df=98
P-Value	0.329	6, NS

**Table 5:** Comparison of distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament separately among males and females

	Male		Female	
	Right	Left	Right	Left
Mean	4.53	4.84	4.33	4.47
SD	1.29	1.35	1.12	1.12
Median	4.35	5.0	4.3	4.75
SEM	0.2362	0.2477	0.2507	0.2510
Range	1-6.9	1-6.8	1-6.6	1.9-6.8
P-Value	0.9057 NS		0.6850, NS	
T-Value	0.9057 df=58		0.4087 df=38	

Table 6: Distribution of Internal Diameter of Femoral Artery among the study group

	Mai	le(30)	Female(20)		
In mm.	Right	Left	Right	Left	
4.1-5.0	2 (6.67%)	1 (3.33%)	2(10%)	2 (10%)	
5.1-6.0	1 (3.33%)	2 (6.67%)	3 (15%)	2 (10%)	
6.1-7.0	3(10%)	3 (10%)	14 (70%)	15(75%)	
7.1-8.0	21(70%)	22 (73.33%)	1 (5%)	1 (5%)	
8.1-9	2 (6.67%)	1(3.33%)	0(0)	0 (0)	
9.1-10	1(3.33%)	1(3.33%)	0(0)	0(0)	

Male **Female** Right Left Right Left 7.46 7.43 6.33 6.29 Mean 0.97 0.93 0.6898 0.6932 SD 7.50 Median 7.6 6.500 6.500 SEM 0.1781 0.1703 0.1543 0.155 Range 5-9.9 4.8 - 9.84.8 - 7.44.8 - 7.30.1601 DF=38

Table 7: Comparison of Internal Diameter of Femoral Artery between right and left side in males and females

Table 8: Gender wise comparison of Internal Diameter of Femoral Artery

0.1082 DF= 58

0.9142, NS

	Right		Left	
	Male	Female	Male	Female
Mean	7.46	6.33	7.43	6.29
SD	0.97	0.68	0.93	0.69
Median	7.6	6.5	<i>7</i> .5	6.5
SEM	0.1781	0.1543	0.1703	0.1550
T value	4.494 □	4.494 DF= 48 4.674 DF=		DF= 48
Range	5-9.9	4.8-7.4	4.8-9.8	4.8-7.3
P-Value	0.0001	0.0001, HS 0.0001, HS		1, HS

The mean value of Internal Diameter of Femoral Artery was found to be 7.43 mm in males and 6.29 mm in females on left side.

Gender wise comparison of mean value of internal diameter of femoral artery on both sides showed statistically **highly significant** difference by unpaired t-test.

This shows that male femoral artery have significantly larger diameter than female femoral artery.

#### Discussion

T-Value P-Value

Profunda Femoris Artery is the main source of blood supply in the thigh region. It has an important role in arteriography, ultrasound, doppler imaging, digital subtraction angiography and MRI [11].

In the recent era, profunda femoris is being used for haemodialysis other than femoral artery.

Damage to this artery can cause life threatening complications. It is an important branch of Femoral Artery which is commonly used for catheterization in interventional radiology. So clinicians and surgeons must be aware of normal anatomy and variations in this region.

Anatomical variations reported at the level of the division of the femoral artery can be explained as follows. In the lower animals, the profunda femoris artery is a branch of the internal iliac artery. During course of evolution, the origin shifted distally from the femoral artery. Ontogeny repeats phylogeny. Hence, developmental arrest at different stages may lead to anatomical variations related to the division of the femoral artery [12].

0.8737, NS

Vaas F [13] reported that the profunda femoris artery acts as a collateral vessel in the occlusion of the femoral artery and for this important function, it has to have a large caliber, which can be explained based on the aforementioned comparative anatomy.

# Variations in the arterial patterns may be due to

- 1. Divergence in the mode and proximodistal level of branching.
- 2. Presence of unusual compound arterial segments.
- Aberrant vessels that connect with principal vessels, arcades or plexuses.
- 4. Vessels that occupy exceptional tissue planes (e.g. superficial fascia instead of sub fascia).
- 5. Have unsuspected neural myological or osteoligamentous relationships based on the aforementioned comparative anatomy.

Many workers have reported variability in the origin and branching pattern of Profunda Femoris Artery still, combined study on the anatomical variations of the origins of the profunda femoris, and internal diameter of femoral artery is rare in literature. Hence, present work was undertaken on cadavers to study.

Site of origin of the Profunda Femoris Artery

Dixit DP [7] et al 2001, did cadaveric study and found that the profunda femoris artery originated from the posterolateral aspect of the femoral artery in 17 out of 48 cases i.e. 35.41% and from the posterior aspect in 15 out of 48 cases i.e. 31.25%.

Samarawickrama MB [15] et al 2009, observed that profunda femoris artery originated from either posterior (12/26) i.e 46.15% cases, posterolateral (8/26) i.e. 30.76% or lateral (6/26) i.e. 23.07% aspect of the common femoral artery.

Prakash [12] et al 2010, in a cadaveric observed that 32 out of 64 (50%) extremities, the profunda femoris artery originated from the postero-lateral aspect of the femoral artery; whereas it originated from the posterior aspect in 30 out 64 (46.9%) specimens.

Daksha D [16] et al 2011, dissected 228 lower limbs. The profunda femoris originated from the posterolateral aspect of femoral artery in 96 cases i.e. 42.1%, from the posterior aspect in 68 cases i.e. 28.5%, from lateral side in 43 cases i.e. 18.8%.

Thitilertdecha S [17] et al 2012, observed that PFA was found mostly separated from posterior aspect of FA in 100 cases (44.64%) followed by posterolateral aspect in 68 cases (30.36%), from lateral aspect in 48 cases (21.43%).

In the present study, site of origin of the Profunda Femoris Artery was from the posterolateral aspect of the Femoral Artery in 46% on right side and 44% left side. So the Profunda Femoris Artery originated commonly from the posterolateral aspect of the Femoral Artery on both sides. The site of origin of Profunda Femoris Artery between the right and left sides, showed statistically non significant difference.

The findings of the present study were similar with the findings of the study conducted by the Dixit, D.P. et al (35%), Prakash et al (50%), and Daksha Dixit 2011 (42.1%) et al. Marina et al also found most common site as posterolateral aspect. However when compared with the findings of MB Samarawickrama et al, Siriporn Thitilertdecha et al, it indicated differences. They found most common site from the posterior aspect of the Femoral Artery which was 46.15% and 44.15% respectively. These differences may be due to various ethnic origins.

Distance of origin of Profunda Femoris Artery from midpoint of inguinal ligament

Siddharth P [9] et al 1985, dissected 100 legs and observed: The deep femoral artery originates a median distance of 4.4 cm from the inguinal ligament.

Dixit DP [7] et al 2001, observed that the distance of origin of profunda femoris from the midpoint of the inguinal ligament on the right side was mostly between 41 and 52 mm whereas on the left side it was between 46 and 54 mm.

Baptist M [18] et al 2007, observed that the distance of origin of profunda femoris artery on the right side, was observed to be commonly between 30 - 40 mm (40% cases). On the left side also it was 30-40 mm (35% cases).

Nachiket S [19] et al 2009, during routine dissection of a middle aged male cadaver, an unusual origin of the deep artery of thigh was observed bilaterally.

It arose from the femoral artery less than 1 cm distal to the inguinal ligament. On both sides, its diameter was greater than that of the femoral artery.

Prakash [12] et al 2010, observed that the median distance of separation of the profunda femoris artery from the femoral artery was 4.2 cm distal to the midpoint of the inguinal ligament.

Thitilertdecha S [17] et al 2012, observed that the average distance was 34.6mm (37.68 mm in males and 31.54mm in female). Moreover, there were 36.22mm on the right and 33mm on the left.

Mamatha H [20] et al 2012, observed that the PFA originated at about 4.5 cm from the mid-inguinal point and got the results like higher origin of the profunda femoris artery in one specimen.

Shiny Vinila BH [21], et al 2013, observed that the mean distance of origin of profunda femoris artery was observed as 4.13cm and standard deviation was observed as 0.80cm.

Anwer D [22] et al 2013, observed that the average distance of origin of profunda femoris from the midpoint of inguinal ligament was found to be 37.12mm.

In the present study the Profunda Femoris Artery originated commonly from a distance of 4-5 cm. from the midpoint of inguinal ligament. The average distance on right side was found to be 4.45 mm whereas on left side 4.69 cm. The comparison of mean value of distance of origin of Profunda Femoris Artery from the midpoint of Inguinal Ligament on Right and Left side showed statistically non significant difference.

These findings are comparable with findings of Siddharth et al, Dixit et al, Prakash et al, Mamatha H.et al, Shiny V et al, Suthar K. et al 2013.

However, Firdose sultana et al, Siriporn Thitilertdecha et al and Danish Anwer et al 2013 got average distance in the range of 3-4cm which is less than the present study. These differences may be due to differences in various ethnic origins. Still the findings are nearer to the present study.

Nachiket S. 2009 observed origin of profunda femoris from less than 1 cm distal to the inguinal ligament. In the present study such findings observed in 3 legs.

The advantage of such a high origin of profunda femoris artery is that it can be used for catheterisation and further investigation of any arterial system of the body.

### Internal Diameter of Femoral Artery

Sandgren T [23] et al 1999, stated that male subjects have larger arteries than female subjects this is related to age, body size, and sex after investigating on 122 healthy volunteers (59 male, 63female) by echotracking B-mode ultrasound scan.

Schnyder G [24] et al 2001, assessed the angiographic size of the common femoral artery (CFA) and the influence of demographics and comorbidites. Consecutive CFA angiograms (n = 200) were prospectively analyzed. CFA diameter was  $6.9\pm1.4$  mm By multivariate analysis, only diabetes (P < 0.001), female gender (P < 0.0005), and small body surface area (P < 0.01) predicted small vessel size.

Minami T [25] et al 2006, observed that men had significantly larger arterial diameters than women for femoral artery (9.8±1.5 vs. 7.2±1.7 mm, P<0.001) arteries an ultrasound study.

Baptist M [18] et al 2007, observed that on the left side 70% cases were in the range of 7.1 to 8.0 mm and 75% cases on the right side were in the range of 7.1-8.0 mm.

Shiny Vinila BH [21] et al 2013, observed that the average internal diameter of femoral artery was observed as 7.02±0.85mm.

In the present study, the internal diameter of Femoral Artery was recorded in the range of 7.1-8 cm in 70% cases on right side and 73.33% cases on the left side. Whereas in females 70% of the cases on right side and 75% cases on the left side in the range of 6.1-7 cm.

The mean value was found to be 7.46 mm on right side and 7.43 mm on left side in males.

In females the mean value was found to be 6.33 mm on right side and 6.29 mm on left side.

Gender wise comparison of mean value of internal diameter of femoral artery between males and females showed statistically significant difference on right side as well as on left side. Findings of present study are comparable with findings of the above studies however Taro et al got larger diameter of femoral artery than the present study. This difference may be due to different method of study by Taro et al and the different ethnic origins between the two study group.

This shows that male femoral artery have significantly larger diameter than female femoral artery.

## **Summary**

The results of above observations were summarized as,

1. The site of origin of the Profunda Femoris Artery was observed to be from the posterolateral aspect of the Femoral Artery most commonly.

It originated on right side in 46% cases and 44% on left side from the posterolateral aspect, from the posterior aspect in 34% on both sides and from the lateral aspect in 20% on right side and 22% on left side

The site of origin of Profunda Femoris Artery between the right and left sides, of the study group showed statistically non significant difference.

The site of origin of Profunda Femoris Artery between the right and left sides in males showed statistically non significant difference. On both sides it arosed most commonly from posterolateral aspect.

In males 43.33% on right side and 36.67% on left side.

In females also it showed statistically non significant difference. On both sides it arosed most commonly from posterolateral aspect i.e. 50% on right side and 55% on left side.

- 2. Distance of origin of Profunda Femoris Artery from midpoint of inguinal ligament was recorded most commonly in the range of 4.1-5cm on both sides.
- The average distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament on right side was observed to be 4.45 cm while on left side was observed to be 4.69cm.

The comparison of mean distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament on Right And Left side showed statistically non significant difference.

The mean distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament on right side was observed to be 4.53 cm and on left side 4.84cm in males.

In females it was observed to be 4.33 cm on right side and on left side 4.47cm.

The comparison of mean distance of origin of Profunda Femoris Artery from Midpoint of Inguinal Ligament separately for males and females on Right And Left side showed statistically non significant difference

3. The internal diameter of Femoral Artery was recorded in the range of 7-8 cm in 70% cases on right side and 73.33% cases on the left side.

Whereas in females 70% of the cases on right side and 75% cases on the left side in the range of 6-7 cm.

The mean value of Internal Diameter of Femoral Artery was found to be 7.46 mm on right side and 7.43 mm on left side in males.

In females the mean value was found to be 6.33 mm on right side and 6.29 mm on left side.

The comparison of mean value of internal diameter of the male subjects between right and left legs showed statistically non significant difference

Similarly in females too it was non significant.

The mean value of Internal Diameter of Femoral Artery was found to be 7.46 mm in males and 6.33 mm in females on right side. The mean value of Internal Diameter of Femoral Artery was found to be 7.43 mm in males and 6.29 mm in females on left side.

Gender wise comparison of mean value of internal diameter of femoral artery on both sides showed statistically highly significant difference.

This shows that male femoral artery have significantly larger diameter than female femoral artery.

#### Conclusion

Profunda femoris artery is an important artery of the thigh and the largest branch of femoral artery. It originates from the femoral artery on the posterolateral aspect commonly. Alteration in the developmental pattern of the axial or Ischiadic artery is the main cause for the anatomical variations in lower limb arteries. The knowledge of these variations is of importance during surgical and radiological procedure to avoid any catastrophical complications.

*In the present study;* 

1. Most common site of origin of profunda femoris artery was observed to be the posterolateral aspect of the femoral artery. Variations seen in the form of posterior and lateral origins.

- The knowledge of the site of origin of profunda femoris artery is important while performing clinical procedures in the femoral region and hip joint replacement and also for avoiding iatrogenic arteriovenous fistula or severe secondary haemorrhage while performing femoral artery puncture.
- 3. The average distance of origin of profunda femoris artery was observed between 4-5cm.
- 4. In the present study 3 cases of high origin of profunda femoris artery observed. The advantage of such a high origin of profunda femoris artery is that it can be used for catheterisation and further investigation of any arterial system of the body
- 5. The internal diameter of the femoral artery was observed significantly more in males than females.
- 6. The knowledge of the internal diameter of femoral artery at the femoral triangle is useful to surgeons and interventional radiologists as this artery is used in certain clinical procedures like cardiac catheterization, trans- arterial chemo embolization in the treatment of malignancy, arteriography in peripherial vascular diseases.

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