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Research Article

MORPHOLOGICAL AND HISTOPATHOLOGICAL CHANGES IN GREAT SAPHENOUS VEIN AND ITS EFFECT ON DURATION AND SEVERITY OF VARICOSE VEINS

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A B S T R A C T

Chronic venous disorders remain a common problem worldwide. However, despite increasing research into novel endovenous therapies for the treatment of superficial venous disease, the pathogenesis of primary varicose veins remains poorly understood. Various studies have evaluated the correlation of vessel wall changes with duration and severity of varicose veins. We carried out a prospective study to evaluate the morphological and histopathological changes in great saphenous vein and its correlation with duration and severity of disease in varicose veins. The results of our study concluded that morphological and histopathological changes in great saphenous vein plays a significant role in pathogenesis of primary varicose veins. Also, these changes in the Great Saphenous Vein wall could result in the secondary Sapheno-Femoral Junction incompetence in these patients.

INTRODUCTION

Varicose veins are dilated and tortuous veins of leg and include telangiectasias and fine reticular veins that instead of conducting blood upward, back to heart, conduct blood downward in reversed fashion, back to the foot. Valvular incompetence of superficial, deep and perforating systems in extremities is one of the major causes for varicose veins and chronic venous stasis. This venous dilatation may be due to weakness of the vein wall as a result of structural problems.[1-6] Several studies have evaluated the correlation of vessel wall changes with duration and severity of varicose veins, but with variable results. We carried out a prospective study to evaluate the morphological and histopathological changes in great saphenous vein and its correlation with duration and severity of disease in varicose veins.

MATERIAL AND METHODS

The present study was conducted in 40 patients admitted in the Department of Surgery or Cardiothoracic and Vascular Department of our Institute. The patients were divided into two groups. Group A comprised of 30 patients having clinical features suggestive of varicose veins and Group B comprised of 10 patients who did not have clinical features suggestive of any venous disorder.

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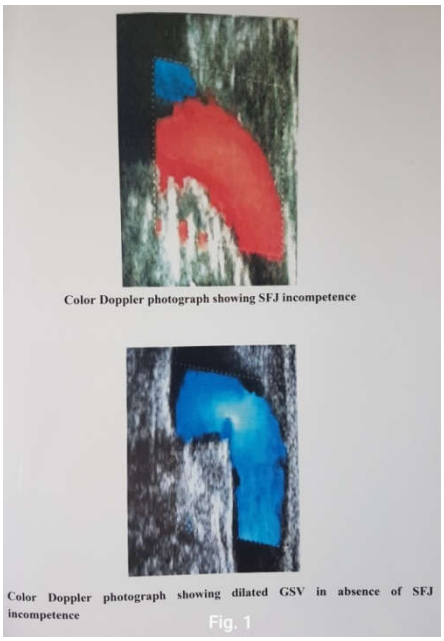
Specimen of normal vein were obtained from Group B patients who were undergoing any cardiac or peripheral bypass surgeries where vein was required for arterial graft or coronary graft. The left out piece of vein was taken for histopathological study.

In Group A patients, a detailed history was taken including the history of duration of disease, pain, swelling and any skin changes in lower limbs etc and severity of the illness was recorded. Then a thorough physical examination was carried out. In Group B patients, a detailed history was taken to exclude any venous disorder like history of dilated veins in lower limbs, pain, swelling and any skin changes in lower limbs. Physical examination was also being done to rule out any venous disorder in Group B patients.

Clinical severity of the disease in a given patient was assessed by standard clinical, etiologic, anatomic, and pathological (CEAP) classification as recommended by the American Venous Forum committee on venous outcome assessment. Colour duplex ultrasound assessment was performed in all Group A as well as Group B patients to rule out chronic or recent deep venous thrombosis and to measure great saphenous vein diameters. Diameters measurement was performed at 3 different levels: saphenofemoral junction at the groin and at middle and lower thigh. Status of saphenofemoral junction, saphenopopliteal junction and various incompetent perforators in the lower limb were also studied with the help of colour doppler. (Fig. 1).

Ligation of the saphenofemoral junction with ligation of all the tributaries and perforators was done. Long saphenous vein was stripped out from groin to knee (Fig. 2 & 3). Multiple stab avulsions of distal calf varicosities were also done in all cases. Saphenopopliteal junction was also ligated if it was found to be incompetent. All vein specimens were sent for histopathological examination.

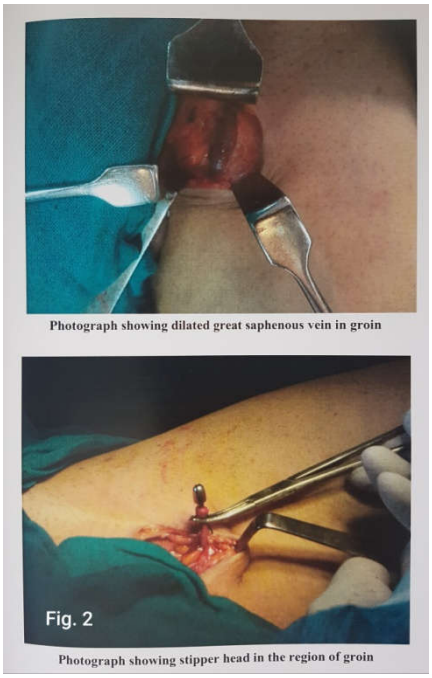


Color Doppler photograph showing SFJ incompetence

Color Doppler photograph showing dilated GSV in absence of SFJ incompetence

Fig. 1

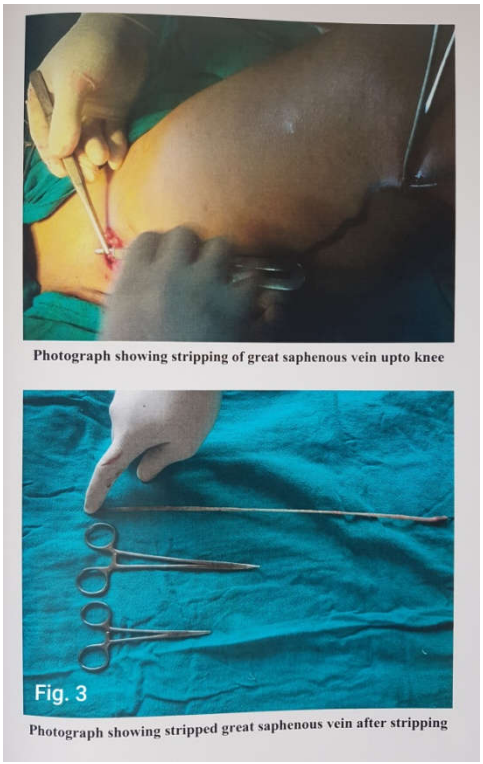
Quantitative measurements were carried out to measure intimal thickness, medial thickness, color area percentage of collagen fibers in intima, color area percentage of collagen fibers in media, color area percentage of smooth muscle and color area percentage of elastin at the junction between intima and media (Fig.4, 5 & 6). Data was analysed to find any correlation between morphological and histopathological changes in great saphenous vein with duration and severity of disease.



Photograph showing dilated great saphenous vein in groin

Fig. 2

Photograph showing stipper head in the region of groin



Photograph showing stripping of great saphenous vein upto knee

Fig. 3

Photograph showing stripped great saphenous vein after stripping

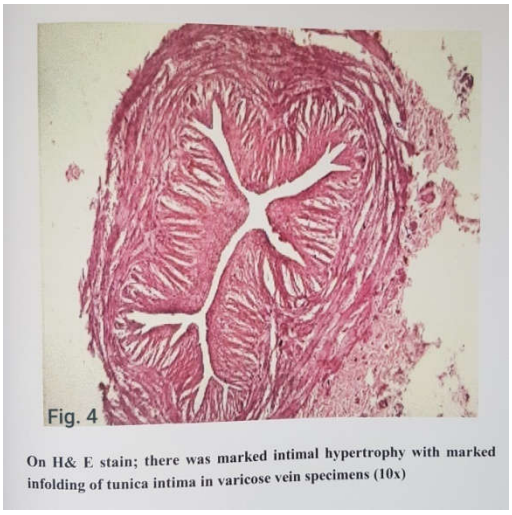
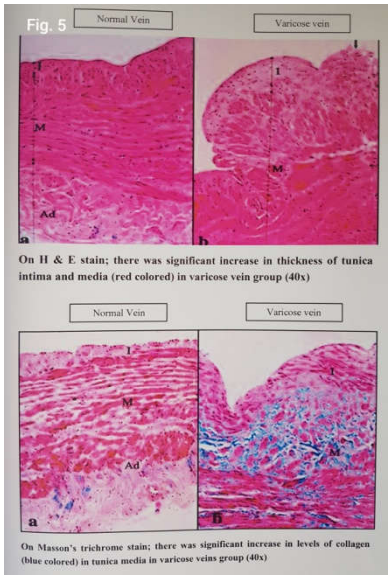


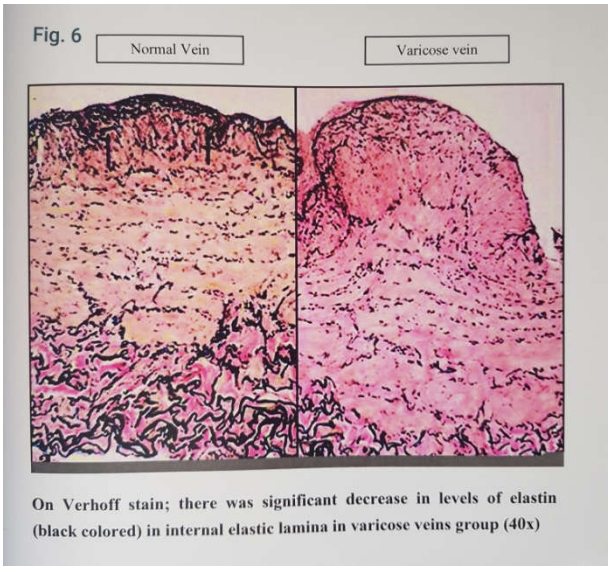
Fig. 4

On H& E stain; there was marked intimal hypertrophy with marked infolding of tunica intima in varicose vein specimens (10x)



On H & E stain; there was significant increase in thickness of tunica intima and media (red colored) in varicose vein group (40x)

On Masson's trichrome stain; there was significant increase in levels of collagen (blue colored) in tunica media in varicose veins group (40x)



On Verhoff stain; there was significant decrease in levels of elastin (black colored) in internal elastic lamina in varicose veins group (40x)

RESULTS

Majority of patients in our study were between 20-30 yr of age, ranging from 20 to 62 years. In our study left lower limb was more commonly involved as compared to right side (63.6%). In Group A patients, dilated and tortous veins were present in all the 30 (100%) patients. Twenty five (83.3%) patients complained of pain while walking while 19 (63.3%) patients had swelling around ankle indicating moderate stage of disease. Pigmentation of skin was seen in 11 (36.6) patients while healed ulcer and active ulcers were found in 3 (10%) and 2 (6.6%) patients respectively. Duration of symptoms varied from 4 months to 24 months and maximum number of patients 21 (70%) presented with symptoms of more than one year.

Disease severity ranged from C2 to C6. Majority of the patients (11 out of 30) had C2 severity of disease. Eight patients presented with C3 severity while six patients had C4 severity. There were three patients of C5 severity and two patients of C6 severity of disease (fig. 6). In Group A patients, SFJ was incompetent in 17 out of 30 patients. Majority of the patients (16 out of 30) had 3 or more than 3 incompetent perforators at the time of surgery.

In Group A patients, maximum diameter of GSV in thigh was noted to be 13.6 mm in C4 severity of varicose vein while minimum diameter was found to be 6.1 mm in C2 severity of varicose veins. But while calculating the mean diameter of GSV in each grade of severity, C6 severity patients had maximum mean diameter of 13 ± .9 mm and C2 and C3 severity of varicose veins had minimum mean diameter of 8.2 ± 2.6 mm and 8.2 ± 1.2 respectively.

In Group A patients, we found that with increase in the duration of disease there was increase in the diameter of GSV in thigh. Mean diameter of GSV was found to be maximum with maximum duration of disease i.e. 10.6 ± 2.5 mm at 19-24 months of duration while mean diameter was found to be minimum at 0-6 months of duration i.e.7.9 ± 2.2 mm. But this increase in diameter of GSV with duration of disease was found to be statistically insignificant (p value < 0.05).

In our study, while comparing the histological parameters of GSV wall in Group A versus Group B, it was found that, there was significant increase in the thickness of tunica intima and media in Group A as compared to Group B (p value .0001, .0026 respectively). The thickness of tunica intima in Group A was154.08 ± 17.68 µm as compared to 93.85± 8.26 µm in Group B and thickness of tunica media was found to be 528.25 ± 73.70 µm in Group A as compared to 378.33± 54.67 µm in Group B. It was found that there was significant increase in the color area percentage of collagen in tunica media in Group A as compared to Group B (p value .01). The color area percentage of collagen in tunica intima was found to be 0.17 ± .01 in Group A as compared to 0.15± .04 in Group B which was not found to be statistically significant (p value 0.321). While comparing the color area percentage of SMCs in tunica media, it was found to be 0.36 ± .01 in Group A as compared to 0.34± .02 in Group B which was found to be statistically significant (p value 0.026). There was significant decrease in the color area percentage of elastin at the junction of tunica intima and media in Group A as compared to Group B. It was found to be 0.01 ± .00 in Group A as compared to 0.03 ± .01 in Group B which was found to be statistically significant (p value 0.0025).

In our study, while comparing the histopathological parameters of GSV wall in patients with SFJ incompetence versus patients with competent SFJ, it was found that there was no significant difference in the thickness of tunica intima and media in the two groups (p value .58 and .86 respectively). The thickness of tunica intima in patients with SFJ incompetence was 156.08 ± 11.54 µm as compared to 151.06 ± 9.68 µm in patients with competent SFJ and thickness of tunica media was found to be 531.15 ± 53.70 µm in the patient with incompetent SFJ as compared to 526.25 ± 56.34 µm in patients with competent SFJ.

It was found that there was no significant difference in the color area percentage of collagen in tunica intima and media in the two groups of patients (p value 0.73 and 0.65 repectively). The color area percentage of collagen in tunica intima was found to be 0.17 ± .12 in patients with SFJ incompetence as compared to 0.17 ± .23 in patients with competent SFJ which was found to be statistically insignificant (p value 0.73). While comparing the color area percentage of collagen in tunica media, it was was found to be 0.22 ± .18 in Group A as compared to 0.22 ± .36 in Group B which was also found to be statistically insignificant (p value 0.65).

There was no significant difference in the color area percentage of elastin at the junction of tunica intima and media in two groups of patients. It was found to be 0.01 ± .007 in patients with SFJ incompetence as compared to 0.01 ± .09 in patients with competent SFJ which was found to be statistically insignificant (p value 0.61).

In Group A patients, thickness of tunica intima was found to be maximum i.e. 213µm at C6 severity of disease while it was minimum i.e. 136 µm at C2 severity of disease. While calculating the mean tunica intima thickness in each group it was found that with increase in the severity of disease, the thickness of tunica intima also increases. It was found to be 140.96 ± 2.3 µm at C2 severity, 151.63 ± 5.2 µm at C3, 154.35 ± 3.5 µm at C4, 173.23 ± 7.8 µm at C5 and at C6 it was found to be 206.55 ± 9.1 µm.

In Group A patients, thickness of tunica media was found to be maximum i.e. 684 µm at C6 severity of disease while it was minimum i.e. 440.1 µm at C2 severity of disease. While calculating the mean tunica media thickness in each group it

was found that with increase in the severity of the disease, the thickness of tunica media also increases. It was found to be 466.29 ± 18.06 μm at C2 severity, 513.36 ± 29.67 μm at C3, 545.85 ± 26.63 μm at C4, 657.4 ± 25.47 μm at C5 and at C6 it was found to be 682.1 ± 2.68 μm.

In Group A patients color area % age of collagen in tunica intima was found to be maximum i.e. 0.19 at C6 severity of disease while it was minimum i.e. 0.16 at C2 severity of disease. While calculating the mean color area % age of collagen in tunica intima in each group it was found that with increase in the severity of the disease, the color area % age of collagen in tunica intima also increases. It was found to be 0.168 ± .004 at C2 severity, 0.176± .005 at C3 severity, 0.181 ± .004 at C4 and 0.190 ± .002 at both C5 and C6 severity of disease.

In Group A patients color area % age of collagen in tunica media was found to be maximum i.e. 0.29 at C6 severity of disease while it was minimum i.e. 0.18 at C2 severity of disease. While calculating the mean color area % age of collagen in tunica media in each group it was found that with increase in the severity of the disease, the color area % age of collagen in tunica media also increases. It was found to be 0.192 ± .006 at C2 severity, 0.213 ± .005 at C3 severity, 0.266 ± .005 at C4, 0.283 ± .005 at C5 and it was found to be .290 ±.000 at C6 severity of varicose veins.

In Group A patients color area % age of SMCs in tunica media was found to be maximum i.e. 0.39 at C6 severity of disease while it was minimum i.e. 0.35 at C2 severity of disease. While calculating the mean color area % age of SMCs in tunica media in each group it was found that with increase in the severity of the disease, the color area % age of SMCs in tunica media also increases. It was found to be 0.355 ± .005 at C2 severity, 0.367 ± .004 at C3 severity, 0.381 ± .004 at C4, 0.385 ± .005 at C5 and it was found to be 0.390 ± .000 at C6 severity of varicose veins.

In Group A patients color area % age of elastin at junction of tunica media and intima was found to be maximum i.e. 0.03 at C2 severity of disease while it was minimum i.e. 0.01 at C6 severity of disease. While calculating the mean color area % age of elastin at junction of tunica media and intima in each group it was found that with increase in the severity of the disease, the color area % age of elastin at junction of tunica media and intima decreases. It was found to be 0. 03 ± .00 at C2 as well as C3 severity, 0.02 ± .000 at C4 severity and 0.01 ± .000 at C5 and C6 severity of disease.

In Group A patients it was found that with increase in duration of disease the thickness of tunica intima also increases. The mean value of tunica intima thickness was found to be 146 ± 6.5 μm at 0-6 months of duration, 144.2 ± 6.1 μm at 7-12 months of duration while at 13-18 months and 19-24 months it was found to be 157.3 ± 23.6 and 158.1 ± 16.2 μm respectively.

It was also found that with increase in duration of disease the thickness of tunica media also increases. The mean value of tunica media thickness was found to be 493.9 ± 4.0 μm at 0-6 months of duration, 478.4 ± 35.7 μm at 7-12 months of duration while at 13-18 months and 19-24 months it was found to be 530 ± 83.9 and 564.7 ± 72.1 μm respectively. But on the analyzing data, it was found that this increase in the thickness of tunica intima and media with duration of disease were found to be statistically insignificant (p value <0.05).

In Group A patients it was found that with increase in duration of disease the color area % age of collagen in tunica intima and media also increases. The mean value of color area % age of collagen in tunica intima was found to be 0.175 ± .007 at 0-6 months of duration, 0.171 ± .006 at 7-12 months of duration while at 13-18 months and 19-24 months it was found to be 0.176 ± .008 and 0.181 ± .009 respectively. The mean value of color area % age of collagen in tunica media was found to be 0.200 ± .014 at 0-6 months, 0.202 ± .011 at 7-12 months of duration while at 13-18 months and 19-24 months it was found to be 0.225 ± .041 and 0.228 ± .034 respectively. It was found that with increase in duration of disease the color area % age of SMCs in tunica media also increases. The mean value of color area % age of SMCs in tunica media was found to be 0.365 ± .007 at 0-6 months, 0.361 ± .009 at 7-12 months of duration while at 13-18 months and 19-24 months it was found to be 0.377 ± .012 and 0.369 ± .013 respectively. Also, with increase in duration of disease the color area % age of elastin at junction of tunica media and intima decreases. The mean value of color area % age of elastin at junction of tunica media and intima was found to be 0.030 ± .000 at 0-6 months as well as 7-12 months of duration while at 13-18 months and 19-24 month it was found to be 0.025 ± .008 and 0.020 ± .007 respectively. On analyzing the data, it was found that all these changes in the histological parameters in GSV wall with duration of disease were found to be statistically insignificant (p value <0.05).

DISCUSSION

It is estimated that at least 10% of the world's population has varicose vein in the lower extremities.[7] Varicose veins can be classified as primary or secondary. Primary varicose veins result from intrinsic abnormalities of the venous wall, while secondary varicose veins are associated with deep and/or superficial venous insufficiency.

This venous dilatation may be due to weakness of the vein wall as a result of structural problems.[1-6] Vein wall distensibilty is controlled by SMCs, collagen and elastin. Smooth muscles in the tunica media are responsible for wall tone, which is influenced by autonomic nerves and circulating stimulants. Passive tone is provided by collagen and elastin. Loss of tone in varicose veins could be due to defect in the wall components.[5]

The clinical features of varicose veins include visible dilated tortuous veins, tiredness and aching sensation in calf at the end of the day, night cramps, ankle swelling, pigmentation, ulceration and eczema.

The basic aim of clinical evaluation is to localize the problem whether the deep system is involved or superficial system is involved, if superficial system is involved then the problem may be at saphenofemoral, saphenopopliteal or perforator level. The patients are clinically examined and specific tests are done like Trendelenberg's test, Perthe's test, Fegan's test, Pratt's test and Schwartz's test.[8] Duplex ultrasonography of venous system is a useful investigation in the work up of patients of varicose veins.[9]

Varicose veins are managed according to severity of disease either conservatively using elastic compression stockings or

injection sclerotherapy for mild form of disease or by surgical intervention for severe form of disease, Now a day, minimally invasive procedures like RFA (Radiofrequency ablation) and EVLA (Endovenous laser ablation) are found to be more popular for the management of varicose veins in comparison to the surgery.

We carried out this prospective study to evaluate the morphological and histopathological changes in great saphenous vein and its correlation with duration and severity of disease in varicose veins. In the study majority of patients were between 20-30 years of age. This age group was indulged in maximum long standing activities for earning for their families. The mean age in our study was 37.8 years. In literature, the age distribution of varicose veins in most of studies varied from 30-40 years.[10] But a few studies have reported a variable age of presentation.[11-21]

There was predominance of male patients with a ratio of 1.9:1 in the present study. Vashist *et al* and Baron *et al* have also reported male preponderance.[18,22] However, in the recent Edinburg Vein Study prevalence was found to be nearly equal in both the sexes.[23] Left side was more involved (63.3%) than right side (36.6%). In the series of Killewich *et al* left side was involved in 47%, right side in 31% and 22% had bilateral varicose veins.[24]

Most common complaint was dilated and tortuous vein (100%) followed by pain in leg (83.3%), edema (63.3%), pigmentation (36.6%), healed ulcer (10%) and active ulcer (6.6%). Hamilton in his trial of 516 patients reported dilated veins in 79%, pain in 50%, edema in 42% and ulcers in 2.5% of cases.[25] Vashist *et al* in their study found dilated veins in 90%, pain in 78%, swelling in 60% ulcer and pigmentation in 26% of patients.[22] Most of the patients (70%) presented with symptoms for more than one year duration. Vashist *et al* in their study had majority of patients (82%) with symptoms of less than 3 years of duration.[22]

Majority of the patients (11 out of 30) had C2 severity according to CEAP scoring. Disease severity varied from C2-C6 in the present study. In a study by De Messener *et al*, 80% of the patients had disease of C1-C3 severity.[26] Incidence reported by Allegra *et al* in their study involving 1326 limbs was 68.5% for C1-C3 severity of varicose veins.[17]

There was significant increase in diameter of GSV in thigh with increase in severity of disease (CEAP scoring) (p value <0.05). In a study by Madez-Herrero *et al* on 145 lower limbs it was concluded that diameter of GSV was more in more severe form of disease. Navarro *et al* carried out their study over 85 patients and found that GSV diameter is a relatively accurate predictor for assessing severity of disease.[27] In the present study, while comparing duration of disease with diameter of great saphenous vein there was increase in diameter of great saphenous vein with duration of disease. But it was found to be statistically insignificant (p value 0.214). No study could be found in the literature to correlate diameter of GSV with duration of symptoms in varicose veins.

There was significant increase in the tunica intima and media thickness in GSV wall in varicose veins group when compared with control group (p values 0.0001, 0.0026). This increase in the thickness could be due to increase in the connective tissue component and due to migration of SMCs from tunica media to intima. There was significant increase in the color area percentage of collagen and smooth muscle cells in tunica media in GSV wall in varicose veins group when compared with control group (p values 0.01, 0.026). This increase in the level of collagen causes separation of SMCs in the tunica media. Thus these SMCs were not able to act properly to maintain the venous tone. Although there was increase in muscle thickness in the varicose veins, still there was loss of venous tone. This dysfunction was basically due loss of regular arrangement of SMCs in tunica media. There was significant decrease in the color area percentage of elastin in GSV wall in varicose veins group when compared with control group (p value 0.0025). This decrease in the level of elastin results in increase in the stiffness in the vein wall. Such types of veins were not able to bear any change in venous pressure and leads to varicose veins. There were conflicting results in the literature about the changes in great saphenous vein wall in patients with varicose veins and a few of them are tabulated in Table-1.

Table 1

References	Year of study	Tunica intima thickness in GSV wall	Tunica media thickness in GSV wall	Collagen content in GSV wall	SMCs in GSV wall	Elastin in GSV wall
Andreoti *et al*[28]	1978	-	-	Decrease	-	Decrease
Travers *et al*[5]	1996	-	Increase	Increase	Increase	No change
Krisch *et al*[29]	2000	-	-	Increase	-	Decrease
Bujan *et al*[30]	2000	Increase	Increase	Increase	Apoptosis	-
Khan *et al*[31]	2001	Increase	Increase	Increase	Increase	-
Wali *et al*[32]	2003	Increase	Decrease	Increase	Decrease	Decrease
Elsharawy *et al*[33]	2005	Increase	Increase	Increase	Increase	Decrease
Janoski *et al*[30]	2007	Increase	Increase	Increase	Increase	Decrease
Present study	2012	Increase	Increase	Increase	Increase	Decrease

There was no significant difference in the histopathology of GSV wall in patients with SFJ competence and SFJ incompetence in varicose veins group (p value >0.05). It means these changes in the vein wall are independent of the status of saphenofemoral junction. This means the saphenofemoral incompetence may be secondary to the changes in the vessel wall. Golledge *et al* in 2003 compiled data from many studies and concluded that the structural changes in the vessel wall were responsible for the secondary valvular incompetence. These stuctural changes include weakness in the vein wall, loss of venous tone and deranged endothelial activity.[34] They also found that these changes in the wall of GSV had no correlation with status of SFJ. Elsharawy *et al* in 2005 in their study also found that there was no difference in the histopathology of GSV wall in patients with or without SFJ incompetence.[33] They also concluded that these changes in the GSV wall are the primary changes already present in the vein wall and not secondary to venous hypertension.

There was significant increase in the thickness of tunica intima and media of GSV with increase in the severity of disease (p value <0.05). Many of the studies in the literature also support the same results. Khan *et al* in the year 2001 found that there was intimal hypertrophy in almost all the sections of great saphenous vein in the specimens taken from patients with varicose veins.[31] Wali *et al* in the year 2003 also found marked intimal hypertrophy due to connective tissue infiltration in the tunica intima layer of GSV as in the present study.[32] Mironiuc *et al* in their study found intimal hypertrophy in C2 and C3 while intimal fibrosis in the late stages of disease i.e. C4-C6.[35] Travers *et al* in 1996 found out in their study that thickness of tunica media significantly increased in all the specimens from varicose vein patients.[5] Elsharawy *et al* in 2005 came with the

same results as in the present study. [33]

There was significant increase in the level of collagen in tunica intima and media with increase in severity of disease (p value <0.05). Also, there was significant increase in smooth muscle cells in tunica media with increase in the severity of disease i.e. from C2 to C6 (p value <0.05). Elsharawy *et al* and Janowski *et al* in their study also found an increase in the number of collagen fibers and smooth muscle cells with increase in the severity of disease.[33,36]. There was significant decrease in the level of elastin at the junction of tunica media and intima with increase in the severity of disease i.e. from C2 to C6 (p value <0.05). Wali *et al*[32], Elsharawy et at and Janoski *et al* demonstrated that elastic fibers were significantly decreased in internal elastic lamina of varicose veins when compared to normal.[33,36]

There were insignificant changes in the histopathology of GSV wall with increase in duration of disease (p value >0.05). We found that changes in the great saphenous vein progress with increase in severity of disease but does not progress with duration of disease. This shows that these changes in the great saphenous vein wall are not secondary to the venous hypertension but these are actually the precursor of varicose veins which were already present in the vein wall that leads to varicose veins in such an individual. We could not find any study in the literature to correlate histopathological changes in GSV wall with duration of symptoms in varicose veins.

In the present study, we concluded that GSV wall plays a significant role in pathogenesis of primary varicose veins. The main histopathological changes observed in the present study were increase in tunica intima and media thickness, increase in the amount of collagen in tunica media and decrease in the amount of elastin at internal elastic lamina. These changes were more pronounced in higher grade of disease. These changes in the GSV wall may be the precursor for varicose veins which may have been already present in veins of these individuals and later on resulted in the varicose veins. It was also concluded that these changes in the GSV wall could result in the secondary SFJ incompetence in these patients.

Our study design should however, be applied to a larger group of patients to further evaluate the validity of our results. This can contribute to the quest for surgical excellence and better patient care for one of the most commonly performed surgical procedures in the world.

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