CHAPTER- 2
REVIEW

Varicose veins are abnormally swollen (dilated) and tortuous (twisted) veins and usually situated quite near the surface and visible beneath the skin. For many years, veins have been thought to function only as passageways for blood to flow back into the heart but in recent years it has been understood that the venous system perform many functions that are vital to the whole circulatory network; such as their capability of constricting and dilating, storing large volumes of blood for use in other areas of the circulation, and even to regulate cardiac output. The alteration of venous blood flow can result in a number of conditions including: Chronic venous insufficiency (CVI), varicose veins, venous thrombosis, pulmonary embolism (a complication of deep vein thrombosis (DVT)), hemorrhoids, lower limb edema and venous ulcers. Venous insufficiency has a complex pathology, having a dramatic impact on the quality of life of the patient (Vanhoutte et al, 1997). Varicose veins of the leg encompass the most frequent physical signs of chronic venous insufficiency and is one of the most prevalent conditions in the general population (Weksberg 1993, Baccaglini et al. 1996, Grange et al. 1998, Dunn et al. 1999, London 2000, Marting 2000, Bergan et al. 2002, Charlesworth 2003 and Merck 2003). In recent decades, there have been several epidemiologic studies of chronic venous disease, the majority focusing on the most common manifestation of varicose veins (Evans et al. 1999, Heit et al. 2001, Ruckley et al. 2002 and Meissner et al. 2007). The etiology of varicose veins is still incompletely understood despite the fact that it is a very common disease affecting all ages from teenagers to elderly people.

2.1. HISTORICAL ASPECTS:

The first written reference of varicose veins appears to be the—Ebers Papyrus” dated 1550 B.C. Varicose veins are illustrated on a votive table from Askepieion in Athens and the first patient who underwent operation for his varicose vein appears to be Canus Marius, the Roman tyrant. “Hippocrates” (460-377 B.C.): described the use of compressive bandages and was advisor of small punctures in varicose veins, which should not be opened freely because of possibility of ulceration.

The history of varicose veins and leg ulcers when traced has noted the influence of various theories, which are:

1. The Humoral Theory

Galens theory of humour's taken from Hippocrates, together with the idea of to and fro movements of blood with its various spirits dominated medical thought for fifteen centuries. Varices was attributed to weight of stagnant gross blood on the walls of veins. “Haly Abbas”: believed they were filled with black bile and occurred in those who worked hard and stood long. France and Heister (1768) considered ulcer to be a drain for humour's which if not expelled, would cause serious illness. “Ambriose Pare and Ettmuller”: believed that menstrual blood is 'gross' and collects in the leg during pregnancy causing varicose veins and ulcers.

2. The Mechanical Theory

Humoral theory received a blow when Harvey discovered the circulation of the blood and found out vessels contain valves. He came to two conclusions, the blood movement is not possible to and fro, and blood was pumped throughout the body by heart. “Wiseman 1678” realized the valvular incompetence results from dilation of vein and considered ulcers might be the direct result of a circulation defect and used the term „venous ulcer. “Whites and Dionis”: attributed the varicose veins in pregnant women to the pressure of the uterus on the iliac vein. In 1930, “Linton” emphasized the pathological contribution of incompetent perforating veins to venous insufficiency.
2.2 EVOLUTION OF CONCEPT AND RECENT EVIDENCES

Trendelenburg’s proposal implicating valvular incompetence as the etiology for varicose veins received wide acceptance in the late 1800s (Trendelenburg 1891). Although an eponymous test may be used to assess the phenomenon of vascular incompetency, this has largely been superseded by Doppler imaging. Further theories proposed that varicose veins were caused by a combination of valvular incompetence and venous hypertension, propagating in a descending fashion from segments of valvular reflux at the saphenofemoral or saphenopopliteal junction (Meissner et al. 2007). However, these theories cannot explain why varicosities are found below competent valves, why normal valves are often seen between segments exhibiting varices, or why dilation often precedes valvular incompetence (Cotton 1961, Alexander 1972 and Meissner et al. 2007). Studies of surgical specimens and sonographic evaluations of affected patients suggest that primary valvular incompetence is actually a multicentric process that develops simultaneously in discontinuous venous segments (Labropoulous et al. 1997). Evidence of a uniform valvular abnormality, which causes primary venous disease, remains elusive. Recently, emphasis has shifted to intrinsic and structural abnormalities of the vein wall, with the hypothesis that varicose veins develop because of a combination of altered venous tone and underlying connective tissue defects (Leu et al. 1979, Clarke et al. 1992 and Meissner et al. 2007). This hypothesis is consistent with recent studies suggesting that impaired regulation of ECM degradation and deposition may be involved in the development of varicosities (Travers et al. 1996, Venturi et al. 1996, Kockx et al. 1998, Sansilvestri et al. 1998, Baider et al. 2000, Gillespie et al. 2002 and Woodside et al. 2003). Several constituents of the ECM, such as collagens and elastins, are modified in the varicose state, as evidenced by a decrease in the elastin/collagen ratio (Venturi et al. 1996 and Woodside et al. 2003). Effective contraction may be further compromised by fragmentation of the muscle layers (Gandhi et al. 1993, Travers et al. 1996 and Eklof et al. 2004). Also, activated leukocytes have been observed in varicose veins, resulting in free radical release, protease activation, and consequent ECM degradation (Michiels et al. 1997 and Woodside et al. 2003). In summary, altered connective tissue proteins and increased proteolytic enzyme activity appear to be central to the pathophysiology of varicose veins. Moreover, genetic traits of the
individual with resultant or independent biochemical changes that may arise from predisposing risk factors are likely equally important in the development of varicose veins. Abnormalities in vein wall architecture probably precede the development of valvular incompetence and overt varicosities. Similar pathologic changes are present in limbs at risk for developing varices as well as in the forearm veins of patients with lower-extremity varices (Clarke et al. 1992, Vanhoutte et al. 1997 and Meissner et al. 2007). Together, these findings point strongly to the role of reduced contractility, genetics and compliance in the development of varicose veins.

2.3. DEFINITION

The term varicose is derived from the Latin word meaning —dilated”. One of the most used definitions has been according to Arnoldi (1957) “any dilated, elongated, or tortuous veins, irrespective of size” and the other from the Basle study, where varicosities were classified into three types (spiderwebs, reticular varices or trunk varices) and each of these into three grades of severity (da Silva et al. 1974). WHO defined varicose veins as “Vein with a saccular dilatation which is often tortuous.” The term varicosity is generally applied to elongated, tortuous, pouches, thickened, inelastic and friable vessels which have permanently lost its valvular efficiency.

The term, varicose veins commonly refers to the veins in the leg, although these can occur in any other part of body. These are most common in the superficial veins of the legs, which are subject to high pressure when standing. These veins cause swelling of the lower limb or legs because of incompetent valves as a consequence of structural failure, which cause vein wall dilation and deep vein damage (Thulesius 1996). Consequently venous reflux (retrograde flow) occurs during limb dependency, leading to sustained periods of distal high venous pressure which is not regulated even by exercise (Recek et al. 2004). Valvular failure and elevated venous pressure can cause varicose veins. Besides cosmetic problems, varicose veins are often painful, especially when standing or walking. Varicose veins are the bulging veins that are larger than spider veins, typically 3mm or more in diameter (Eklof et al. 2004). Less commonly, but not exceptionally, varicose veins can occur due to other causes, as incompetence and arteriovenous malformations (Claude 1996).
2.4. CLASSIFICATION OF VARICOSE VEINS

The terminology used to define and classify varicose veins in subjects is not consistent. Specifically, the comparison with earlier studies is challenging due to the lack of precision in diagnosis before the CEAP classification. Several overlapping clinical manifestations of the same disease process have been defined as “varicose veins”. This lack of a uniform classification system for chronic venous disorders was until the 1980s when the first proposed reporting standards for publications dealing with venous disease were published. Based on that report, the American Venous Forum developed a more detailed descriptive classification system, CEAP, for chronic venous disorders in 1994 (Eklöf et al. 2004). It was based on Clinical manifestations (C), Etiological factors (E), Anatomic distribution of disease (A), and underlying Pathophysiological findings (P) (Porter and Moneta 1995). In 2004 a revised version of the basic CEAP classification (Table-1) and advanced CEAP classification was published (Eklöf et al. 2004).

Table 1. The basic CEAP classification system.

| Clinical signs* | Class 0- No visible or palpable signs of venous disease |
| Class 1- Teleangiecetasies or reticular veins |
| Class 2- Varicose veins (> 3mm in diameter) |
| Class 3- Edema |
| Class 4a- Pigmentation or eczema |
| Class 4b- Lipodermatosisclerosis (Inflammation of the layer of fat under the skin of epidermis) |
| Class 5- Healed venous ulcer |
| Class 6- Active venous ulcer |

| Etiologic factors | Congenital, primary, secondary or no venous cause identified |
| Anatomic distribution | Superficial, perforator, deep veins or no venous location identified |
| Pathophysiologic findings | Reflux or obstruction, alone or in combination or no venous pathophysiology identifiable |

In India Mirji et al. studied that Majority of patients were, patients of CEAP class 2 and 3 which included patients presenting with only varicose veins and patients with limb edema (Mirji et al. 2011) (Table- 2).
Table 2: Clinical Class of CEAP*

<table>
<thead>
<tr>
<th>Class</th>
<th>Limb</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>40.00</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>28.57</td>
</tr>
<tr>
<td>4</td>
<td>04</td>
<td>11.43</td>
</tr>
<tr>
<td>5</td>
<td>01</td>
<td>2.86</td>
</tr>
<tr>
<td>6</td>
<td>06</td>
<td>17</td>
</tr>
</tbody>
</table>

*Mirji et al. 2011*

Before the CEAP consensus statement, the definition of varicose veins in different studies was diverse, making it difficult to compare the results of epidemiologic studies.

2.5. PATHOPHYSIOLOGY OF VARICOSE VEINS

Understanding varicose veins means understanding the complex system of veins that make up our legs. Our legs are comprised of a network of veins that are similar to branches on a tree. They contain large or major veins and increasingly smaller veins. The veins of the leg are divided into superficial and deep vein system. The superficial and deep veins of the lower legs communicate through perforating veins. The direction of flow is normally from the superficial to the deep system aided by the function of the calf muscle pump. From the venules to the pelvic veins, the veins contain valves that can resist gravitational and muscles pressure and direct the blood flow towards the heart. Besides serving as conduit for the blood, the veins also have storage function and are the part of the regulatory system of the body temperature. The venous system has a large surface with variety of function such as release of substances involved in blood coagulation. The diameter of vein varies with total blood volume, temperature and body posture (Jogestrand et al. 2002 and Norgren et al. 2004). Thus even in completely normal vein, the volume of blood in the vein of leg can vary considerably, which marks the contribution of increased volume from diseased vein difficult to predict. In circulatory system oxygenated blood is constantly
being pumped from the heart to the rest of our bodies through arteries. *It is the job of our veins to carry deoxygenated blood back to the heart.* Healthy veins valves open and close to assist the return of blood to the heart. Venous disease (also called vein insufficiency or venous reflux), occurs if these valves become damaged, allowing the backward flow of blood in the legs. Because gravity works on the legs more than on other parts of the body, these vein walls are under tremendous pressure. When blood cannot be properly returned through the vein, it can pool, leading to a feeling of heaviness and fatigue, causing varicose veins and other skin changes (Figure-1). Over time, this increased pressure can cause additional valves to fail. If left untreated, it can lead to leg pain, swelling, ulcers, and other health problems.

One of the prevailing theories of the pathogenesis of CVI proposes that varicose veins develop because of failure or incompetence of the valves that leads to reflux of blood from the deep to the superficial system resulting in venous hypertension, and dilation of the involved veins. However, this theory does not explain all of the changes that occur in the venous system with patients that have varicose veins (London et al. 2000). Varicose veins or varicosities of the saphenous vein or its tributaries may develop before or without valvular incompetence. The effect of increased hydrostatic pressure is also uncertain since larger varicosities affecting the lower extremity are not usually distributed in the most dependent segments where hydrostatic pressure would be expected to be at the highest. In addition, if valvular dilation were the initial event one would expect dilation proximal to a valve site and not distally as is often the case (Proto 1995). These observations suggest that varicose veins may be the result of intrinsic changes within the venous wall.

The primary structural changes in the valves may start the pathophysiological process of varicose veins through progressive reflux to the secondary changes in the vein wall (Raffetto and Khalil 2008) or alternatively. In the same time, the valves may become incompetent secondary to vein wall abnormality near the valve junctions predisposing to venous dilation, and causing the reflux (Cooper et al. 2003, Elsharawy et al. 2007, Raffetto and Khalil 2008).
Fig: 1-Formation of Varicose Veins.

A) Normal vein with a working valve and normal blood flow.
B) Varicose vein with a deformed valve, abnormal blood flow, and thin, stretched walls.
C) Sites where varicose veins might appear in a leg.
2.6. SIGN AND SYMPTOMS

Aching, heavy legs (often worse at night and after exercise), appearance of spider veins in the affected leg, ankle swelling, a brownish-blue shiny skin discoloration near the affected veins are generally found in varicose patients. Redness, dryness, and itchiness of areas of skin, termed stasis dermatitis or venous eczema, because of waste products building up in the leg also occur in patients. Cramps may develop especially when making a sudden move as standing up. Minor injuries to the area may bleed more than normal and/or take a long time to heal. In some people the skin above the ankle may shrink because the fat underneath the skin becomes hard. Restless legs syndrome appears to be a common overlapping clinical syndrome in patients with varicose veins and other chronic venous insufficiency. Whitened, irregular scar-like patches can appear at the ankles.

In Japan prevalence and risk factors of varicose veins, were investigated on 541 patients. The total prevalence was 45%, saphenous types was observed in 22%, segment type in 22%, reticular type in 28% and web type in 16% cases (Herai et al. 1990).

A cross sectional population study which was conducted in Edinburgh to examine the relation between age, sex, lower limb symptoms, the presence and severity of varicose veins. The results showed that women were significantly more likely to report lower limb symptoms such as heaviness or tension (54.7%), swelling (24.6%), aching (63.1%), restless legs (49.6%), cramps (45.5%), and itching (38%) (Bradury et al. 1999).

In a study in Bahawalpur, Pakistan, 80% of varicose veins patients found with dilated veins (Malik et al. 2004). In his trial of 516 patients, Jakobsen reported dilated veins in 79%, pain in 50%, oedema in 42% and ulcer in 2.5% of cases (Jakobsen et al. 1979). Munn gave a very brief description of preoperative features of 57 patients involved in his trial; where ulceration was found in 8% and pigmentation in 22% of cases (Munn et al. 1983). In a group of 350 patients who underwent varicose vein surgery at the Mayo clinic, Lofgren reported pain in leg in 71%, swelling in 60%, dilated veins in 25%, pigmentation in 16% and ulcer in 8% of cases (Lofgren et al.
1985). In a study of 114 patients, Frank found swelling in 21% and pain in 45% of patients (Frank et al. 1992) and in a trial of 156 limbs, Kam et al. found dilated veins in 98%, pain in 56%, swelling in 12% and ulcer in 17% of patients (Kam et al. 2003).

An Indian study revealed that 77% of the 138 teachers suffered from varicosity or enlargement of the veins of legs. Among these nearly 84 people suffered from spider webs, the first stage of varicose veins. While 23 had severely established varicose veins which means they suffered from severe aches, swelling and heaviness in the legs. This study concluded that varicose veins is a condition that makes walking and standing extremely difficult and painful and if treated early at the stage of spider veins they are preventable (Sharma et al. 2010). Dilated veins, pain (night cramps), edema and ulcer were also reported in two recent Indian studies (Vashist et al. 2010 and Mirji et al. 2011) and found that dilated vein was highly affected (90%) in varicose veins whereas in Mirji et al. found low frequency of dilated veins i.e. 12.5%.

From all previous studies it is evident that cosmetic purpose is not a factor which prompts the people to seek treatment for varicose veins as do those in the west (Callam 1994). In all studies, dilated and prominent veins were the commonest presenting symptom while other symptoms were present in variable percentage in different studies depending on the stage of disease

2.7. COMPLICATIONS ASSOCIATED WITH VARICOSE VEINS

Although often perceived as a cosmetic problem, most cases of venous varicosis are accompanied by varying levels of discomfort, which may be described as heaviness, bleeding, femoral vein injury and untreated varicose veins tend to worsen over time and can lead to hemorrhage (in rare cases, fatal hemorrhage), thrombophlebitis, deep vein thrombosis and venous ulcers (Pulliam et al. 1991, Sarin et al. 1993, Chengelis et al. 1996, London et al. 2000, Nicholls 2005 and Byrad et al. 2007). Approximately 500,000 patients in the United States have venous ulcers (Rhodes et al. 1998), and physical impairment seen with venous ulcers is comparable with that of congestive heart disease and chronic lung disease (Carradice et al. 2011). In addition to causing great individual distress, ulcers have serious economic and psychological effects and are a considerable drain on medical resources. In United
States alone, the population-based costs for treatment of problems arising from chronic venous insufficiency or varicose veins have been estimated at $3 billion per year, and venous stasis ulcers are estimated to be responsible for the annual loss of more than 2 million work days (Hume 1992(2), Patel et al. 2006 and Meissner et al. 2007).

Bleeding as a complication from large varicosities typically follows local trauma; however, bleeding may occasionally occur spontaneously. Elderly patients with thin-walled veins are at increased risk. Patients may be unaware of the venous rupture and first notice the problem when they feel blood running down the leg or even after feeling faint. The bleeding may be profuse and even life threatening (Harman 1974). Application of tourniquets that are not tight enough to occlude arterial inflow but enhance venous congestion may increase rather than reduce the rate of hemorrhage.

Deep vein thrombosis (DVT) is a serious complication of varicose veins. Superficial thrombosis or varicose vein is frequently associated with DVT which may be clinically silent (Bergqvist et al. 1986, Skillman et al. 1990 and Jorgenson et al. 1993). Three recent series in which ultra sonography used for diagnosis showed 20% to 40% prevalence of DVT with superficial vein disease (Lutter et al. 991, Jorgenson et al. 1993 and Ascer et al. 1995).

Recurrence of varicose veins is also a serious condition affecting varicose patients even after varicose surgery or after surgical removal of varicose veins (Andre et al. 2003). Andre et al. found recurrence of varicose occurred at sites where surgery had been clearly demonstrated as complete (Andre et al. 2003). Other previous studies were found that there is 20% chance of recurrence at 5 years and 60% by 10 years (Winterborn et al. 2004 and 2008 and Perkins 2009). So, despite successful surgical removal of the sites of reflux varicose veins recur again. This is contributed to by the underlying degenerative process of varicose veins, the disturbed venous physiology, lifestyle and genetic mutation, which at present are beyond control of the surgeon. All patients presenting with a complaint of varicose veins require detailed and thoughtful evaluation, thorough diagnostic evaluation, and carefully considered intervention when appropriate. Many may require sustained long-term follow-up.
2.8. PREVALENCE OF VARICOSE VEINS

The prevalence of varicose veins in general population increases in those over 35 years of age, ranging from 30% with minor varicosities to 6% with severe symptoms (Evans et. al. 1999). The most striking about the epidemiology of varicose veins is the geographical variation in prevalence rate. Western countries have high rate of prevalence as compared to traditional living countries (Burkitt 1972). Current statistics reveal that nearly 2.7 million people worldwide, suffer from varicosities and the number is ever increasing. Where India is concerned, experts are witnessing a growing prevalence of varicosities especially among women. Nearly, 20-15 per cent of women and 10-15 per cent of men suffer from varicose veins in India (Express Health Care Jan 2011).

According to different studies the prevalence of varicose veins ranges from 2% to 57% in men and from <1% to 73% in women (Beaglehole 1986, Callam 1994, Evans et al. 1994, Beebe-Dimmer et al. 2005 and Robertson et al. 2008). Beside age other related factors are weight and height, pregnancy, menopause, dietary factors, and occupation.

Geographic variation in the occurrence of varicose veins may be due to differences in population sampling (especially age, gender and racial mix), in varicose vein definition and diagnosis. It can also be explained by a real effect of differences in lifestyle and genetic factors. Geographic variation is usually construed as a strong indicator for the presence of environmentally induced variation (Khoury et al. 1993). However, geographic variation is consistent with genetic contribution as well (Khoury et al. 1993).

2.9. RISK FACTORS

2.9.1. Age

Indian railroad workers (Malhotra 1972) and Japanese women (Hirai et al. 1990). An Italian study among elderly people (their age ranging from 66 to 96 years) reported a similar prevalence throughout age classes (Canonico et al. 1998). In the Framingham Study age had no obvious effect on the incidence of varicose veins (Brand et al. 1988). In the Tampere Varicose Vein Study the highest incidence was in the cohort of 50-year-olds compared to the cohorts of 40 and 60-year-olds, but the difference was statistically significant only in women (Mäkivaara et al. 2004). However, a Turkish study on persons aged 60 or over found the prevalence of varicose veins to increase with age in men, but not in women; the prevalence was higher in the group of 70 to 79-year-olds compared to the group of 80+ year-old women (Komsuoglu et al. 1994). In an Indian study the age distribution was found majority of patients are between the age of 20 to 40 years (Mirji et al. 2011).

The prevalence of varicose veins increases with age in previous studies was because only a few are treated (Ahti 2010). Varicose veins are not lethal and appear throughout the adult life, therefore it is expected that the prevalence of varicose veins increases with increase in age.

2.9.2. Gender

Women have greater risk of varicose veins, because the female sex hormone estrogen and progesterone cause blood vessels to relax, thus separating the valves. So that they don’t meet to block the back flow of blood and varicose occurs in women.

There were reports of higher prevalence of varicose veins in women than men (Weddell 1969, Coon et al. 1973, Abramson et al. 1981, Maffei et al. 1986, Franks et al. 1992, Laurikka et al. 1993, Sisto et al. 1995, Canonico et al. 1998, Criqui et al. 2003, Kroeger et al. 2004 and Bawakid et al. 2005), but in some of them the difference between genders was not statistically significant (Beaglehole et al. 1975, Komsuoglu et al. 1994 and Cesarone et al. 2002). The Framingham Study, found an annual incidence of varicose vein of 2.6% in women and 1.9% in men (Brand et al. 1988). In the well designed cross-sectional Edinburgh Vein Study that screened 1566 subjects for CVD involved 12 general practices and evaluated patients who were 18–64 years old, and found that women were more likely to report leg symptoms (Bradbury et al.
Also, by duplex ultrasound evaluation for reflux found CVD in 9.4% of men and 6.6% of women, which rose significantly with age (21.2% in men older than 50, and 12.0% in women older than 50) (Ruckley et al. 2002). In Finland the incidence rate was significantly higher in women in all cohorts studied (from 40 to 60-year-olds) (Mäkivaara et al. 2004).

A study of general population at four locations in France (n=8,000) found a prevalence of varicose veins 30% in men and 51% in women (Carpentier et al. 2004). In Poland, 28% of the men and 35% of the women had varicose veins in a study on 40,095 participants aged 16–97 (Jawien et al. 2003).

However in some studies prevalence of varicose veins was higher in men (Colin 1972, Stanhope 1975, Chiesa et al. 2005a and Chiesa et al. 2007). The same was found in the Bochum study examined German school children on three occasions during their period of education, and, by the age of 18 to 20 years, men were found to have a higher prevalence of trunk varices than women (Schultz et al. 1992). Higher male to female ratio was detected from studies of Widmer and Vaidyanathan reported almost equal male to female ratio. Report from Callam and Sakuari detected 1:2 and 1:3 respectively (Callam 1994). In one study done by Evans, reported that venous incompetence, measured by duplex scanning, was significantly more in men than in women (Evans et al. 1998). In a follow-up study, the age-adjusted prevalence of truncal varicose veins was 40% in men and 32% in women, and the prevalence of varicose veins and CVD increased with age (Evans et al. 1999). A cross sectional study was conducted on Health status of traffic police personnel in Brahmapurin in India. Out of total 48 traffic police personnel 43 (89.6%) were males and 5 (10.4%) were females. Majority (89.6%) were between 30-50 years (Satapathy et al. 2009). Another Indian study showed only 25% female patients (Mirji et al. 2011).

2.9.3. Weight, height and body mass index (BMI)

Higher risk of varicose veins in the overweight group compared to the control group in women was reported in literature (Seidell et al. 1986). In the Framingham Study the incidence of varicose veins was higher among women who were obese than those who were of normal weight (Brand et al. 1988). In the same study the incidence
was also higher for obese men, but the difference was not statistically significant. Many cross-sectional studies have shown an association between obesity and varicose veins for both sexes (Laurikka et al. 2002) or at least for women (Abramson et al. 1981, Sisto et al. 1995, Canonico et al. 1998 and Lee et al. 2003).

Height was also considered as an independent determinant for varicose veins in both sexes (Laurikka et al. 2002). Increased height showed a significant relationship with varicose veins in the Edinburgh Vein Study both in males and females (Lee et al. 2003). Whereas in Finnish study (Sisto et al. 1995) and in French study (Carpentier et al. 2004) height was found as significant in women only.

On the basis of everyday clinical practice clinicians are well aware of the fact that high BMI (Body Mass Index) has an indisputable relation to the development of VV and other symptoms of CVI, mainly the venous ulcer (Švestková and Pospíšilová 2008). However, the proofs are much clearer in women than in men. Body mass index >25kg/m2 is used as an indicator of overweight. The Framingham study described the risk of VV occurrence by 33 % higher in women with BMI above 27 (Brand et al. 1988). Two population studies (Canonico et al. 1998 and Kontosic et al. 2000), also found a significant positive association of BMI and risk of varicose veins in women only.

2.9.4. Female hormones and pregnancy

There are physiologic states, such as menopause and iatrogenic states, in which the level of female hormones in the circulation is far from normal and those states have been associated with varicose veins.

Pregnancy appears to be a major predisposing factor for the development of varicose veins and is likely a major reason why the prevalence of varicose veins is twice as high in women as in men (Bassi 1967, Nahoum et al. 1974, Widmar 1978, Basellini et al. 1985 and Guerrine et al. 1987). The development of new varicose veins occurs in up to 28% of pregnancies and the incidence rises with increasing parity (Stansby 2000). In the Tampere study, the prevalence of varicose veins in women with zero, one, two, three, and four or more pregnancies was 32%, 38%, 43%, 48%, and 59%, respectively (Laurikka et al. 2002).
Majority of earlier prevalence studies have found a risk between varicose veins and parity (Arnoldi 1957, Mekky et al. 1969, Weddell 1969, Maffei et al. 1986, Sadick 1992, Komsuoglu et al. 1994 and Jawien et al. 2003). Basellini et al. have observed a higher prevalence of varicose disease in patients who had undergone more than one pregnancy in comparison to nulliparae, in a 1:5 proportion, but have not observed a higher incidence with the increase in the number of pregnancies (Basellini et al. 1985). Maffei, in his study, indicates that there was a positive correlation between the prevalence of varicose veins and number of pregnancies, even with age adjustment (Maffei et al. 1986). Boivin & Hutinel have referred that the prevalence of varicose veins in men and women could be classified in two different orders: between men and nulliparae a proportion of 1:1.2 was found, whereas between men and multiparae, it is 1:4.6 (Boivin and Hutinel 1987). Some of the studies reported already one pregnancy to increase the risk for developing varicose veins (Stvrtinova et al. 1991, Canonico et al. 1998 and Carpentier et al. 2004), whereas in the other studies more than one delivery had a significant influence (Hirai et al. 1990 and Kroeger et al. 2004).

Early in pregnancy there is a significant increase in plasma volume (Bernstein et al. 2001) and blood flow (Fawer et al. 1978), also a significant dilatation of the veins of lower extremities either in women with normal (Cordts et al. 1996, Pemble 2007) or varicose veins (Sparey et al. 1999). However, the results of the above mentioned studies were inconsistent with respect to the reversibility of the pregnancy induced dilatation. A study in primipara women (n=39 gravida (the number of times the woman has been pregnant), n=69 nulliparous controls) found that the reversal of the dilation after delivery is not complete (Pemble 2007). This finding indicates permanent structural changes in the veins, which may deteriorate in subsequent pregnancies and explain the increased risk of developing varicose veins in multiparous women (Pemble 2007).

The effects of estrogen are generally mediated by specific receptors, which act as transcription factors, regulating gene expression when they are activated by estrogen binding. By that mechanism estrogen affects the proliferation of vascular smooth muscle cells and the facilitation of angiogenesis (Gungor et al. 2009). Another rapid, “non-genomic” pathway of estrogens has been reported. One of its effects is
endothelium-dependent vasodilatation in the arteries (Gilligan et al. 1994 and Gungor et al. 2009). Two subtypes of the human estrogen receptor have been identified (ERalpha and ER-beta) (Simoncini et al. 2004). Knaapen and associates (2005) reported that smooth muscle cell enlargement in varicose veins correlated with the expression of estrogen receptor-beta which facilitate in the occurrence of varicose veins.

Progesterone and progestins (the synthetic forms of progesterone) act by binding to progesterone receptors (Wei and Horwitz 1985). Both genomic and non-genomic effects have been demonstrated, however, the effects on the cardiovascular system are unclear (Gungor et al. 2009). Either estrogen or progesterone receptors have been found in peripheral veins (Bergqvist et al. 1993). Mashiah et al. (1999) reported more estrogen and progesterone receptors in varicose segments of saphenous vein compared to adjacent non-varicose segments of the same vein.

2.9.5. Occupation and physical activity

Significant associations were found with a standing posture at work and varicose veins in both sexes (Abramson et al. 1981, Tuchsen et al. 2000 and Kroeger et al. 2004). Work involving heavy lifting was also related to the higher prevalence of varicose veins in one study (Weddell 1969). A study conducted by Krijnen et al. on 387 male European workers showed that the number of years of working in standing position was associated with the severity of chronic venous insufficiency, indicating working in standing position is an aggravating factor of lower limb VV (Krijnen et al. 1997). However in a study done by Lateef, only 35% of patients had varicose veins due to prolonged standing (Lateef et al. 1995).

Working in a standing position was even associated with subsequent hospitalization due to varicose veins for both men and women according to a Danish study (Tuchsen et al. 2000). It was reported that mainly the seated position at work decrease the risk for trunk varices in women (Lee et al. 2003). In a study which was conducted on the effect of standing in the workplace and the development of varicose veins of the superficial venous system in the legs revealed that mechanical hydrostatic pressure generated by long periods of standing at the workplace is a major etiologic
factor in the development of varicose veins of the superficial venous system in the leg (Bass et al. 2007).

A cross sectional study was done to assess the prevalence of varicose veins, risk factors and the complications of varicose veins among school teachers. Samples of 100 teachers were taken in Thiruvananthapuram. The study showed the prevalence of varicose vein was 19% among the school teachers. Among those affected with varicose veins, 89.5% had history of standing for long duration. Ratio of 26.3% had complications from this disease. Thus conclusion was made that standing for long hours was a major risk factor as compared to other known risk factors (Jacob et al. 2008). Hence it is very much essential to prevent the occurrence of these risk factors.

According to literature 81% of the varicose veins patients had occupation history of prolonged standing, which suggests that occupation has a definite role as a causative or a contributing factor. It was also reported that varicose veins are more common among urban housewives, probably as a result of their habit of prolonged standing during work (Mirji et al. 2011) (Table- 3).

Table- 3 Occupation Distribution by Place of Work in India (Mirji et. al, 2011).

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Occupation</th>
<th>Patient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>House Wife</td>
<td>6</td>
<td>18.75</td>
</tr>
<tr>
<td>2</td>
<td>Coolie</td>
<td>7</td>
<td>21.87</td>
</tr>
<tr>
<td>3</td>
<td>Bus Conductor</td>
<td>1</td>
<td>3.12</td>
</tr>
<tr>
<td>4</td>
<td>Police Trainee</td>
<td>1</td>
<td>3.12</td>
</tr>
<tr>
<td>5</td>
<td>Farmer</td>
<td>8</td>
<td>25.0</td>
</tr>
<tr>
<td>6</td>
<td>Machine Tuner</td>
<td>1</td>
<td>3.12</td>
</tr>
<tr>
<td>7</td>
<td>Carpenter</td>
<td>2</td>
<td>6.25</td>
</tr>
<tr>
<td>8</td>
<td>Bakery Supplier</td>
<td>1</td>
<td>3.12</td>
</tr>
<tr>
<td>9</td>
<td>Hotel Cook</td>
<td>1</td>
<td>3.12</td>
</tr>
<tr>
<td>10</td>
<td>Hotel Vendor</td>
<td>1</td>
<td>3.12</td>
</tr>
<tr>
<td>11</td>
<td>School Teacher</td>
<td>2</td>
<td>6.25</td>
</tr>
<tr>
<td>12</td>
<td>Constructor Worker</td>
<td>1</td>
<td>3.12</td>
</tr>
</tbody>
</table>
2.9.6. Dietary factors, alcohol consumption and smoking

Diets deficient in fiber-rich plant foods and consequent constipation contributed dietary factor as risk factors for varicose veins (Cleave 1959, Dodd 1964 and Burkitt 1976). Such a refined diet results in larger, harder stools that are more difficult to pass leading to constipation and regular straining. In 1959, Cleave (Cleave 1959) suggested that constipation led to compression of the iliac veins and obstruction of venous return, while Burkitt (Burkitt 1976) later argued that it led to an increase in intra-abdominal pressure and dilatation of the leg veins. In support of constipation as a risk factor for varicose veins, a population study in western Sicily (Novo et al. 1988) found that subjects who were suffering from constipation had a higher prevalence of varicose veins (42.3%) compared to non-constipated subjects (35.2%). Whereas in the Edinburgh Vein Study there was no association between the prevalence of trunk varices contribution and dietary fiber intake in either sex (Lee et al. 2001, Lee et al. 2003 and Criqui et al. 2007).

In a case-control study conducted in France alcohol abuse indicated a higher risk of lower limb venous insufficiency, but when adjusted for other potential risk factors, the result was no longer statistically significant (Gourgou et al. 2002). In the Tampere study it was found that weekly alcohol consumption contributes to the incidence of varicose veins. The risk in those drinking alcohol weekly was 1.5-fold compared to non-drinkers (or those drinking alcohol occasionally) (Ahti 2010). It is known that alcohol consumption affects the vascular system (Bau et al. 2005, Bau et al. 2007) but in which way and on exactly which part is still uncertain. Studies on varicose veins did not suggest alcohol consumption to be a significant risk factor for varicose veins (Carpentier et al. 2004 and Scott et al. 2004).

A longitudinal follow-up survey on men in Boston reported current smokers to be more likely to develop varicose veins than non-smokers, RR 1.3 (95% CI: 1.01–1.6) (Scott et al. 2004). Similarly in the Framingham Study men with varicose veins had higher smoking rates than those without varicose veins, but the difference was not observed in women (Brand et al. 1988). In a cross-sectional study from France smoking men had more varicose veins than men who did not smoke (Ducimetiere et al. 1981). A case-control study (n=3,612) carried out in France reported lower limb
venous insufficiency to be significantly associated with tobacco smoking with dose effect relation in both genders. Whereas as in some of the studies no association between varicose veins and smoking (Malhotra 1972, Abramson et al. 1981, Hirai et al. 1990, Franks et al. 1992, Lee et al. 2003, Carpentier et al. 2004 and Komsuoglu et al. 2004).

A case-control study in France reported a dose-effect relation of tobacco smoking on lower limb venous insufficiency to be significantly associated with adjusted odds ratio from 1.4 (95% CI: 0.9–2.2) for 10-19 cigarettes/day to 2.1 (95% CI: 1.4–3.2) for >20 cigarettes/day in men and from odds ratio 1.8 (95% CI: 1.3–2.3) to 2.4 (95% CI: 1.7–3.4) in women, respectively (Gourgou et al. 2002).

There are two studies with unexpected results. In a German study of risk factors of varicose veins smoking indicated a protective effect on varicose veins in both genders (Kroeger et al. 2004), whereas in a Finnish study odds ratio <1 was observed only in women (Sisto et al. 1995).

In an Indian study, Tobacco chewing was the most common (48%) form of addiction, followed by alcohol in 20.8% of study subjects. It was observed that 38.3% of subjects were having varicose veins of legs (Satapathy et al. 1993).

2.9.7. Positive Family History

A number of environmental risk factors have been associated with the development of varicose veins, namely age, female sex, obesity, and possibly occupations requiring prolonged periods of standing (Sisto et al. 1995). However, primary varicose veins are also seen in young adults with no specific cause. Current evidence suggests a strong association of varicose veins with a positive family history. Although it is apparent that there are critical genetic components involved in the disease etiology.

There have been several reports of familial clustering in patients with varicose veins. In a large pedigree of 249 probands, Hauge and Gundersen (Hauge et al. 1969), in 1969, concluded that multifactorial inheritance is likely for varicose veins, and Matousek and Prerovsky (Matousek et al. 1974), in 1974, estimated the heritability to
be in the range of 50%. In 1997, patients with lymphedema were noted to have varicose veins with a prevalence as high as 25%. Subsequent evaluation of lymphedema–distichiasis syndrome, which is a condition that comprises intrinsic dysfunction of the lymphatic vessels and extra eyelashes, in 18 families with 74 affected individuals, revealed a prevalence of 49% of varicose veins, with the age of onset ranging from 7 to 28 years and male and female subjects equally affected (Brice et al. 2002). Positive family history is considered as one of the main risk factors for varicose veins (Komsuoglu et al. 1994, Lee et al. 2003, Carpentier et al. 2004 and Kroeger et al. 2004). Studies on genes support a genetic influence on venous function (Brinsuk et al. 2004) and on the etiology of varicose veins (Ng et al. 2005). However, positive family history does not automatically mean a genetic cause. The family usually shares the same environment and lifestyle. They may even have the same occupations and other ways of life exposing them to varicose veins, which could lead to another kind of family-linked cause.

Varicose vein show an autosomal dominant pattern of inheritance with reduced penetrance (Rosbothan et al. 2000). A genetic predisposition to varicose vein has been proposed for many years, and venous function in twins, measured by impedance plethysmography, indicates a strong genetic influence (Brinsuk et al. 2004).


Family history and early and preclinical stages of varicose veins were studied in the longitudinal Bochum Study. Pupils aged 10 to 12 years old at entry were examined at the age of 14 to 16 years and again at the age of 18 to 20 years. Only a weak association was reported between varicose veins and family history. Isolated refluxes were found at the saphenofemoral junction before visible varicose veins. (Schultz-Ehrenburg et al. 1992). A study of 134 families reported that the risk of developing varicose vein was 90% when both parents were affected, whereas the risk
was only 20% for individuals who have unaffected parents (Carnu Thenard et al. 1994). A Chinese analysis of nuclear families reported penetrance of between 70% and 92%, while 37% of their cases were sporadic (Guo 1998).

Edinburgh Vein Study reported an adjusted odds ratio of 1.5 in men and 2.2 in women (Lee et al. 2003) and conclude Individuals are more likely to be affected by varicose vein when parents and siblings have varicose vein. There were many other reports of higher estimates of the risk (Gourgou et al. 2002, Carpentier et al. 2004 and Kroeger et al. 2004).

A Finnish longitudinal study showed a 1.6-fold increased risk of developing varicose veins in those with a family history of varicosities (Ahti et al. 2009). Fiebig et al. examined heritability of CVD and concluded that the additive genetic component was approximately 17% (Fiebig et al. 2010).

In one recent study it was found that having a family history of VV was a risk factor in the younger group (≤45 years old), but the effect was not statistically significant in the older group (>45 years old) (Chen and Guo 2014).

In an Indian study 25% of patients had family history of close relatives suffering from varicose veins. The occurrence of varicose veins in several members of the same family suggests that hereditary factors may be important in causation of varicose veins (Mirji et al. 2011). These studies suggest a strong genetic component in primary venous failure.

2.10. GENETIC ASSOCIATION OF VARICOSE VEINS

Varicose veins is a common condition affecting more than 25 million people in the United States alone (Raffetto and Khalil 2008), with a complex and multifactorial development involving interplay between the genetic makeup of the individual and predisposing risk factors that include age, female sex, family history, pregnancy, obesity, and prolonged standing (Bergan et al. 2006). The genetic basis of varicose veins remains to be elucidated; it is clear they can arise in young individuals with no predisposing risk factors, suggesting that inborn or local genetic traits play key roles in increasing susceptibility to the development of abnormal veins. It is likely that genetic
variation, persistent venous hypertension, and the consequences of chronic inflammation within the venous wall may be independent contributory elements. Genetic analysis of the 18 families revealed an association between chromosome 16q24 region and the transcription factor FOXC2. It was discovered that 72 of 74 patients with lymphedema–distichiasis syndrome had mutations in the FOXC2 gene, which were primarily small insertions and deletions (Brice et al. 2002). This study, for the first time, suggested a possible candidate gene for the development of varicose veins.

A genetic predisposing to varicose veins has been proposed for many years, and venous functions in twins, indicated a strong genetic influence (Brinsuk et al. 2004). A recent study in a twin cohort indicated linkage of varicose veins to candidate marker D16S520 on chromosome 16 (Ng et al. 2005). This region of chromosome 16 contains genes coding for, among others, FOXC2, FOXL1, FOXF1, and IRF8. FOXC2 is the 1st gene in which mutation has been strongly associated with primary venous valve failure in the both superficial and deep veins in the lower limb and is a cause of varicose veins (Russell and Glen 2007). The official name of this gene is “Forkhead box C2 (MFH-1, mesenchyme forkhead 1) and is situated on 16q24.3 chromosome (Fang et al. 2000 and Bell et al. 2001). FOXC2 gene encodes a 2.2Kb transcript with a 1.5Kb single exon coding region that is highly GC rich (>70%) and is expressed in the developing cardio-vascular system (Miura et al. 1997) (Figure-2).

Figure 2- Map of the 16q24.3 region containing the FOXC2 gene. The positions of several sequence-tagged sites and ESTs are indicated. The shaded boxes represent three forkhead genes—FOXF1, FOXC2, and FOXL1. The translocation breakpoint is ~120 Kb distal to the FOXC2 gene.
The forkhead family of transcription factors includes 180 members in various species, these transcription factor bind DNA through a highly conserved 100-aminoacid forkhead motif (Kaestner et al. 1993). In animal models *FOXC2 gene* is expressed in developing mesenchyme cells that later develop into connective tissue, blood vessels, and lymphatic vessels (Miura et al. 1993 and Wilm et al. 2004). At a later stage of development, FOXC2 gene is expressed on both the endothelial and smooth muscle cells of developing blood vessels (Kume et al. 2001) and on the venous and lymphatic valve leaflets (Petrova et al. 2004). The *FOXC2 gene* provides instructions for making a protein that plays a critical role in the formation of many organs and tissues before birth. This protein is a transcription factor, which means that it attaches (binds) to specific regions of DNA and helps control the activity of many other genes. Researchers believe that the FOXC2 protein has a role in a variety of developmental processes, such as the formation of veins and the development of the lungs, eyes, kidneys and urinary tract, cardiovascular system, and the transport system for immune cells (lymphatic vessels). FOXC2 gene is implicated in both lymphatic and vascular development (Kume et al. 2001 and Kriedermam et al. 2003). More than 50 mutations in the FOXC2 gene can cause lymphedema-distichiasis syndrome and varicose veins. About 50% of individuals with Lymphedema-distichiasis syndrome have varicose veins (Brice et al. 2002). Most of these mutations are insert or delete a few DNA building blocks (nucleotides), which results in a premature stop signal in the instructions for making the FOXC2 protein. These mutations lead to the production of a FOXC2 protein that is abnormally small and cannot effectively attach (bind) to DNA. As a result, the altered protein cannot regulate the activity of other genes. Other mutations change one protein building block (amino acid) in the area of the FOXC2 protein that binds to DNA, preventing the protein from regulating gene activity.

FOXC2 has a known association with varicose veins in lymphoedema distichiasis and may have a role in the development of venous valves. It was investigated that differential expression of genes in varicose veins and normal veins has identified 3 cDNAs with prominent expression in patients with varicose veins. These cDNAs had significant similarities to the L1M4 repeat sequence of clone RP11-57L9, clone RP11-29H13, and Alu repetitive sequence of human tropomyosin 4 mRNA; suggesting that altered expression of these elements affects the structure and
function of the vein wall by altering the actin binding proteins involved in the assembly and regulation of the cell’s contractile mechanisms (Kim et al. 2005).

By studying 2060 female twin pairs they concluded that there was a functional variant within the vicinity of the FOXC2 gene which predisposed individuals to varicose veins. A further study by these workers showed that every participant (n ¼ 18) with the FOXC2 mutation had evidence of venous reflux on duplex ultrasound scanning, compared with one in 12 controls (Mellor et al. 2007). The valves in the superficial veins were always affected by the FOXC2 mutation and in 78% of the deep system. This is an example in which a rare monogenic mutation has provided a candidate gene for further study in the more general polygenic condition of varicose veins.

Cytogenetic investigation of primary cell culture of varicose veins has been done in two groups of patients. One group of patients with familial varicosity and other was patients with the sporadic type. Both studies revealed the presence of metaphase with structural abnormalities, clonal trisomies of chromosome 7, 12 and 18. monosomy of chromosome 14 was present only in cases with the familial type, while the sporadic cases had no similar chromosome aberration (Susi 1994).

Analysis of 98 patients with varicose veins of the lower limbs (aged from 24 to 89 years) and 297 control subjects for the alanine-to-valine amino acid substitution in the MTHFR gene was performed (Sverdlova 1998). All patients were referred for operation in the Surgical Clinic of the St. Petersburg Medical University. This study demonstrated an association between the MTHFR genotype and the risk of developing varicose veins in the lower limbs and found a significantly higher prevalence of subjects with at least one C677T MTHFR allele among those with varicose veins than among a control group.

Neuropilin (NRP) 1, previously identified as a neuronal receptor that mediates repulsive growth cone guidance, has been shown to function also in endothelial cells as an isoform-specific receptor for VEGF165 and as a co receptor in vitro of VEGFR2 (Miao HQ et al. 2000 and Oh H et al. 2002). Differential gene expression of VEGF and its receptors and alterations in VEGF, VEGFR1, VEGFR2, and neuropilin-1
interactions may be important determinants of the adaptive response of veins to different stimuli (Woodside et al. 2003).

Varicose veins exhibited transcriptional elevation of vascular endothelial growth factor (VEGF) -121, VEGF-165, and two VEGF receptors (VEGFR), VEGFR1 (flt-1), and VEGFR2 (KDR). However, when the valve at the saphenofemoral junction was functional, the transcription of VEGFR1 was not altered. VEGFR1 occurs in transmembrane and soluble forms and regulates angiogenesis, vascular permeability and endothelial cell proliferation (Shibuya 2006).

Another biomarker associated with varicose vein development is the NOTCH3 gene, which is mutated in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL results from mutations in NOTCH3, a receptor for several membrane-bound ligands that play a central role in development. In a CADASIL pedigree with varicose veins, a novel mutation in NOTCH3, which splices out exon 16, was identified. This mutation probably causes aberrant receptor dimerization and signaling and is thought to be causative of CADASIL and varicose veins in this pedigree (Saiki et al. 2006). Other reports have found associations between varicose veins and mutations in the thrombomodulin promoter (Lee et al. 2001), mutations in the NDP gene (Law et al. 2006).

Another reported mutation was Octamer-binding transcription factor (Jeong et al. 2008). The study was conducted to identify the genes whose expression is different in primary varicose veins compared to normal veins in the legs. To test this hypothesis, the differentially expressed gene technique was performed on a large-scale screen of mRNA from varicose and normal veins. Transcriptional products corresponding to cDNA were compared between the two vein types, and one gene showed the greatest differential expression between the samples in all sets of experiments, confirmed by reverse-Stranscriptase polymerase chain reaction. Octamer-binding transcription factor-1 gene (Oct-1) was upregulated in primary varicose veins. Therefore, it was suggested that Oct-1 may play an important role in the development of primary lower extremity varicose veins.
Genes including desmuslin and thrombomodulin can directly affect vein function with mutations implicated in the development and progression of varicose veins (Le et al. 2001 and Yin et al. 2006). Venous ulcer is the commonest complication associated with varicose veins. Genetic research in venous ulceration has highlighted the importance of understanding the pathophysiological mechanisms that underlie disease development. Mutations in the F13A1 gene as well as variants of the hemochromatosis gene directly affect venous ulcer progression through the inhibition of physiological tissue healing processes (Tognazzo et al. 2006 and Zamboni et al. 2006). SNP array technology through a candidate gene approach has been used to identify further susceptibility loci including SLC40A1, methylenetetrahydrofolate reductase, and fibroblast growth factor receptor-2 (Nagy et al. 2005 and Gemmati et al. 2009). Although ulceration is linked to varicose veins, there are insufficient data to link ulcer-related genes to varicosity formation.

In a study for genetic variation among varicose veins patients, 655bp of the single exon of FOXC2 gene as well as an additional 413 bp of upstream UTR was sequenced. Three SNPs were identified in proximal region, 91 C→G, -41 G→A and -41 G→T (Khalid et al. 2008). Seven different novel mutations were found in the FOXC2 gene in varicose veins patients, of which five were missense and two were frameshift mutations. These mutations alter the transcriptional activity of FOXC2 gene (Steensel et al. 2009).

The current consensus is that both environmental and genetic factors are associated with the development of varicose veins (Ng et al. 2005, White and Ryjewski 2005 and Raffetto and Kahlil 2008) (Figure-3).
Figure 3: Mutation in genes critical to the correct function of the vascular system can occur at any level of the organization of DNA. When combined with environmental effects, these can result in the development of varicose veins.

2.11. DIAGNOSIS

Recognition of the dilated veins is usually made by physical examination. The lack of accuracy of diagnosis based only on visualization and palpation is obvious and many small lesions may escape detection. Varicosity is commonly classified as small, moderate, or large, according to a subjective grading of venous size and reflux (Dubin et al. 1970). Retrograde venography is an objective and precise diagnostic method, but it is invasive and cannot be used for screening. More recently, several noninvasive
methods have been proposed for improving the diagnosis of varicosity, mainly for small lesions in which recognition of venous dilation and reflux is problematic. The use of ultrasonography for varicose veins imaging has been scarcely reported in the radiologic literature (Rifkin et al. 1983, Wolvilsen et al. 1983 and Korne 1985) and did not have impact on current clinical evaluation of varicocele. A recent multicenter trial organized by the World Health Organization (WHO) reported satisfactory results using a combination of Doppler sonography and contact scrotal thermography (WHO, 1985). However, in practice, clinical evaluation of varicose veins most commonly entails imaging with Doppler ultrasound, which is an objective, noninvasive measure of venous insufficiency that is invaluable in identifying valvular incompetence. In Doppler studies, reflux of greater than 0.5 seconds in superficial and deep calf veins is considered abnormal, whereas 1 second is generally used as a cutoff value for the femoropopliteal veins (Labropoulous et al. 1997). Previous examination included the inspection of lower extremities and tests with Doppler reflux verification. But nowadays these tests have been largely superseded by color duplex scanning (Bhasin and Scott 2006 and Campbell 2006).

2.12. TREATMENT

Treatment options have increased over the last 10 years with the advent of endovascular techniques such as radiofrequency ablation (RFA), endovenous laser ablation (EVLA) and foam sclerotherapy in addition to compression hosiery and open surgery (Rebecca 2009).

Compression hosiery has been shown to improve the symptoms of patients with uncomplicated varicose veins. Below-knee Class II (18e24 mmHg) UK stockings are generally prescribed. There is no evidence that compression reduces recurrence or prevents progression of varicose veins. Complications of compression hosiery are few; however, poorly fitted stockings can cause skin necrosis. The risk increases in patients who are diabetic or who have impaired blood supply or sensation. Compression stockings should not be used on legs with an ankle brachial pressure index (ABPI) of less than 0.9 (Palfreyman 2009).
Open surgery remains the gold standard and is the most commonly performed procedure for varicose veins. It is usually performed under general anesthesia as a day case procedure. The superficial vein is disconnected and in the case of sapheno-femoral incompetence the great saphenous vein is stripped to just below the knee. It has been shown that stripping reduces the rate of re-operation and also the rate of recurrence up to 5 years postoperatively (Rebecca 2009).

In summary, varicose veins are the clinical manifestation of venous insufficiency. Although, women are mostly affected and other risk factors include family history and older age. Recently, a variant of the FOXC2 gene and differential expression of human tropomyosin 4 cDNA was linked to a genetic predisposition to the development of varicose veins. Varicose veins have become a serious threat to the lives of millions of people across the globe and is said to be ignored by people living across India. Though there is a high prevalence of varicose vein in India, very few studies have been conducted in India. “There is an urgent need to spread awareness about varicose veins in India. Many people suffer from it, but most tend to ignore it and that is not good as it can lead to complications in the advanced stage”. The present study will help in assessment of risk factors as well as it will be helpful in identifying the genetic predisposition of varicose veins.

Patient-reported quality of life is reduced in patients with CVD and the cost of treating CVD has been estimated at 1% to 3% of the total annual healthcare budget of many Western countries (Nicolaides et al. 2008). Varicose veins are the most common disease of legs, although up to 4% of patients aged ≥65 years may experience venous ulceration (Criqui et al. 2003 and Meissner et al. 2007). Recurrence rates for varicose veins after surgical treatment have been reported to be as high as 20% to 40% (Tsang et al. 2005). Therefore, there is a need to improve understanding of the underlying causes of varicose veins and to identify high-risk groups. This involves recognizing both rare and frequent genetic variants that influence risk of varicose veins and relate these to quantitative phenotypes according to severity of disease. This will enable researchers to establish the critical functions of the susceptibility genes and the translation pathways leading to disease. This approach has the potential to provide improved medical treatment for patients and personalized, targeted preventive
measures tailored to those identified to be at high risk. These preventive measures may include lifestyle changes, occupational advice, use of preventative compression stocking, or a pharmacotherapeutic treatment to prevent the progression of the disease.

Genetic abnormalities for more severe forms of CVD have been described. Identifying a genetic basis for varicose vein will not only help elucidate the molecular abnormalities involved with that gene and its function, but also provide information on individuals at risk and guide in therapeutic decisions during treatment. An understanding of the molecular basis of varicose veins formation with respect to changes in endothelial cell and smooth muscle function, as well as the influence of abnormal apoptotic function and MMP involvement, will provide valuable information on the mechanisms involved in the disease development and progression, and highlight possible targets for pharmacological intervention or genetic manipulation of the disease.

The aim of study is to know the genetic associations with venous disease and to understand of the cause of varicose vein disease. Keeping in view of available information the present study “on dermatoglyphics and molecular cytogenetic characterization of varicose veins” has been carried out.