INTRODUCTION

Obesity is a medical condition in which abnormal or excessive fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems ***{Sharma et al., 2017 }.***

Surgical approaches to weight loss, bariatric surgeries, are commonly performed procedures for morbidly obese individuals; the estimated number of bariatric procedures in the USA alone was close to 180,000 in 2013. Bariatric surgery is effective in achieving weight loss and improving obesity-related complications ***{Kang et al., 2017 }.***

As a result of new technologies with lower risks and better long-term results, bariatric and metabolic surgeries have grown in popularity in recent years. The number of operations performed is rapidly increasing. However, bariatric surgery is associated with numerous peri- and postoperative complications ***{Stroh et al., 2016}***.

Venous thromboembolism is the commonest postoperative complication. Obesity needs to be considered as one of the most serious factors predisposing patients to the development of thrombosis and pulmonary embolism ***{Stroh et al., 2016}.***

Deep venous thrombosis may occur in up to 1.3% of patients after open or laparoscopic bariatric surgery. Despite the

early mobility after laparoscopic surgery, the incidence of DVT may not be reduced as much as expected because the benefit of early mobility may be offset by the tendency of pneumoperitoneum to promote DVT ***{Stroh et al., 2016 }***.

Despite universal agreement on the need for thromboprophylaxis, no clear consensus has been reached regarding the best regimen and treatment duration. Current modalities of thromboprophylaxis include subcutaneous injection of unfractionated or low molecular weight heparin, pneumatic compression devices, elastic stockings, and inferior vena cava filters ***{Vandiver et al., 2016 }***.

Most series evaluating prophylactic strategies for bariatric patients include some form of mechanical prophylaxis. Because of concerns of bleeding complications associated with chemoprophylaxis (2% incidence of bleeding complications in a recent systematic review when a standardized definition of hemorrhage was used), several studies have examined the use of mechanical compression only in bariatric surgery patients ***{Venclauskas et al., 2018 }.***

AIM OF THE WORK

To compare between patients receiving anticoagulant prophylaxis only to patients receiving mechanical prophylaxis only.

Chapter 1

OVERVIEW ON BARIATRIC SURGERY

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems ***{Sharma et al., 2017 }.***

Body mass index (BMI) is a widely and simple used method to estimate body fat mass. BMI is calculated by dividing the subject's mass in kg by the square of his or her height. Any BMI ≥ 35 is severe obesity, BMI of ≥ 40 is morbid obesity and BMI of ≥ 45 is super obese ***(Sturm, 2007).***

Severe obesity is associated with a large number of comorbidities. These start at the head (stroke, diabetic retinopathy,pseudo tumor cerebri, tinnitus) and go to the toes (diabetic neuropathy, venous stasis disease, foot ulcers) and affect almost every organ in between: heart, lungs, liver, gall bladder, spleen, esophagus, intestines, colon, kidneys, bladder, ovaries, prostate, breast, legs, etc… ***{Jakobsen et al., 2018 }***

Bariatric surgery has been demonstrated to be the most effective and sustainable method for the regulation of morbid obesity, superior to both pharmaceuticals and combinations of diet and lifestyle regimens ***{Sharma et al., 2017 }.***

Indications for Bariatric Surgery and Patient Selection:

In 1991 the National Institutes of Health published a consensus statement regarding bariatric surgery. Surgery was indicated in patients with a BMI $\geq$ 40 kg/m^2 and in patients with a BMI between 35 and 40 with other comorbidities **(Table 1)**. Severe sleep apnea, obesity related cardiomyopathy, Pickwickian syndrome, severe diabetes mellitus and life style limitations were all considered comorbidities that would allow the patient to pursue surgery ***{Courcoulas et al., 2014}.***

Table (1): Indications for bariatric surgery and patient selection ***(Schirmer and Schauer, 2010).***

Patient must:
1. Have BMI of ≥40 with or without other co-morbid medical conditions associated with obesity.
2. Have BMI of 35–40 with other co-morbid medical conditions.
In addition, patients:
1. Have failed attempt of other weight loss treatments
2. Must be psychologically stable
3. Must be cooperative, motivated and agree for lifelong follow up.
4. Must be fit for surgery.
5. Aged 18 to 60 years.

Chapter 2

PATHOPHYSIOLOGY OF DEEP VENOUS THROMBOSIS IN OBESITY

Overview of the haemostatic system:

The haemostatic system is a complex, multifaceted host defence mechanism that evolved to protect the integrity of the vascular system. It works in coordination with the mechanisms of inflammation and repair, producing a coordinated response ***{Stone et al., 2017 }.***

Haemostatic systems are normally quiescent and are only activated after injury. Ultimately, the coordinated haemostatic response results in the production of a platelet plug, fibrin-based clot, deposition of white cells at the point of injury, and activation of inflammatory and repair processes ***{Branchford et al, 2018 }.***

After injury and vessel vasoconstriction, reduced blood flow permits contact activation of platelets (Figure1). Subsequently, platelets adhere to exposed connective tissue and release an array of vasoactive proteins that interact with other platelets and leukocytes, enhancing platelet activation and leading to the formation of platelet aggregates to from the initial plug ***(Colman, 2006)***.

At the same time, the vascular endothelium moves from its resting phase (anticoagulant) to a more active (procoagulant) and repair phase. ***(Colman, 2006)***.

In sequence, these active factors generate thrombin, which leads to the formation of fibrin from fibrinogen (to stabilize the platelet plug), cross-linking of fibrin (through activation of factor XIII), further activation of platelets, and activation of fibrinolytic pathways (to enable plasmin to dissolve fibrin strands in the course of wound healing). In addition, thrombin interacts with other non-haemostatic systems to promote cellular chemotaxis, fibroblast growth, angiogenesis, and wound repair ***(Colman, 2006)***.

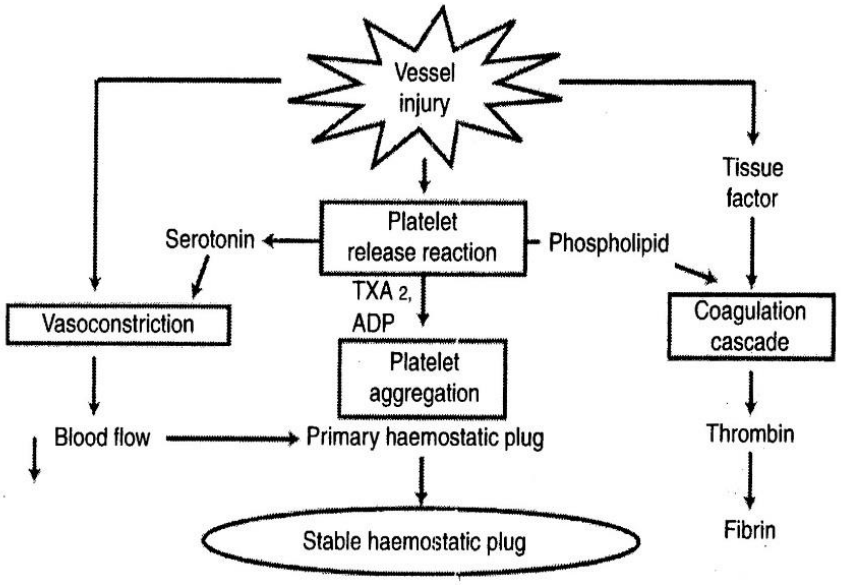

Figure (1): A simplified overview of the haemostatic cascade ***(Colman, 2006).***

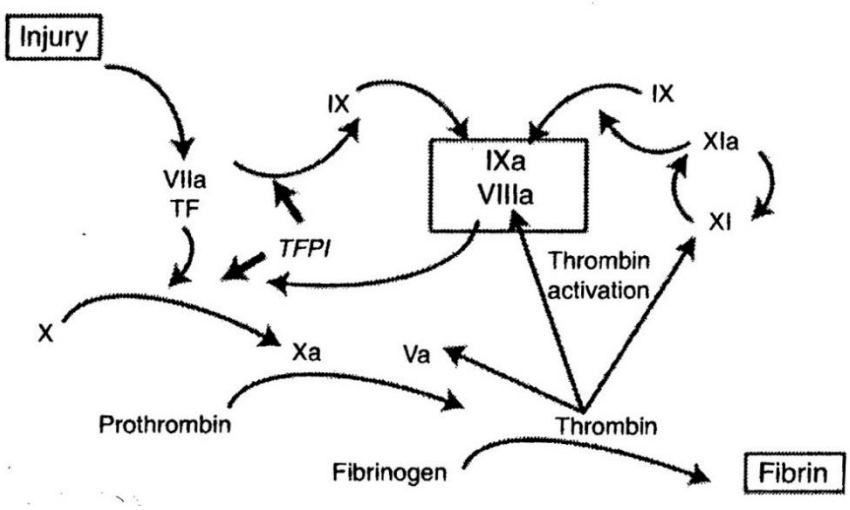

Figure (2): The coagulation cascade ***(Colman, 2006).***

The major role of the coagulation cascade is the production of fibrin-the meshwork that holds together the clot, which is produced through a cleavage of fibrinogen by thrombin ***{Budnik et al., 2018 }.***

Coagulation is initiated by tissue damage, exposing the Transmembrane glycoprotein tissue factor (TF). Tissue factor is expressed on the subendothelial surface of blood vessels and is normally exposed only when normal vasculature is disrupted. Factor VII binds TF, and the TF-factor VII complex directly activates factor X to factor Xa and some factor IX to factor IXa. In the presence of factor Xa, tissue factor pathway inhibitor (TFPI) inhibits further generation of factor Xa and factor IXa. After inhibition by TFPI, the amount of factor Xa produced is insufficient to maintain coagulation ***{Budnik et al., 2018 }***

Additional factor Xa (which allows haemostasis to progress to competion) can only be generated by the factor IX-factor VIII pathway. Enough thrombin exists at this point to activate factor VIII, and together with factor IXa (generated by TF- factor VIIa) to further activate factor X. Factor IX activation is also augmented by thrombin activation of the factor XI pathway. Without the amplification and consolidating action of factor VIII/factor IX, there is insufficient generation of factor Xa to produce sufficient thrombin. When sufficient thrombin is generated, this endolytic serine protease selectively cleaves the Arg-Gly bonds of fibrinogen to form fibrin, releasing fibrinopeptides A and B and so forms the meshwork of the clot ***{Budnik et al., 2018 }***

It is of note that the above physiological description omits the classic extrinsic pathway (factor VII-TF initiated coagulation to common pathway at factor X) and intrinsic pathways activated by factor XII (and through factors XI, IX, and VII to common pathway at factor X). Although factor XII has no role in physiological blood coagulation, it has been considered that it may have a role in cancer-related thrombosis ***(Rebecca et al., 2009).***

Mechanisms for the observed association of obesity and VTE:

The physical aspects of the body size of the obese are likely to contribute to the risk of VTE. More body fat,

especially abdominal fat, might limit venous return. The obese have chronically raised intra-abdominal pressure and decreased blood velocity in the femoral vein. In activity and poor gait may compound the effect ***(Darvall et al., 2007).***

However, there appear to be additional mechanisms responsible. It is postulated that obesity might cause thrombosis via leptin, increased activity of the coagulation cascade, and decreased fibrinolysis. There may be increased inflammation, oxidative stress, and endothelial dysfunction. ***(Van Guilder et al., 2008).***

Leptin:

It is now well recognized that the visceral adipose tissue is metabolically active, producing adipokines such as leptin, which is important in the regulation of body weight. Leptin acts as a hormone via the hypothalamus to decrease appetite and food intake, and increase energy expenditure ***(Dellas et al., 2008)***.

However, the levels of leptin are elevated in obesity as the central nervous system appears to become more and more resistant to its effects. It is uncertain if peripheral cells also become resistant to leptin. Leptin is associated with adenosine diphosphate-induced platelet aggregation and has also been demonstrated to be correlated with tissue plasminogen activator (tPA) antigen ***{Stone et al., 2017 }.***

Higher concentrations of plasminogen activator inhibitor-1 (PAI-1) inhibit fibrinolysis and thereby maintain thrombotic state. Studies with human coronary artery endothelial cells show leptin induces the transcription and translation of PAI-1 ***(Singh et al., 2010)***.

No change in tPA was demonstrated in these cell culture studies. A clear association between adipose PAI-1 mRNA and fat cell volume has previously been reported ***{Stone et al., 2017 }***

Fibrinolysis:

In the Framingham Offspring Study, subjects were assessed for cardiovascular risk factors and the association with selected prothrombotic factors ***(Rosito et al., 2004)***.

It was reported that increased BMI and waist-to-hip ratio were associated with elevated fibrinogen and PAI-1. Thus, obesity is associated with a hypofibrinolytic state and elevated concentrations of PAI-1 are present. As stated above, leptin may have a role to play in PAI-1 overexpression but tumor necrosis factor-a (TNF- α) and transforming growth factor-b (TGF-β) produced in visceral fat have also been proposed to play a role in the regulation of PAI-1 expression in adipose tissue ***{Davies et al., 2017 }***

Coagulation Cascade:

BMI and waist-to-hip ratio have been shown to positively correlate with factor VII (FVII) levels, factor VIIIc (FVIIIc), and fibrinogens well as von Willebrand factor ***{El-Menyar et al., 2018}.***

It might be the chronic inflammation of obesity or hyperinsulinemia which are responsible for the observed elevations ***{Steffen et al., 2009}***.

FVIII concentrations are strongly associated with increased risk of VTE25 as is hyperfibrinogenemia. Increased fibrin formation, platelet aggregation, and increased plasma viscosity promotes venous thrombosis ***{El-Menyar et al., 2018}***

Additional Predisposing Factors:

The relationships between obesity and thrombo-embolism may be confounded by several factors. Metabolic syndrome is associated with VTE and individual components that define the syndrome and likely to occur with obesity, have demonstrated associations. Higher concentrations of triglycerides in patients with VTE have been reported, but the findings are inconsistent ***{Engin, 2017 }.***

Hyperglycemia may result in a hypercoagulable and hypofibrinolytic state by mechanisms independent of obesity ***{Samuels et al., 2019}.***

A meta-analysis reported that diabetics were 1.56 times more likely to develop VTE (95% CI, 1.23–1.98) ***{Liew et al., 2017}.***

Further studies in hyperglycemic and hypertrigly-ceridemic individuals without abdominal obesity are needed to determine their

contribution to the etiology of obesity-related venous thrombosis. There are also several lifestyle factors that might influence the relationship between obesity and VTE. Epidemiological evidence is inconclusive about the effects of physical activity in overweight and obese people ***{Liew et al., 2017 }.***

At the mechanistic level, moderate intensity of regular aerobic exercise in subjects in their late50s (40 to 50 minutes, 5 to 7 days per week) has been demonstrated to improve endothelial tPA release in overweight and obese adults without weight loss ***(Van Guilder et al., 2005)***.

Consumption of some foods may be protective for both obesity and development of VTE. Diets rich in selected fish containing very long chain omega-3 fatty acids favor platelet hypoaggregability and hyperfibrinolysis ***{Dunton, 2018 }.***

With respect to carbohydrate content, those diets with a higher glycemic load (i.e., either higher in total carbohydratecontent or with more high glycemic indexcarbohydrates), might result in an insulin-resistant state and hypercoagulable and hypofibrinolytic milieu ***(Brand-Miller et al., 2009)***.

Chapter 3

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of acute extremity DVT varies with the extent, anatomic distribution, and degree of occlusion of the thrombus. Symptoms tend to be more severe as thrombosis extends more proximally. However, up to 50% of patients with acute DVT may lack specific signs or symptoms ***{Min et al., 2016}.***

The most common presenting symptoms and signs associated with deep venous thrombosis were extremity edema (80%), pain (75%),and erythema (26%). Patients with pulmonary embolism complained most often of dyspnea (85%), chest pain (40%), tachypnea (30%), and tachycardia (23%), Syncope (10%) and hemoptysis (2%) were less commonly reported ***(Angelli et al., 2008).***

Phlegmasia alba dolens is the clinical situation of an iliofemoral vein thrombosis associated with arterial spasm, which is relatively rare. This causes a clinical picture of a very pale and cold leg with weak or absent arterial pulses. In the early stage swelling may be minimal, and the skin might show a mottled blue appearance. Phlegmasia cerulea dolens is another rare complication of DVT with total or near total venous occlusion of

the lower extremity. It is associated with a high degree of morbidity. The clinical presentation of the syndrome usually consists of pain, swelling, rubor, cyanosis and Severe oedema ***(Edwin et al., 2009).***

In 2006, Scarvelis and Wells formulated an acute DVT predictive scoring system to assist clinicians in diagnosing patients with symtpoms suggestive of acute DVT ***(Min et al., 2016).***

Table (2): Wells score ***(Min et al., 2016).***

Clinical feature	*Score*
• Active cancer (treatment ongoing or within previous 6 months or palliative)	1
• Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
• Recently bedridden longer than 3 days or major surgery, within 4 weeks	1
• Localized tenderness along the distribution of the deep venous system	1
• Entire leg swollen	1
• Previously documented deep vein thrombosis	1
• Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
• Pitting edema (greater in the symptomatic leg)	1
• Collateral superficial veins (nonvaricose)	1
• Alternative diagnosis as likely or greater than that of deep-vein thrombosis	–2