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Systematic Review

Risk of Venous Thromboembolism and Efficacy of Thromboprophylaxis in Hospitalized Obese Medical Patients and in Obese Patients Undergoing Bariatric Surgery

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Background: Obesity is considered a highly prevalent risk factor for venous thromboembolism (VTE) in hospitalized patients. However, recommendations for VTE prophylaxis in obese patients are not clear.

Methods: To evaluate obesity as a risk factor for VTE in medical and bariatric patients and the efficacy of VTE prophylaxis, we performed a systematic review in MEDLINE, Cochrane Database of Systematic Reviews and LILACS from 1976 to 2006. Evidence was evaluated independently by 2 authors and presented descriptively.

Results: Of the 124 studies found, 87 were excluded based on predefined criteria. There is no consensus among studies, but prospective cohorts show that obesity is associated with a higher risk of VTE in medical patients. There is evidence that the risk of VTE exceeds that attributable to the surgical procedure alone in bariatric surgery. Only 6 studies evaluated prophylactic methods (unfractionated heparin, low molecular weight heparin and sequential compression devices) in obese patients. Although these studies have some methodological flaws, they suggest efficacy of VTE prophylaxis in medical and surgical obese patients.

Conclusions: Obesity is a risk factor for VTE in obese medical patients and patients undergoing bariatric surgery. Obesity appears to play an adjuvant role for the development of VTE in hospitalized patients with other risk factors. The small number of prospective trials in this population prevents a definite conclusion about the most effective and safe VTE prophylactic method for obese patients. Thus, randomized clinical trials to compare VTE prophylactic methods in obese patients are still highly warranted.

Key words: Obesity, morbid obesity, embolism and thrombosis, prevention and control, risk factors, heparin, bariatric surgery

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Introduction

Venous thromboembolism (VTE) represents a spectrum of diseases including deep venous thrombosis (DVT), catheter-related thrombosis and pulmonary embolism (PE) that commonly affect hospitalized patients.[1] Several surgical and medical conditions related to the reason for hospital admission or to the medical history, such as obesity, are frequently cited as risk factors for VTE. Although the exact incidence of VTE in obese patients is not known, several authors suggest that obesity represents an important risk factor for the development of VTE, particularly when these patients are hospitalized for surgical and medical reasons.

There is evidence that the use of VTE prophylaxis can reduce the morbidity and mortality due to silent and clinically apparent VTE of those at-risk, including obese patients. However, given the variable pharmacokinetics[2,3] and the difficulties in performing diagnostic tests to confirm or exclude VTE in obese patients, results from VTE prophylaxis trials in non-obese patients may not be extrapolated to this population. Therefore, international guidelines for VTE prophylaxis do not give specific recommendations of methods and dosages of heparins for obese patients.[4]

We review the evidence about obesity as a risk factor for VTE and about the efficacy of prophylactic methods in hospitalized obese medical patients and obese patients undergoing bariatric surgery, to help establishing the risk-benefit of VTE prophylaxis in this population.

Materials and Methods

1. Searching Strategy

A computer-based strategy was performed independently by two investigators to identify: 1) studies evaluating obesity as a risk factor for VTE in medical (A.T.R. and A.G.V.) and surgical patients (A.T.R. and E.R.L.N.), and 2) studies evaluating the efficacy of VTE prophylactic methods (low dose unfractionated heparin [LDUH], low molecular weight heparin [LMWH] and mechanical methods) in obese patients (A.T.R. and D.M.A.A.). The search included MEDLINE (from 1976 to May 2006), EBM Reviews – Cochrane Database of Systematic Reviews 4th Quarter 2005 and LILACS (from 1985 to 2005) with studies in English, Portuguese, Spanish, Italian and French. All selected studies were reviewed for additional references. The following group of Medical Subject Headings (MeSH) related to obesity and to venous thromboembolism were used: "Obesity"[MeSH] OR "Obesity, Morbid" [MeSH]) AND ("Thrombosis" [MeSH] OR "Venous Thrombosis" [MeSH] OR "Embolism and Thrombosis" [MeSH] OR "Embolism" [MeSH] OR "Pulmonary Embolism" [MeSH]) NOT ("Atrial Fibrillation" [MeSH] OR "Cerebrovascular Disorders" [MeSH] OR "Arterial Occlusive Diseases" [MeSH])".

2. Study Selection

The studies were selected based on the reading of the abstract and, when necessary, the complete text. The quality of the studies was based on standardized criteria, considering the study design, randomization, recruitment of consecutive patients, adequacy of follow-up, use of objective methods for detection of VTE, blinded evaluation, precision of results and applicability of results to answer the clinical questions about obesity as a risk factor and the efficacy of prophylaxis. In this review, both the risk of VTE and efficacy of VTE prophylaxis were evaluated in obese patients. Therefore, we included preferentially randomized controlled trials (RCT), but also cohort and case-control studies with at least 10 patients.

3) Evidence and Recommendations

The criteria used to classify the scientific evidence were developed by the Oxford Centre for Evidence Based Medicine, May 2001 (*http://www.cebm.net/levels_of_evidence.asp*) and speak to the validity of the evidence about etiology and prevention. The studies were classified from level 1 to level 5 according to the decreasing methodological quality of the evidence. The recommendations about VTE use were classified as A, B, C, or D, depending on the compilation of the evidence (A being the strongest and D the weakest), listed in the right column of Table 3.

Results

Using the searching strategy, we identified 124 studies related to the topic. Eighty-seven studies were excluded because they were not appropriate to answer the clinical questions of this review (studies in trauma [n=1], burn [n=3] and surgical, non-bariatric patients [n=10], non-systematic reviews and letters to the editor). None of the studies were systematic reviews about obesity as a risk factor for VTE in surgical or medical obese patients. Only one study reviewed the incidence of complications of obesity surgery, and included pulmonary embolism (PE). Once data is scant, a metanalysis could not be performed, and the evidence is presented descriptively. The studies about obesity as a risk factor for

medical and bariatric patients are shown separately in Tables 1 and 2. The studies about the efficacy of prophylaxis in bariatric or medical obese patients are shown in Table 3.

Obese Medical Patients

The evidence is controversial about the association between obesity and VTE. Four studies with different methodology provide evidence contrary to this association. In the MEDENOX study,[5] 1,102 patients ≥40 years-old hospitalized for medical conditions were randomized to receive enoxaparin 40 mg daily, 20 mg daily or placebo. The authors showed that approximately 20% of the patients had obesity as a risk factor for VTE, and that the patients receiving 40 mg of enoxaparin daily had significantly lower incidence of VTE than those receiving 20 mg or placebo (5.5% vs 14.9%, $P<0.001$). This study gives indirect evidence that hospitalized medical patients with risk factors, including obesity, have increased risk of VTE. A few years later, Alikhan et al[6] performed a secondary analysis of the MEDENOX study,[5] specifically to investigate the association between medical conditions and VTE. These authors found only a non-significant correlation between obesity and VTE (RR 1.04; 95% CI 0.69–1.60). Grady et al,[7] analyzing data of the "The Heart and Estrogen/progestin Replacement Study" (HERS), which included women with BMI >27, also failed to find a significant correlation between obesity and VTE. It is worth noting that the identification of obesity as a risk factor in both studies was a secondary objective and that the analyses were performed *post hoc*. Cogo et al,[8] in a prospective study of ambulatory patients with clinical suspicion of DVT, subsequently confirmed by phlebography, failed to identify obesity, defined as body weight 30% above ideal, as an independent risk factor for VTE. Heit et al[9] evaluated in a population-based case-control study, 625 patients with objectively confirmed VTE and 625 matched controls by age and gender. These authors also failed to detect a correlation between obesity and VTE, although there were missing data on weight and height of controls, which could have led to bias on the results.

On the other hand, several studies support the association between obesity and VTE. In an autopsy study with 7,227 patients, Blaszyk et al[10] demonstrated that VTE was the cause of death in 433 (6%). Among these individuals, 36 did not have any recognizable risk factor for VTE. However, there was higher prevalence of obesity (67%) in patients who died with fatal PE than in controls who died from other causes (14%), OR 12.4 (95% CI 3.8-40.0). In five prospective cohorts, obesity was identified as a risk factor for VTE. In the case-control study SIRIUS, Samama et al[11] evaluated 636 ambulatory patients with the first episode of DVT confirmed objectively and 636 controls. They found a positive correlation between obesity (BMI >30) and VTE, RR 2.39 (95% CI 1.46-3.87). Abdollahi,[12] in similar study, demonstrated that BMI ≥30 increased by two the chance of thrombosis (95% CI 1.5-3.4) among patients with the first episode of objectively confirmed DVT, when adjusted for age and gender. Nevertheless, in some studies, obesity was identified as a risk factor for VTE only in specific subgroups of patients. Tsai et al[13] found a positive trend for the association between increase in BMI and VTE; for the morbidly obese (BMI ≥40), the RR was 2.7 (95% CI 1.3-5.8). Hansson et al,[14] studying prospectively 855 men ≥50 years old, with objective methods for detection of VTE, found a RR of 3.92 (95% CI 2.10-7.29) with abdominal obesity (waist circumference ≥100 cm). Similarly, Goldhaber et al[15] found an association between obesity (BMI >29) and VTE in 112,822 women with ages 30 to 55 years participating of the "Nurses' Health Study", RR 2.9 (95% CI 1.5-5.4).

Although there is no consensus among studies, the best available evidence (prospective cohorts, level 1B, which had as their main objective the evaluation of obesity as a risk factor for VTE), demonstrated that obesity is associated with a higher risk of VTE in medical patients. The strength of the association shown on these studies is intermediate, RR around 3. Nevertheless, when there are other risk factors for VTE besides obesity, such as oral contraceptive use, the RR changes from 2 to 10.[12] Therefore, we conclude that obesity is indeed a risk factor for VTE that plays an adjuvant role on the development of VTE in medical patients.

VTE Prophylaxis for Obese Medical Patients

We found only four studies evaluating VTE prophylaxis in obese hospitalized medical patients (Table 3). Two of these studies evaluated medical patients in gen-

Table 1. Evaluation of evidence regarding obesity as a risk factor for VTE in medical patients

Author year	Study design	Patients, N	Evidence, RR or OR	Level of Evidence
Goldhaber[36] 1983	Prospective cohort	Ambulatory patients with PE confirmed by autopsy, 46/1,044	RR 2.0 for >40% excess weight in women.	1C
Cogo[8] 1994	Prospective cohort	Ambulatory patients with clinical suspicion of DVT, confirmed by venography	Most common risk factors surgery, immobility and trauma. Obesity was not independently associated with DVT.	1B
Goldhaber[15] 1997	Prospective cohort	Women ages 33 to 55 years-old, 112,822	RR 2.9 (95% CI 1.5 to 5.4) for BMI >29 kg/m^2.	1B
Blaszyk[10] 1999	Retrospective cohort	Autopsy series in 11 years with fatal cases of PE without predisposing factors and controls, 72	OR 12.4 (95% CI 3.8 to 40.0) for BMI >30 kg/m^2.	3B
Hansson[14] 1999	Prospective cohort	Men ≥50 years-old screened objectively for VTE, 855	RR 3.92 (95% CI 1999 2.10 to 7.29) for abdominal obesity.	1B 1B
Grady[7] 2000	Prospective cohort	Women ages 44 to 79 years-old, with BMI >27 kg/m^2 randomized for hormonal therapy or placebo, 1,543	RR 1.0 (95% CI 0.5 to 1.7) for BMI >27 kg/m^2.	
Heit[9] 2000	Ecologic case-control study	Patients with objectively confirmed VTE and controls, 1,250	BMI was not independently associated with TEV*. OR 0.98 (95% CI 0.98 to 1.00).	2C
Samama[11] 2000	Ecologic case-control study	Consecutive ambulatory patients, with objectively confirmed DVT and controls, 1,272	OR 2.39 (95% CI 1.48 to 3.87) for BMI ≥30 kg/m^2 in men and BMI >28.6 kg/m^2 in women.	2C
Tsai[13] 2002	Retrospective cohort	Ambulatory patients in 11 years, adjusted for age, gender and race, 19,293	OR for BMI 25-30, 30-35, 35-40 and ≥40 were 1.5; 2.2; 1.5 and 2.7, respectively (P<0.001).	2B
Abdollahi[12] 2003	Ecologic case-control study	Patients with objectively confirmed DVT and controls, 908	RR 2.0 (95% CI 1.5 to 3.4) for BMI >30 kg/m^2.	2C
Alikhan[6] 2004	Randomized controlled trial	Hospitalized obese medical patients >40 years-old, randomized for enoxaparin 40 mg/day or placebo, 866	RR 1.04 (95% CI 0.68 to 1.60) for BMI ≥30 kg/m^2 in men and BMI >28.6 kg/m^2 in women	2B

Incomplete data about height and weight of controls may have caused bias. BMI, body mass index; DVT, deep venous thrombosis; PE, pulmonary embolism.

eral, and are mentioned here because the other two studies that evaluate specifically obese patients were derived from them. The analysis of subgroups of the MEDENOX study (evidence level 1B for medical patients in general and 2B for obese patients)[16] showed that 40 mg of enoxaparin daily reduced the incidence of VTE in obese medical patients from 15.5% vs 7.5%, when compared with placebo. However, this difference did not reach statistical significance, probably because of the small number of obese patients. In the PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients) study,[17] which included 3,706 hospitalized medical patients randomized to receive dalteparin or placebo, 30% of patients had obesity as a risk factor. In this study, dalteparin 5,000 IU daily was effective as VTE prophylaxis, RR 0.55 (95% CI 0.38-0.80). The PREVENT study is another level 1B evidence for medical patients in general. On the analysis of subgroups of obese patients in this RCT, Kucher et al[18]

Table 2. Evaluation of evidence about obesity as a risk factor for VTE in bariatric patients

Author year	Study design	Patients, N	Evidence, RR or OR	Level of Evidence
Eriksson[19] 1977	Retrospective cohort	Patients undergoing bariatric surgery with prophylaxis, 328	Incidence of symptomatic DVT of 1.2% and of PE of 1.2% (0.3% fatal).	2B
Printen[22] 1978	Retrospective cohort	Patients undergoing bariatric surgery, 564	Incidence of symptomatic PE: 1.2% (0.7% fatal).	2B
Thompson[37]	Retrospective cohort	Patients undergoing bariatric surgery, 149	Incidence of symptomatic PE of zero.	2B
Mason[38] 1992	Prospective cohort	Registry of patients undergoing bariatric surgery, 3,174	Incidence of symptomatic DVT of 0.3% and of PE of 0.03%.	2B
Bajardi[20] 1993	Retrospective cohort	Patients undergoing bariatric surgery, 53	Incidence of symptomatic DVT of 1.6% and of PE of 3.2% (1.8% fatal).	3B
Sugerman[39] 2001	Prospective cohort	Patients undergoing bariatric surgery with and without peripheral vascular disease 1,918	Incidence of fatal VTE of 0.3%. RR 19.5 (95% CI 3.7 to 103.8) for obese with peripheral vascular disease.	1B
Melinek[26] 2002	Retrospective cohort	Autopsy series on patients undergoing bariatric surgery, 10	Incidence of fatal PE of 30% and microscopic evidence of PE in 80%.	1C
Westling[21] 2002	Prospective cohort	Patients undergoing bariatric surgery and screened with Doppler ultrasound on pre- and postoperative periods, 116	Incidence of DVT of 1.7% and of PE of 0.85%.	1B
Podnos[23] 2003	Systematic review	10 studies of laparoscopic bariatric surgery with 3,464 patients and 8 studies of open bariatric surgery with 2,771 patients	Incidence of symptomatic PE: 0.41% with laparoscopic bariatric surgery and 0.78% with open bariatric surgery	3A
Sapala[40] 2003	Retrospective cohort	Patients undergoing bariatric surgery, 5,554	Incidence of fatal PE of 0.21%. Prevalence of BMI ≥60 in 50%, of combination of BMI ≥60, chest obesity and OHS/OSA in 33% of cases	2B
Omalu[25] 2004	Prospective cohort	Registry of patients undergoing bariatric surgery, 3,097	Mortality of 0.5%: 13% due to PE.	2B
Carbajo[41] 2005	Retrospective cohort	Patients undergoing bariatric surgery, 209	Incidence of fatal PE of 0.5%.	3B

OHS/OSA, obesity hypoventilation syndrome related to obstructive sleep apnea; DVT, deep venous thrombosis; PE, pulmonary embolism.

demonstrated that the primary outcome occurred less often in the dalteparin group than in the placebo group (2.8% vs 4.3%, respectively), RR of 0.64 (95% CI 0.32-1.28). The efficacy of dalteparin as VTE prophylaxis receives evidence level 2B, because of the wide confidence interval found in this study.

Even though there are currently few studies evaluating the effectiveness and safety of prophylaxis in obese medical patients, we recommend that these patients be considered for pharmacological prophylaxis for VTE. No studies evaluating LDUH in standard or higher prophylactic doses in obese medical patients were found. The LMWH, enoxaparin (40 mg daily) and dalteparin (5,000 IU daily), should be considered as alternatives in obese patients hospitalized for acute medical illnesses (RECOMMENDATION B).

Table 3. Efficacy of VTE prophylaxis in obese patients

Author year	Study design	Patients, N	Evidence, RR or OR	Level of Evidence
Borow[27] 1991	Prospective study, non-controlled, non-randomized	General surgical patients receiving several methods of prophylaxis (e.g. SCD and LDUH) and controls, 500	Incidence of PE of 0.8% and of DVT higher in control group (37.3%) than with SCD (11.9%) or LDUH (26.9%).	2B
Samama[5] 1999	Randomized, controlled trial	Hospitalized medical patients >40 years-old, including 20% of obese patients randomized to enoxaparin 40 mg/day or placebo, 738	RR 0.37 (IC de 97.6% 0.22 to 0.63) with enoxaparin 40 mg/day. Major hemorrhage in 1.7% vs. 1.1% in the placebo group.	1B
Kalfarentzos[30] 2001	Randomized, controlled trial	Patients undergoing bariatric surgery, randomized to 5,700 IU or 9,500 IU of nadroparin, 60	Incidence of DVT equal to zero in both groups receiving nadroparin. Major hemorrhage in 6.7% in the group receiving higher dose of nadroparin.	2B
Scholten[29] 2002	Prospective study, non-controlled	Patients undergoing bariatric surgery receiving prophylaxis with 30mg 12-12h or 40 mg 12-12h of enoxaparin, 481	Incidence of symptomatic VTE of 5.4% with enoxaparin 30mg 12-12h, and of 0.6% with 40mg12-12h. Major hemorrhage in 1.0% and 0.25% in the two groups of enoxaparin, respectively.	2B
Gonzalez[28] 2004	Prospective study, non-controlled	Patients undergoing bariatric surgery with SCD, 380	Incidence of symptomatic DVT of 0.26%.	2B
Alikhan[16] 2003	Randomized, controlled trial	Hospitalized obese medical patients >40 years-old, randomized to enoxaparin 40 mg/day or placebo, 866	RR 0.49 (95% CI 0.18 to 1.36) with enoxaparin 40 mg/day.	2B
Shepherd[32] 2003	Prospective study non-controlled	Patients undergoing bariatric surgery receiving prophylaxis with continuous intravenous UH (anti-factor Xa heparin activity levels of 0.11-0.25 units/mL) during the perioperative period, 700	Incidence of objectively confirmed, symptomatic PE of 0.4%, and no episodes of DVT. Postoperative hemorrhage in 2.3%; requiring transfusions in 1.0%.	2B
Miller[31] 2004	Single center retrospective cohort	Patients undergoing bariatric surgery receiving prophylaxis with LDUH 5,000 IU or 7,500 IU 8-8h, 255	Overall incidence of VTE of 1.2%. Postoperative hemorrhage in 2.4%.	2C
Shepherd[34] 2004	Prospective study, non-controlled	Patients undergoing bariatric surgery receiving prophylaxis with continuous intravenous UH (anti-factor Xa activity 0.15-0.20 units/mL) during the perioperative period, 19	No events of objectively confirmed, symptomatic VTE. Major hemorrhage in 10.5%.	2B
Leizorovicz[17] 2004	Randomized, controlled trial	Hospitalized medical patients >40 years-old, including 30% of obese patients randomized to dalteparin 5.000 IU/day or placebo, 3.706	RR 0.55 (95% CI 0.38 to 0.80) with dalteparin 5.000 IU/day. Major hemorrhage in 0.49% vs. 0.16% in the placebo group.	1B

Table 3 continued

Author year	Study design	Patients, N	Evidence, RR or OR	Level of Evidence
Kucher[18] 2005	Randomized, controlled trial	Hospitalized obese medical patients >40 years-old, randomized to dalteparin 5.000 IU/day or placebo, 1118	RR 0.64 (95% CI 0.32 to 1.28) with dalteparin 5.000 IU/day. Major hemorrhage in 0% vs. 0.7% in the placebo group.	2B
Hamad[42] 2005	Multicentric retrospective cohort	Patients undergoing bariatric surgery receiving prophylaxis with enoxaparin 30mg (daily or 12-12h) or 40mg (daily or 12-12h) or no prophylaxis, 668	Overall incidence of objectively confirmed, symptomatic PE of 0.9%, and DVT of 0.1%; highest incidence without prophylaxis. Major hemorrhage in 0.9%.	2C
Quebbemann[33]	Prospective study, non-controlled	Patients undergoing bariatric surgery receiving prophylaxis with continuous intravenous UH at 400 U/h from the preoperative period until discharge, 822	Overall incidence of objectively confirmed, symptomatic VTE of 0.1%. Major hemorrhage in 1.3%.	2B

SCD, sequential compression devices; LDUH, low dose unfractionated heparin; UH, unfractionated heparin; DVT, deep venous thrombosis; PE, pulmonary embolism.

Bariatric Surgical Patients

Bariatric surgery is indicated for the treatment of obese individuals with BMI >40 kg/m^2 or >35 kg/m^2, when associated with failure of medical therapy for at least two consecutive years and at least two co-morbities. We found several studies (1 study 1B; 1 study 1C, 6 studies 2B; 1 study 3A and 2 studies 3B) that support the association between VTE and bariatric surgery, and only two that dispute this association (one study 1B and one study 2B). In patients undergoing bariatric surgery, the incidence of DVT and PE varies from 1.2 to 1.6%[19-21] and from 0.8 to 3.2%,[19-23] respectively, depending on the method of detection of VTE used. A retrospective cohort study showed that bariatric patients had a mean of 3.4 risk factors (2-7) for the development of VTE.[24]

One of the studies that question the association between VTE and obesity was a retrospective cohort with 149 patients undergoing bariatric surgery and that had no episode of clinically relevant VTE. The study by Westling et al[21] was a prospective cohort of 116 patients undergoing bariatric surgery who were examined by Doppler ultrasound for the presence of DVT pre- and postoperatively. This study showed that the prevalence of DVT detected by Doppler ultrasound was relatively low (1.7%). However, in this cohort, all patients received some form of VTE prophylaxis: 500 ml of dextran 70 perioperatively (n = 100), enoxaparin (n = 10) or a combination of the two (n = 6). The authors cite a metanalysis of 15 cohort studies with 5,598 bariatric patients (Holmes NJ, 1994), which reportedly showed incidences of clinically apparent DVT varying from 0.5% to 6.0%, of PE from 0.2% to 3.0% and of fatal PE from 0.2% to 1.4%. However, this reference was not found as a published study in any indexed journal. Nevertheless, the incidences mentioned in this report are not too low when considering that clinical signs and symptoms of VTE have low sensitivity for its detection, and that in half of these studies patients received prophylaxis for VTE.

In a registry with 3,097 patients who underwent bariatric surgery, 15 patients died within 6 months of surgery; 80% of the deaths were related to co-morbidities of obesity, and PE was the cause of death in 13%.[25] In a series of 10 autopsies following bariatric surgery, PE was the cause of death in 30% and 8 patients had microscopic evidence of PE despite the use of prophylaxis.[26] Therefore, based on all the evidence found, we conclude that obese patients undergoing bariatric procedures have indeed an increased risk for VTE that exceeds the risk due to the surgical procedure alone.

VTE Prophylaxis for Bariatric Surgical Patients

The efficacy of VTE prophylaxis specifically in obese surgical patients has been studied in few prospective studies (Table 3). We found only one prospective study that compared several methods of prophylaxis in obese surgical patients in general, but that had some methodological flaws, such as non-randomization, the use of variable methods for detection of DVT and the number of thromboses per limb (instead of the of thrombosis per patient) as the unit of analysis.[27] In this study, Borow et al[27] evaluated five prophylactic methods for VTE in the post-operative period and compared the results with a control group. The incidence of DVT in the control group (37.3%) was significantly higher than in the study groups. Surprisingly, among the study groups, the highest incidence of DVT was in the group receiving LDUH (26.9%); however, the dose of LDUH used was low and there was a high rate of bilateral thromboses. Sequential compression devices (SCD) resulted in the lowest incidence of thrombosis (11.9%) among the study groups. In this study, obesity was found to be an independent risk factor for DVT in surgical patients in general.

We found eight studies (6 level 2B and 2 level 2C) about the utilization of VTE prophylaxis specifically in bariatric patients. Gonzalez et al[28] evaluated clinically 380 patients undergoing bariatric surgery for the presence of DVT while using prophylaxis with SCD. They report a low incidence of clinically apparent VTE: nine patients had venous insufficiency preoperatively, one patient developed DVT (0.26%) and none developed symptomatic PE. It is worth noting that the clinical diagnosis of DVT has low sensitivity, particularly in obese patients. In a retrospective cohort study, 668 patients who underwent bariatric surgery at 5 centers received enoxaparin preoperatively or postoperatively (30 mg or 40 mg daily or every 12 hours), or upon discharge (30 mg daily for 10 days). There were 6 (0.9%) objectively diagnosed cases of PE, 1 (0.1%) DVT and 6 (0.9%) severe bleeding complications. The authors mention that the highest incidence of VTE was at the center where patients did not receive perioperative thromboprophylaxis (3 VTE).

In a prospective cohort of obese patients undergoing bariatric operations, two prophylactic regimens of LMWH were evaluated in sequence: enoxaparin 30 mg twice daily in 90 patients and 40 mg twice a daily in the next 389 patients.[29] The incidence of DVT was significantly lower in patients taking enoxaparin 40 mg twice daily than in those taking 30 mg twice daily (0.6% vs 5.4%, $P<0.01$), and there was one hemorrhagic event in each group. Although the superiority of one regimen of enoxaparin over the other is suggested by this historic cohort, these results must be confirmed by prospective randomized trials.

Kalfarentzos et al[30] evaluated in a small RCT the effect of two regimens of nadroparin for prophylaxis in 60 patients with BMI >36 kg/m^2 undergoing bariatric surgery. Regimens of 0.6 ml (5,700 IU) or 1 ml (9,500 IU) daily of nadroparin were given, and there was no thrombotic event in the postoperative period in either group. Nevertheless, two major hemorrhagic events were observed in the higher dose group.

Four studies evaluated unfractionated heparin for VTE prophylaxis in bariatric patients. A single center retrospective study reported the use of subcutaneous LDUH, 5,000 IU or 7,500 IU preoperatively and every 8 hours thereafter, during hospitalization in 255 morbidly obese patients undergoing bariatric operations. SCD were also utilized during and after surgery, and early ambulation was enforced. The overall incidence of VTE after 30 days of follow-up was 1.2% and the incidence of postoperative bleeding was 2.4%.[31] In one study, 700 patients undergoing laparoscopic Roux-en-Y gastric bypass were given intravenous unfractionated heparin the day before gastric bypass surgery and during the operation, according to an infusion protocol to achieve a subtherapeutic peak anti-factor Xa heparin activity levels of 0.11 to 0.25 units/mL. No patients were diagnosed with a DVT, but three (0.4%) had non-fatal PE. Bleeding occurred in 2.3% of patients; half required blood transfusions and 0.6% had minor wound hematomas.[32] One study evaluated the incidence of clinically significant VTE and bleeding events in 822 consecutive patients undergoing bariatric procedures after continuous infusion of intravenous unfractionated heparin at 400 U/h (9,600 U/day) starting in the preoperative period and maintained until discharge. There was only one (0.12%) clinically evident thromboembolic event in the entire cohort. Bleeding requiring transfusion occurred in 1.3% of patients, but in 5% of patients,

heparin therapy was terminated or temporarily held due to acute drop in hematocrit.[33]

In the study by Shepherd et al,[34] 19 obese patients with additional risk factors for VTE were given intravenous unfractionated heparin the day before gastric bypass surgery and during the procedure, according to an infusion protocol that used a target prophylactic anti-factor Xa activity range of 0.15 to 0.20 units/mL. There were no DVT events. However, 11% of patients experienced perioperative hemorrhagic complications in spite of anti-factor Xa activity levels in the targeted range. Although the regimens of VTE prophylaxis using intravenous unfractionated heparin were associated with a low incidence of thromboembolic events, they seemed to be associated with a higher bleeding rate than the other thromboprophylactic regimens.

Prophylaxis must be employed in obese surgical patients once they have increased risk of VTE due to both the surgical procedure and the obesity. However, the limited number of prospective, controlled studies comparing different regimens of prophylaxis, allows us to conclude only that mechanical methods of prophylaxis, such as SCD, LDUH (5,000 IU or 7,500 IU 8-8 h) and the LMWH, enoxaparin (30 mg 12-12 h and 40 mg daily or 12-12 h) and nadroparin (5,700 IU daily), have been used in obese patients. These regimens seem safe and could be considered as alternatives for VTE prophylaxis in obese patients hospitalized for bariatric procedures (RECOMMENDATION B).

Discussion

During the last decades, obesity has reached epidemic proportions all over the world. In the United States, >50% of adults are above the ideal body weight, leading to a prevalence of obesity of 20 to 25%. Because overweight has been considered a potential risk factor for thrombosis, obesity can, consequently, have a considerable impact on the global incidence of VTE. Thus, the estimation of VTE risk based on the recognition of risk factors, including obesity, is crucially important for the adequacy of VTE prophylaxis utilization by medical practitioners. In a survey performed among surgical residents, it was found that although obesity, cancer, immobility and previous history of VTE were usually recognized by the residents as important risk factors for VTE, the low recognition of other important factors such as age >40 years-old, lupus anticoagulant, factor V Leiden, acute myocardial infarction and varices were association with inadequate utilization of prophylaxis.[35] One of the primary objectives of this study was to systematically review the supporting evidence about obesity as a risk factor for VTE, and estimate the strength of the association between this condition and VTE, according to the level of scientific evidence. The next step was to study the existing evidence about the efficacy of VTE prophylaxis in obese medical and bariatric patients.

The consideration of obesity as a risk factor for VTE still elicits much discussion. One of the reasons for this is that the definition of obesity, currently accepted as BMI $\geq$30 kg/m^2, is not adopted by all authors. Nevertheless, several studies discuss the topic directly or indirectly and were critically considered in this review. After evaluating all the evidence, we conclude that obesity is indeed a risk factor for VTE in medical patients, as well as in patients undergoing bariatric surgery. Although the risk of VTE attributable to obesity does not appear very high when present alone, obesity seems to be an important adjuvant for the development of VTE in patients with other risk factors, such as patients hospitalized due to acute medical illnesses, patients with reduced mobility, with central venous catheters and those undergoing surgical procedures.

In regards to prophylaxis, we did not find studies supporting level A recommendations for any of the methods of VTE prophylaxis for obese medical or surgical patients. Nevertheless, the use of some form of prophylaxis for obese patients, both medical and surgical, is necessary. There have been suggestions that bariatric patients may have higher risk of VTE than other surgical patients in general. Accordingly, the majority of bariatric surgeons routinely prescribe some form of VTE prophylaxis in the perioperative period, and in many cases, a combination of prophylactic measures, such as preoperative hemodilution and subcutaneous heparin, elastic bandages or SCD for the lower extremities during the procedure, and incentive to early postoperative ambulation.[20] However, the limited number and quality of prospective studies comparing different methods and regimens of VTE prophylaxis (mechanical or pharmaco-

logical) in obese patients, does not allow a definition about a prophylactic regimen that is more effective and safer than the others. Although there are recommendations for continuing pharmacological VTE prophylaxis for acutely ill medical patients for at least 10 ± 4 days, even after hospital discharge, the ideal duration of prophylaxis for bariatric patients is not yet known. Therefore, given the high prevalence of obesity in our society and the risk of VTE associated with it, prospective, controlled trials to investigate ideal regimens of VTE prophylaxis in obese patients are still highly warranted.

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