Plasma Levels of Free Thyroxine and Risk of Major Bleeding in Bariatric Surgery

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Key Words

Thyroid function · Thyroxine · Thyroid tests · Thyroid hormone · Surgery · Obesity

Abstract

Background: In a recent study of patients using vitamin K antagonists, those with low free thyroxine (FT₄) levels within the normal range had a 3- to 5-fold increased risk of major bleeding. We tested the hypothesis that low levels of preoperative FT₄ within the reference range are associated with an increased risk of major bleeding during and after bariatric surgery. **Methods:** The charts of 2,872 consecutive patients undergoing bariatric surgery were retrospectively screened for bleeding episodes. Patients with major bleeding until 1 month after surgery were compared to randomly selected control patients without bleeding, in a ratio of 1:4. We evaluated the association between preoperative FT₄ levels and the risk of major bleeding by logistic regression. **Results:** Seventy-two cases (2.5%) with major bleeding were identified and 288 controls were selected. The median plasma level of FT₄ was 13 pmol/l (interquartile range: 12–14) in the cases as well as in the controls. No clear effect was observed

of low levels of FT₄ on the risk of major bleeding: odds ratio 1.48 (95% CI: 0.46–4.80) for patients with an FT₄ level <11 pmol/l, 1.03 (0.49–2.18) for patients with an FT₄ level <12 pmol/l, and 1.12 (0.65–1.94) for patients with an FT₄ level <13 pmol/l as compared to patients with FT₄ values greater than or equal to these cutoff levels. **Interpretation:** We did not observe an increased risk of major bleeding with low levels of FT₄ in patients undergoing bariatric surgery.

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Introduction

Thyroid hormone affects metabolism in virtually every organ system. Several studies have indicated that thyroid hormone also influences the hemostatic balance and that these changes are associated with a risk of venous thromboembolism (VTE) or bleeding. Higher plasma levels of free thyroxine (FT₄) have been associated with an increased VTE risk [1–3]. Conversely, lower levels of FT₄ seem to be associated with a bleeding tendency [4, 5]. An observational cohort study of consecutive hypothyroid

patients showed a high prevalence of acquired von Willebrand syndrome [6]. In a case-control study in subjects using vitamin K antagonist (VKA) treatment, patients with an FT₄ level within the lower part of the reference range had an increased risk of major bleeding compared to those with higher FT₄ levels, suggesting that FT₄ levels play a role in the etiology of major bleeding in VKA users.

Bleeding is one of the major short-term complications after bariatric surgery (weight loss surgery). The Medical Center Slotervaart is a referral center for bariatric surgery in the Netherlands. In the majority of patients, a Roux-en-Y gastric bypass is performed. This population is homogenous and the number of operations each year is considerable. In all patients undergoing preoperative screening for bariatric surgery, plasma FT₄ and thyroid-stimulating hormone (TSH) are measured. From previous work, we know that more than 2% of these patients experience major bleeding after bariatric surgery (unpubl. data). Given the earlier literature on increased risk of major bleeding in patients with FT₄ levels within the lower part of the reference range, we hypothesized that lower levels of preoperative FT₄ are also associated with an increased risk of major bleeding after bariatric surgery. This may help to identify patients before surgery who may benefit from extra monitoring during and after surgery.

Methods

Study Design

A case-control study was performed on the association between plasma levels of FT₄ before surgery and the risk of major bleeding within 1 month after bariatric surgery. All consecutive patients who underwent bariatric surgery at the Medical Center Slotervaart between August 2012 and October 2015 were screened for the occurrence of major bleeding until 1 month after bariatric surgery (cases) by one independent investigator (either H.A.B. or M.I.M.). In case of uncertainty, the adjudication was performed by a second investigator (L.P.B.E.), and in case of disagreement, a third investigator (H.R.B.) was consulted to resolve this by discussion. For all patients with major bleeding, general characteristics, information on bariatric surgery, and laboratory values including levels of FT₄ and TSH were documented in a standardized case record form. From the remaining patients without major bleeding, control patients who had surgery within the same year were randomly selected in a ratio of 1:4. For the control patients, the same case record form was completed. The Ethics Committee of Medical Center Slotervaart and Reade reviewed this study and determined, based on the Dutch Medical Research Involving Human Subjects Act, that these research activities did not require METC approval.

Study Population

Inclusion criteria were: ≥ 18 years of age at the time of bariatric surgery and laparoscopic or open bariatric surgery [gastric bypass,

sleeve gastrectomy, revisional procedures (redo) or another similar operation]. Cases and controls who fulfilled one of the following criteria were excluded: when only a gastric band was removed, deviation from the standard local protocol for thromboprophylaxis (Clexane 40 mg s.c. at around 5:00 pm postoperatively on the day of operation, Clexane 40 mg twice daily subcutaneously from day +1 until 2 weeks after the operation), VKA treatment, liver cirrhosis, hemophilia A or B, acquired or congenital von Willebrand disease, unstable thyroid disease defined as the need for change of thyroid medication during the 12 months before surgery (stable thyroid disease was included), and the use of dual platelet aggregation inhibitors until the moment of surgery. Patients for whom markers of thyroid function (FT₄ and TSH) before bariatric surgery were not available were also excluded. In case a control patient met any of the exclusion criteria, we randomly selected another control patient.

Outcome Measures

Major bleeding was defined according to the ISTH criteria regarding surgical procedures (details provided in online suppl. material, see www.karger.com/doi/10.1159/000446431) [7].

Data Collection

Medical charts from included cases and controls were reviewed by one investigator. The following data assessed during the first visit for bariatric surgery were documented for all cases and controls: date of birth, sex, length, weight, BMI, intoxications, medical history specifically for thyroid disease (hypothyroidism or hyperthyroidism, current treatment, stability of disease), former bleeding and obesity-associated comorbidities (diabetes, hypertension, dyslipidemia, obstructive sleep apnea), presence of other established risk factors for bleeding (heart failure, renal insufficiency, bleeding disorder, prior abdominal surgery, and use of anticoagulation or nonsteroidal anti-inflammatory drugs before surgery) (definitions are provided in the online suppl. material). The following data concerning the bariatric surgery was documented: age at time of bariatric surgery, initial type of bariatric surgery, open or laparoscopic surgery, extra interventions during bariatric surgery (cholecystectomy, splenectomy or other), and data about bleeding complications (type of bleeding, time of bleeding, decrease in hemoglobin, blood transfusion, hemodynamic instability, longer admission or readmissions, admission to medium or intensive care, and reinterventions because of the bleeding). The type of bleeding was categorized as follows: gastrointestinal bleeding, intra-abdominal bleeding, or hematomas from the abdominal layers in combination with extensive outside wound bleedings. In case of symptoms of multiple types of bleeding, we registered the most evident type of bleeding.

Statistical Analysis

Data of continuous variables are summarized using medians and interquartile ranges (IQRs). Data for qualitative variables are presented as proportions (n and %). Odds ratios (ORs) and 95% CI for the risk of major bleeding were calculated with the use of binary logistic regression, using the following cutoff levels: <11 , <12 , <13 , <14 , and <15 pmol/l. To study the effect of different levels of FT₄ on bleeding risk, we contrasted individuals with levels below the cutoff with those with levels equal to or higher than the cutoff level. A multivariable model was used to adjust for age, BMI, or the use of any platelet aggregation inhibitor as possible confounding

Fig. 1. Flowchart of selection of patients for this study. PAI = Platelet aggregation inhibitor.

factors. These analyses were performed for all major bleedings (definite and possible) and also solely for the definite major bleedings. A sensitivity analysis was performed excluding the patients using levothyroxine. Statistical analysis was performed with the use of SPSS 21 software package (SPSS Inc., Chicago, Ill., USA).

Results

Patients

We screened all 2,872 patients amongst whom 72 patients (2.5%) with major bleeding were identified (cases) and 288 control patients were selected. The reasons for exclusion of cases and controls are depicted in figure 1. Of the 72 patients with major bleeding, 58 had a definite major bleeding, and in 14 patients the bleeding was classified as possible. All major bleedings were surgical site bleedings. The characteristics of the cases and controls are summarized in table 1. The prevalence of heart failure, renal insufficiency, bleeding disorder, prior VTE, and myocardial infarction was $\leq 5\%$ in both groups. Five cases (7%) had a history of ischemic stroke compared to 3 controls (1%). The frequency of any former bleeding,

prior abdominal surgery and usage of NSAIDs did not differ between the cases and the controls. Fifteen cases (21%) used one platelet aggregation inhibitor compared to 13 controls (5%). All patients with a medical history of hypothyroidism used levothyroxine [5 cases (7%) and 15 controls (5%)]. The laparoscopic procedure had to be converted to open surgery in 2 patients with major bleeding (2.8%) and in 1 control (0.3%).

Levels of FT_4 and the Risk of Major Bleeding

The median (IQR) time between FT_4 measurement and bariatric surgery was 3 months (2–5). The median (IQR) FT_4 level was 13 pmol/l (12–14) for both cases and controls (reference values: 9–19 pmol/l). The median (IQR) TSH level was 1.74 mU/l (1.18–2.21) in the cases and 1.89 mU/l (1.38–2.63) in the control patients. Table 2 provides a description of the types of major bleeding events. ORs (95% CI) for developing major bleeding within 1 month after bariatric surgery for different cutoff values of FT_4 are shown in table 3. For patients with an FT_4 level < 11 pmol/l, the crude OR (95% CI) for developing major bleeding was 1.48 (0.46–4.80) compared with patients with higher FT_4

Table 1. Characteristics of patients

Parameter	Patients with major bleeding (n = 72)	Controls (n = 288)
Age, years	48 (41–54)	44 (36–51)
Male	19 (26)	51 (18)
BMI, kg/m ²	41 (38–45)	42 (40–46)
Currently smoking	8 (11)	47 (16)
Medical history		
Hypothyroidism	5 (7)	15 (5)
Hyperthyroidism	–	–
Diabetes	21 (29)	52 (18)
Hypertension	46 (64)	113 (39)
OSA	7 (10)	27 (9)
PT, s	10.5 (10.2–11.0)	10.4 (10.1–10.7)
aPTT, s	26.5 (25.3–27.9)	25.9 (24.4–27.3)
Platelets, ×10 ⁹ /l	265 (238–308)	282 (241–328)
Type of bariatric surgery		
Gastric bypass	59 (82)	257 (89)
Sleeve gastrectomy	2 (3)	7 (2)
Redo	10 (14)	23 (8)
Other	1 (1.4)	1 (0.3)

Data are expressed as medians (IQR) or n (%). OSA = Obstructive sleep apnea; PT = prothrombin time; aPTT = activated partial thromboplastin time.

Table 2. Major bleeding events

Type of bleeding	Definite major bleeding (n = 58)	Possible major bleeding (n = 14)
Gastrointestinal	25 (43)	4 (29)
Intra-abdominal	22 (38)	2 (14)
Hematoma	7 (12)	2 (14)
Wound bleeding	1 (2)	1 (7)
Unknown	3 (5)	5 (36)

Data are expressed as n (%). Major bleeding events were defined as unknown if there were physical signs or symptoms in combination with a fall in hemoglobin level at least of 20 g/l (1.24 mmol/l) and/or hemodynamic instability highly suggestive for bleeding, but no evident bleeding was visualized.

levels. For all other cutoff values, the ORs were approximately 1 (ORs ranging from 0.95 to 1.12). Restricted analyses for definite major bleeding and adjustment for age, BMI, or the use of any platelet aggregation inhibitor did not materially change the results. Excluding patients using levothyroxine also did not change the results (data not shown).

Discussion

Although an effect of FT₄ levels <11 pmol/l cannot be excluded, we can conclude that low levels of FT₄ within the reference ranges do not seem to be a risk factor for developing major bleeding within 1 month after bariatric surgery.

Previous literature suggests that not only hypothyroidism leads to an increased risk of bleeding, but also lower levels of FT₄ within the reference range. An observational cohort study of consecutive hypothyroid patients showed a high prevalence of acquired von Willebrand syndrome [6]. In a recent case-control study in subjects using VKA treatment, patients with an FT₄ level within the lower part of the reference range (cutoff of 13 or 14 pmol/l) had a 3- to 5-fold increased risk of major bleeding compared to those with higher FT₄ levels [8].

There are several potential explanations for the differences observed in our current study and the study in patients using VKA treatment. First, both populations are clearly different: our study population was younger (median age of 48 and 44 years versus 66.5 and 70.9 years in the cases and the controls, respectively) and most importantly, all patients were on VKAs while we excluded patients on VKAs. Furthermore, our study population consisted of patients with obesity that is associated with hypercoagulability and an increased VTE risk [9]. All major bleeding events were attributed to a surgical procedure in contrast to the (mainly) spontaneous bleeding events in patients on VKAs. Second, an explanation for the increased risk of major bleeding in the study of Debeij et al. [8] could be that lower levels of FT₄ influence VKA stability, which was observed in a pilot study [10]. However, the same study observed that patients with subclinical hypothyroidism had a diminished sensitivity for VKAs, which would make them less prone to bleeding. The literature on overt hypothyroidism also argues against this explanation since overt hypothyroidism seems to diminish the effect of VKAs by decreasing the clearance of coagulation factors [11].

In the present study, 21% of the cases used one platelet aggregation inhibitor compared to 5% of the controls. Since in the literature it was suggested that the use of platelet aggregation inhibitors could influence FT₄ levels [12], we also performed our analyses with the use of any platelet aggregation inhibitor added to the model. However, this did not change our results.

There are several limitations to this case-control study. The relatively low values of FT₄ in the population undergoing bariatric surgery are striking [median (IQR): 13

Table 3. Risk of major bleeding in patients undergoing bariatric surgery with different levels of FT₄

	Bleeding events/patients	Controls	Crude OR (95% CI)	OR (95% CI) adjusted for age	OR (95% CI) adjusted for BMI	OR (95% CI) adjusted for any PAI
<i>All major FT₄ cutoff</i>						
<11 pmol/l	4/68	11/277	1.48 (0.46–4.80)	1.41 (0.43–4.64)	1.52 (0.47–4.93)	1.15 (0.33–4.03)
<12 pmol/l	10/62	39/249	1.03 (0.49–2.18)	1.04 (0.49–2.22)	1.00 (0.47–2.11)	0.91 (0.42–2.00)
<13 pmol/l	24/48	89/199	1.12 (0.65–1.94)	1.21 (0.69–2.12)	1.13 (0.65–1.97)	1.09 (0.61–1.92)
<14 pmol/l	37/35	152/136	0.95 (0.56–1.59)	1.01 (0.60–1.71)	0.94 (0.56–1.59)	0.94 (0.55–1.59)
<15 pmol/l	56/16	222/66	1.04 (0.56–1.93)	1.05 (0.56–1.97)	1.03 (0.55–1.91)	0.99 (0.52–1.87)
<i>Definite major FT₄ cutoff</i>						
<11 pmol/l	4/54	11/277	1.87 (0.57–6.08)	1.78 (0.54–5.87)	1.90 (0.58–6.19)	1.45 (0.41–5.10)
<12 pmol/l	8/50	39/249	1.02 (0.45–2.32)	1.03 (0.45–2.35)	1.00 (0.44–2.27)	0.93 (0.40–2.17)
<13 pmol/l	18/40	89/199	1.01 (0.55–1.85)	1.08 (0.58–2.00)	1.01 (0.55–1.87)	1.00 (0.53–1.87)
<14 pmol/l	29/29	152/136	0.90 (0.51–1.57)	0.94 (0.53–1.67)	0.89 (0.51–1.57)	0.89 (0.50–1.59)
<15 pmol/l	43/15	222/66	0.85 (0.45–1.63)	0.87 (0.45–1.67)	0.84 (0.44–1.61)	0.82 (0.42–1.59)

The reference group is the group equal to or higher than the cutoff value for the lower-than cutoffs. PAI = Platelet aggregation inhibitor.

(12–14) pmol/l in both cases and controls]. The median FT₄ level in the study of Debeij et al. [8] was 17.7 pmol/l, and in the MEGA Study [1], which was a large case-control study investigating risk factors for VTE, the median FT₄ level was 16.6 pmol/l in the controls. The literature about the association between (morbid) obesity and levels of FT₄ is limited, but it seems that lower levels of FT₄ are associated with higher BMI, suggesting that thyroid function (also within the normal range) could be one of several factors acting in concert to determine body weight in a population [13, 14]. If low levels of FT₄ within the reference ranges influenced bleeding risk, this would result in a higher bleeding risk for the entire population in our study, which consisted of patients who were (morbidly) obese. Another prominent finding in our study is the small IQR of the rounded FT₄ levels in both the cases and controls, which hindered the possibility to perform an analysis in as many categories under the 50th percentile of FT₄ as was performed in the study by Debeij et al. [8]. An explanation for the lack of an observed association between FT₄ and major bleeding could be, in addition to the relatively low values of FT₄, the presence of other stronger risk factors such as the use of a platelet aggregation inhibitor. Nevertheless, the results of this study cannot be generalized to other patient populations, e.g. lean subjects. Another limitation of this study is the adjudication of the major bleeding events due to the inconclusive

definition of major bleeding according to the ISTH criteria regarding surgical procedures (details provided in online suppl. material) [7]. As a result, 19% of all major bleeding events were adjudicated as possible major bleeding. However, the results of the analyses in all major bleeding events are in accordance with the analyses in solely the definite major bleeding events. Because of the study size, the confidence intervals presented were relatively wide and therefore we cannot exclude a small effect for patients with a FT₄ <11 pmol/l. However, for the other cutoff values, the power of the study is sufficient to rule out a strongly increased risk of major bleeding. It could be argued that the level of FT₄ at the time of screening for bariatric surgery is not representative for the FT₄ level at the time of the surgery itself and the moment of the occurrence of major bleeding. The patients underwent surgery after a median of 3 months after screening for bariatric surgery and thus the measurement of FT₄. Levels of FT₄, however, are stable over time [15, 16]. Furthermore, such misclassification would be random and lead to an underestimation of the risk.

In conclusion, this study shows that in patients undergoing bariatric surgery, lower levels of FT₄ are not associated with an increased risk of major bleeding. We cannot exclude a small effect for patients with a FT₄ <11 pmol/l. This study also points out the relatively low levels of FT₄ in obese subjects undergoing bariatric surgery. For future

research, the clinical relevance of low levels of FT₄ within the reference range could be of interest in other (surgical) patient populations. In addition, further investigation could determine whether FT₄ levels contribute to the prediction of major bleeding in prediction models.

Disclosure Statement

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