Lowering blood glucose during hip surgery does not influence coagulation activation

Marjolein K. Sechterberger [a,*], Jeroen Hermanides [b], Rudolf W. Poolman [c], Jasper E. Kal [d], Joost C.M. Meijers [e,f], Joost B.L. Hoekstra [a], J. Hans DeVries [a]

[a] Dept of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands
[b] Dept of Anaesthesiology, Academic Medical Center, Amsterdam, The Netherlands
[c] Dept of Orthopaedic Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[d] Dept of Anaesthesiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
[e] Dept of Experimental Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
[f] Dept of Plasma Proteins, Sanquin Research, Amsterdam, The Netherlands

ARTICLE INFO

ABSTRACT

Background: Hyperglycaemia during and after hip surgery is associated with coagulation activation and an increased risk of venous thromboembolism. Whether lowering of glucose levels during hip surgery diminishes coagulation activation is unknown. We investigated the efficacy of the human GLP-1 analogue liraglutide to lower glucose during and after hip surgery and studied its influence on coagulation activation.
Methods: A total of 37 obese subjects who underwent hip surgery were randomized to subcutaneous liraglutide or placebo for 4 consecutive days, starting one day prior to surgery. Glucose levels and coagulation indices at three fixed time-points (pre-operative, 2 h post-operative and 3 days post-operative) were measured.
Results: Liraglutide reduced glucose at day three post-surgery (median glucose (IQR) liraglutide 5.5 (5.2–5.7) vs. placebo 5.8 (5.5–6.2); difference 0.3 mmol/L, $P = 0.04$). Changes in 6 out of 8 coagulation indices studied did not differ between the two groups. Only D-dimer levels were significantly lower in the liraglutide group at day three post-surgery and FVIII levels were significantly higher in the liraglutide group 2 h post-surgery.
Conclusion: Although the human GLP-1 analogue liraglutide moderately reduced post-operative blood glucose levels in non-diabetic and prediabetic obese patients undergoing elective hip surgery, no changes were observed with respect to coagulation activation.

1. Introduction

Patients undergoing hip surgery have a risk to develop postoperative venous thromboembolism (VTE). It is estimated that symptomatic VTE occurs in approximately 0.5 to 2.0% of patients, even if adequate thromboprophylaxis is provided [1,2]. While the procedure-related tissue damage is the major activator of coagulation, several risk factors, such as postoperative immobilization, increasing age and high body mass index, have been associated with a higher incidence of VTE [3]. In addition, we have recently shown that post-surgical 'stress-induced' hyperglycaemia in patients undergoing elective hip surgery is associated with an increased risk for symptomatic VTE, independent of diabetes mellitus and other confounders [4].

That surgery itself can precipitate acute hyperglycaemia, or 'stress hyperglycaemia', is well known and appears to be due to alteration of endogenous hormone production and metabolites [5]. Growing evidence supports the hypothesis that 'stress hyperglycaemia' leads to a hypercoagulable and hypofibrinolytic state [6]. In experimental settings as well as in patients with diabetes, hyperglycaemia contributes to coagulation activation and downregulation of fibrinolytic activity, as demonstrated by increased levels of several procoagulant factors, such as thrombin–antithrombin (TAT) complexes, soluble tissue factor, fibrinogen, von Willebrand (vWF), factor VII, factor VIII and decreased levels of antifibrinolytic factors (plasminogen activator inhibitor-1 (PAI-1)) [7–9]. Moreover, hip surgery in patients without diabetes mellitus has been shown to induce hyperglycaemia peaking the days after the procedure, which was followed by a rise of factor VIII, vWF and prothrombin fragment 1 + 2 (F1 + 2) [10].

In diabetic patients, the effect of hyperglycaemia on coagulation seems to be modifiable, as improvement of glycaemic control among

* Corresponding author at: Department of Internal Medicine, F4-257, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5663637; fax: +31 20 56914904.
E-mail addresses: m.k.sechterberger@amc.uva.nl (M.K. Sechterberger), j.hermanides@amc.uva.nl (J. Hermanides), r.w.poolman@olvg.nl (R.W. Poolman), j.e.kal@olvg.nl (J.E. Kal), j.c.meijers@amc.uva.nl (J.C.M. Meijers), j.b.hoekstra@amc.uva.nl (J.B.L. Hoekstra), j.h.devries@amc.uva.nl (J. Hans DeVries).

these patients led to downregulation of coagulation activation [11,12]. Whether establishing glycaemic control during hip surgery will influence the coagulation activation is unknown.

Insulin therapy is the most widely used method to induce glycaemic control. However, insulin therapy is time consuming and is accompanied by an increased risk of hypoglycaemia, which is related to serious morbidity [13]. The human glucagon-like peptide-1 (GLP-1) analogue liraglutide is an alternative glucose lowering agent which acts in a glucose-dependent manner, i.e. it stimulates insulin secretion only when blood glucose levels are above normal. Consequently, it has negligible risk of hypoglycaemia [14]. In the current study we aimed to investigate the efficacy of the human GLP-1 analogue liraglutide to lower glucose during and after hip surgery and its influence on coagulation activation.

2. Materials and methods

2.1. Study design and participants

This was a randomized, double-blind, placebo-controlled trial performed at the orthopaedic department of a teaching hospital (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands) involving 37 patients. Participants were recruited between August 2012 and September 2013. Inclusion criteria were: men and women between 18 and 75 years of age, scheduled for elective hip surgery, dabigatran used as anticoagulant drug after surgery and signed informed consent. Exclusion criteria were: type 1 or type 2 diabetes mellitus, use of oral corticosteroids, use of Vitamin K antagonists, known coagulation disorders, known active cancer, a history of chronic pancreatitis or idiopathic acute pancreatitis, impaired liver function (defined as alanine aminotransferase (ALAT) 2.5 times upper normal limit) or renal function (defined as serum-creatinine 133 μmol/L for males and 115 μmol/L for females), females of child bearing potential who are pregnant or breast-feeding and spinal anaesthesia. The study protocol was approved by the institutional review board (medical ethical committee of the Academic Medical Center, Amsterdam and Onze Lieve Vrouwe Gasthuis, Amsterdam). All participants provided written informed consent. This trial is registered at the Dutch trial register, www.trialregister.nl, number NTR3547.

2.2. Study procedures

Participants were randomized to receive either liraglutide or matching placebo by block randomisation (block size was 4) via a pre-generated fixed list with successive numbered treatment options. Both participants and investigators were blinded to treatment assignment. Treatment with liraglutide (0.6 mg) or placebo started one day prior to surgery. Participants underwent dose escalation to 1.2 mg/day at the day of surgery until day 3 post-operative. Liraglutide (6.0 mg/mL) and placebo were provided in identical FlexPen® devices (Novo Nordisk A/S, Bagsværd, Denmark) and were given by subcutaneous injection in the abdomen at 5 pm daily. Adverse events were recorded daily by study personnel. The total planned treatment period was 4 days. All participants received general anaesthesia and identical anti-emetic prophylaxis (droperidol 0.625 mg during induction, granisetron 1 mg post-operatively). None of the subjects received corticosteroids. Venous blood samples for laboratory tests were taken at 3 fixed points in time (before induction of anaesthesia, 2 h after the end of surgery and three days post-operative. All blood samples were taken by venapuncture in the fasting state. In all participants, 220 mg dabigatran once-daily in the morning starting from the day after surgery was given as thromboprophylaxis. All subjects were allowed to resume their daily diet when they were transferred to the surgical ward.

2.3. Outcome measures

The primary outcome was the difference in glucose at day 3 post-surgery between the study groups. Secondary outcomes were the

difference in coagulation indices at day 3 post-surgery and included prothrombin fragment 1 + 2 (F1 + 2), thrombin–antithrombin complex (TAT), plasmin–alpha2-antiplasmin complex (PAP), D-dimer, coagulation factor VIII (FVIII), von Willebrand factor (vWF), antithrombin (AT) and plasminogen activator inhibitor-1 (PAI-1).

2.4. Laboratory assessments

All blood samples were centrifuged within 1 h at 1500 g at 4 °C for 10 min, plasma was separated (separated plasma of citrate samples was centrifuged again for 10 min) and stored immediately at −70 °C. Plasma glucose concentrations were measured with a glucose hexokinase method (Roche/Hitachi, Indianapolis, USA). D-dimer, factor VIII activity and AT were measured on an automated coagulation analyser (Siemens BCS-XP system) using protocols and reagents from the manufacturer (Siemens Healthcare Diagnostics, Marburg, Germany). Antigen levels of vWF were assayed by ELISA using antigens from DAKO (Heverlee, Belgium). F1 + 2 and TAT were determined by ELISA from Siemens Healthcare Diagnostics, PAI-1 was determined by ELISA from BioMed and PAP was determined by ELISA from DRG diagnostica (Marburg, Germany).

2.5. Statistical analysis

The study was powered to detect a difference (± SD) of 1.0 ± 0.8 mmol/L in glucose three days post-surgery between the two study groups. This difference was based on a 2 mmol/L increase in glucose level in a prior study [10] and an expected 50% reduction in glucose with use of liraglutide. Taking into account a drop-out rate of 10%, the sample size calculation indicated that 18 patients per group were needed in order to detect the effect on glucose between the two study groups with 80% power and an alpha level of 0.05. Analyses were based on the intention-to-treat principle. Data of the patients who were withdrawn from the study before day three post-surgery were used for the analyses as far as possible. Results are expressed as percentages for categorical variables, mean and standard deviation (SD) for continuous normally distributed variables, and median and interquartile range (IQR) for continuous non-normally distributed variables. Groups were compared by using Fisher's Exact test, Student's *t* test or Mann Whitney rank-sum test where appropriate. Primary and secondary outcomes were analysed by use of the Mann Whitney rank-sum test. In addition, mixed between-within ANOVA analyses were performed to assess the treatment effect over time. A secondary analysis was performed to assess the influence of surgery-induced stress on coagulation. Data from the placebo group were used to assess equality of the laboratory parameters at three time points using the Friedman test. Where the Friedman test resulted in statistical significance, subsequent tests were performed using the Wilcoxon Signed rank test. All analyses were performed using PASW statistics software version 20.0 (SPSS Inc, Chicago, IL, USA); a *P*-value of <0.05 was considered statistically significant.

3. Results

In total, 37 patients were randomized and 36 received study medication in the trial. Thirty-two patients completed the trial (Fig. 1). One patient withdrew informed consent prior to start of treatment and was replaced. Two patients in the liraglutide group withdrew from the study due to adverse events (moderate/severe nausea, starting at the dose of 1.2 mg/day). Furthermore, in each study-group one patient discontinued the study due to non-compliance with the protocol (not willing to undergo blood sampling). Baseline characteristics are summarized in Table 1. More women were randomized to the placebo group, which did not reach statistical significance. Most patients included in the trial were overweight (average BMI of 28 kg/m²).
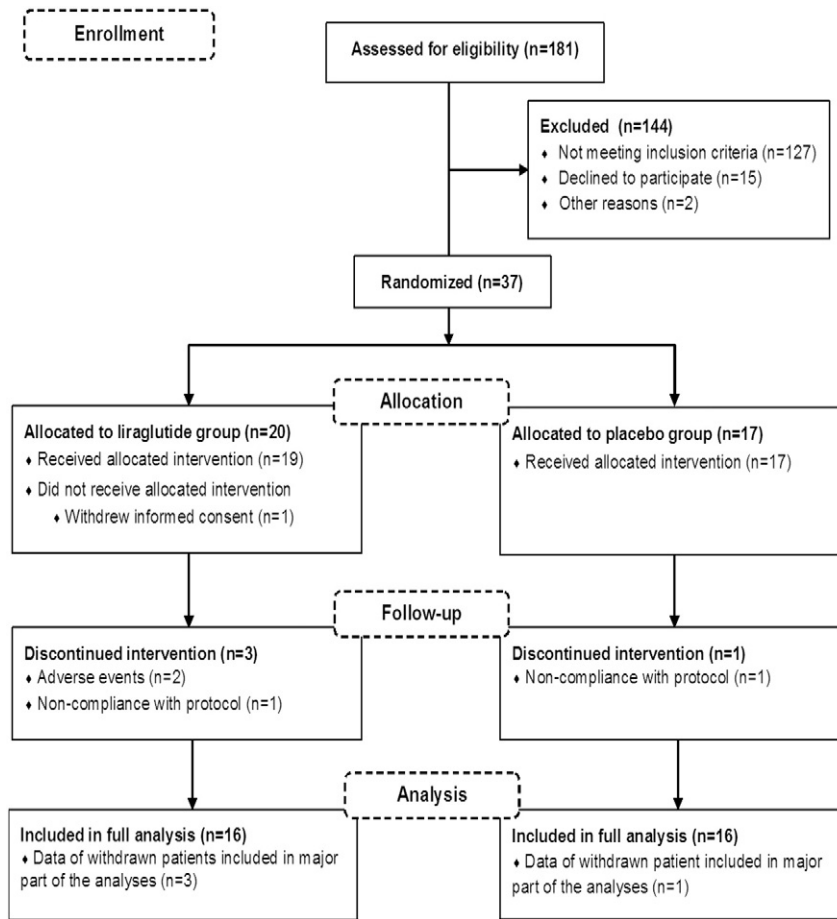
Fig. 1. Flow chart of study participants; assessment, randomization and analysis.

3.1. Glucose levels

Plasma glucose levels per time point per treatment group are depicted in Fig. 2. Glucose at day three post-surgery was significantly lower in the liraglutide group (median glucose (IQR) liraglutide 5.5 (5.2–5.7) vs. placebo 5.8 (5.5–6.2); difference 0.3 mmol/L, $P = 0.04$). However, liraglutide treatment did not significantly reduce glucose levels during the full treatment period ($P = 0.36$).

3.2. Coagulation markers

Fig. 3 shows coagulation indices per time point per treatment group. A significant difference between the groups was only found in D-dimer levels at day three post-surgery (median D-dimer (IQR) liraglutide 1.5 (1.2–1.9) vs. placebo 1.9 (1.6–2.4); difference -0.4 mmol/L, $P = 0.04$)

Table 1
Baseline characteristics of the patients included in the trial.

	Liraglutide ($n = 19$)	Placebo ($n = 17$)
Age—years (mean $\pm$ SD)	57 $\pm$ 12	59 $\pm$ 11
Sex, female n (%)	9 (47)	13 (77)
Body-mass index—kg/m^2 (mean $\pm$ SD)	28 $\pm$ 5	27 $\pm$ 5
Ethnic origin, n (%)		
- White	16 (84)	17 (100)
- Surinam/Antilian	2 (11)	–
- Other	1 (5)	–
Reason surgery, n (%)		
- Coxarthrosis	18 (95)	16 (94)
- Other	1 (5)	1 (6)
Type of hip implant fixation, n (%)		
- Cemented	12 (63)	10 (59)
- Cementless	3 (16)	3 (18)
- Hybrid[a]	4 (21)	4 (23)
Relevant medical history, n (%)		
- Cardiovascular disease	–	–
- COPD/asthma	2 (11)	1 (6)
- History of VTE	–	–
HbA1c—mmol/mol (mean $\pm$ SD)	38 $\pm$ 3	36 $\pm$ 3
Duration of surgery in minutes (mean $\pm$ SD)	89 $\pm$ 23	101 $\pm$ 27

COPD: chronic obstructive pulmonary disease; VTE: venous thrombo-embolism; HbA1c: glycated haemoglobin.
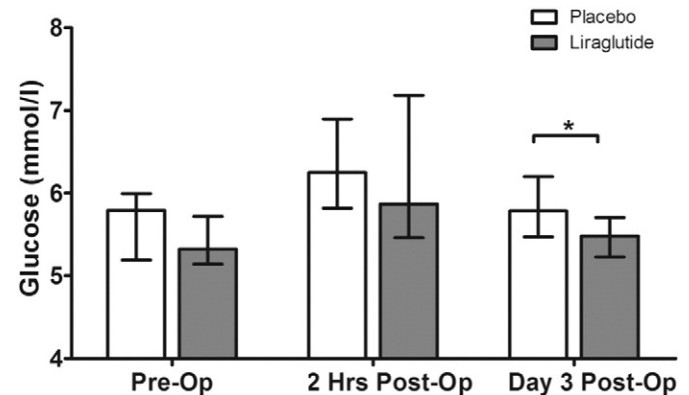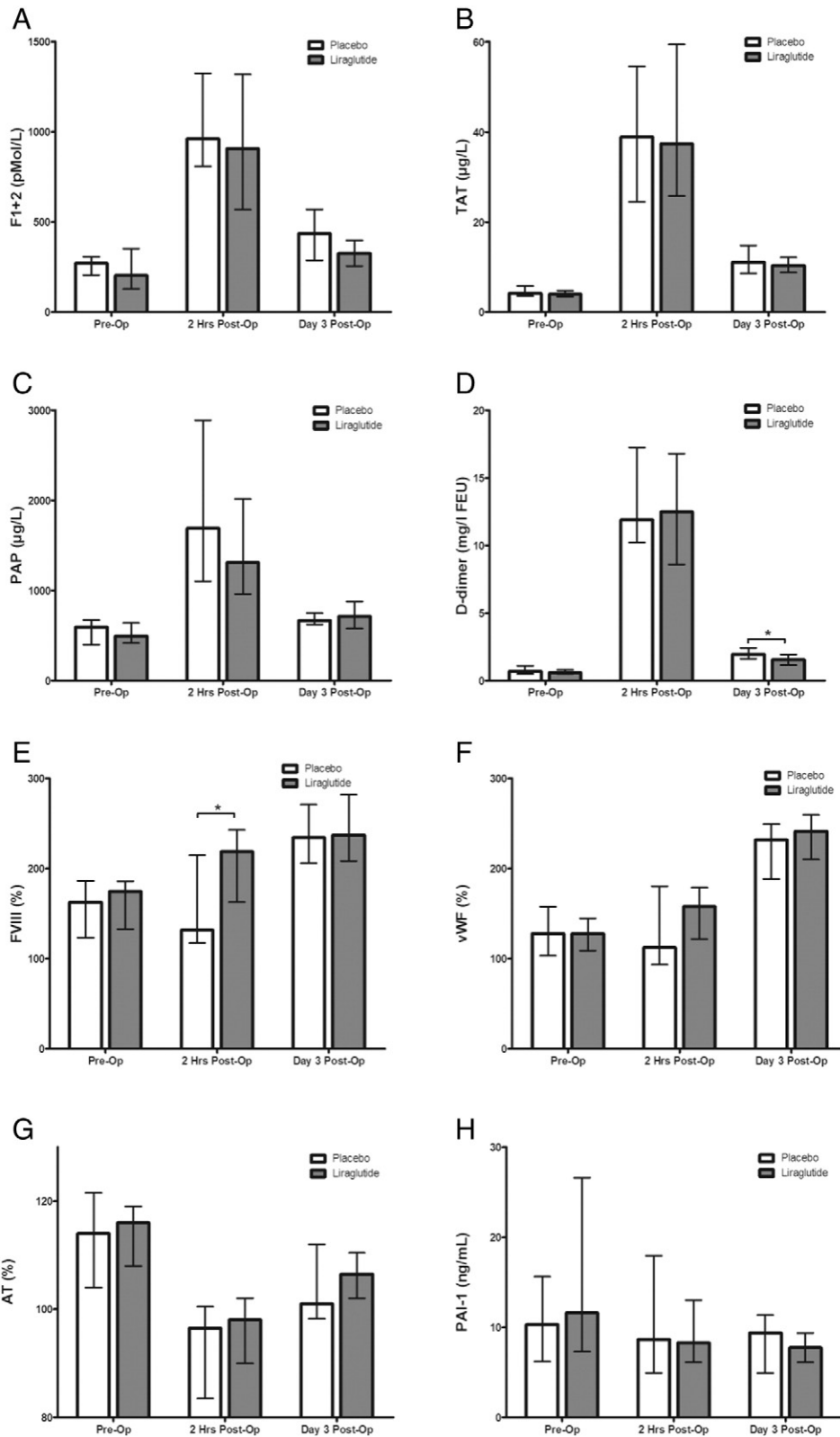[a] Cup inserted without cement, stem inserted with cement.

Fig. 2. Median peri-operative glucose levels with interquartile range per treatment group. *$P < 0.05$.

Fig. 3. Coagulation markers per treatment group during the study period. F1 + 2: prothrombin fragment 1 + 2; TAT: thrombin–antithrombin complex. PAP: plasmin alpha2-antiplasmin complex; vWF: von Willebrand Factor; AT: antithrombin; PAI-1: plasminogen activator inhibitor-1. All data are median with interquartile range. * $P < 0.05$.

and in FVIII levels 2 h post-surgery (median FVIII (IQR) liraglutide 219 (163–243) vs. placebo 132 (118–215); $P = 0.04$). However, liraglutide treatment did not significantly change D-dimer levels ($P = 0.56$) and FVIII levels ($P = 0.28$) during the full treatment period.

3.3. Adverse events

The reported adverse events during the trial are shown in Table 2. Common adverse events in the liraglutide group were nausea (47%)

Table 2
Adverse events reported during the treatment period.

	Liraglutide ($n = 19$)	Placebo ($n = 17$)	P-value
Nausea	9 (47%)	5 (29%)	0.32
Vomiting	3 (16%)	–	0.23
Loss of appetite	4 (21%)	1 (6%)	0.34
Dizziness	3 (16%)	1 (6%)	0.61
Headache	2 (11%)	1 (6%)	1.0
Reaction injection location	–	1 (6%)	0.47
Vasovagal collapse	1 (5%)	–	1.0
Diarrhoea	–	–	–
No adverse events reported	7 (37%)	10 (59%)	0.32

and loss of appetite (21%). In the placebo group nausea occurred in 29% of patients. No statistical differences were found between the groups.

3.4. Influence of surgery-induced stress on glucose levels and coagulation indices

In the placebo group, glucose levels 2 h post-operatively significantly increased compared to pre-operative glucose levels (Table 3). With regard to coagulation, F1 + 2, TAT, PAP and D-dimer significantly increased and AT significantly decreased during the post-operative period. FVIII and vWF were significantly increased at day three post-operatively, but not 2 h post-operatively (Table 3).

4. Discussion

The present study shows that the human GLP-1 analogue liraglutide moderately reduced post-operative blood glucose levels with 0.3 mmol/L in nondiabetic and prediabetic patients undergoing elective hip surgery. However, this decrease in glucose levels did not influence coagulation activation.

Little is known about the impact of hospital-related hyperglycaemia in non-diabetic orthopaedic patients. Richards et al. performed a prospective observational study in stable non-diabetic patients with orthopaedic injuries and showed that stress hyperglycaemia was associated with surgical site infection [15]. However, randomized trials evaluating hyperglycaemia treatment in hospitalized non-diabetic, non-critically ill patients are lacking. This investigation is the first randomized trial that focused on the treatment of postsurgical stress-induced hyperglycaemia in an orthopaedic non-diabetic population.

Interestingly, despite the presence of obesity and prediabetes, in both treatment groups only 25% ($n = 4$ in each group) of the patients exceeded the threshold of stress-induced hyperglycaemia postoperatively as defined by Dungan et al. (fasting glucose > 6.9 mmol/L) [5]. In addition, none of the patients were hyperglycaemic three days post-surgery. These findings are different from our previous observational study, in which we found increased (non-fasting) mean glucose levels (>7.8 mmol/L) postoperatively from the second postoperative

day up to the 4th day after surgery [10]. In order to explain these conflicting results we compared baseline- and treatment characteristics between the studies. Patients included in the previous study were on average 4 years older, the mean duration of surgery was longer (121 vs 101 min), their BMI was one point higher and half of the patients received dexamethasone as anti-emeticum, which causes hyperglycaemia post-operatively [16]. Whether these differences do explain the lower rate is unclear.

Overall, our current study population consisted of overweight individuals, with an average BMI of 28 kg/m^2. It is known that obesity is common among patients undergoing hip replacement surgery. Moreover, obesity is a clear risk factor for developing osteoarthritis, the most common indication for hip replacement surgery [17].

Interestingly, 14 of 36 patients (39%) had prediabetes glycated haemoglobin levels (between 38–46 mmol/mol), thus being 'prediabetic'. Twenty-one patients (58%) had glycated haemoglobin levels below 38 mmol/mol and one patient had a glycated haemoglobin level of 47 mmol/mol. With regard to pre-operative fasting glucose levels, 17 of 36 patients (47%) had blood glucose levels between 5.6 and 6.9 mmol/L, thus impaired fasting glucose. It should be mentioned that all patients already received the study-therapy, either verum or placebo, no off-treatment baseline values were available. Only 5 of the 17 patients (29%) who had impaired fasting glucose levels also had HbA1C-levels in the prediabetic range. Perhaps, blood glucose-levels at the day of surgery are already increased due to stress related to the upcoming procedure.

The fact that we did not find a marked increase in glucose levels in the placebo group during the treatment period may have contributed to the small difference in glucose levels (0.3 mmol/L) between the treatment groups three days post-operatively. The smaller difference in glucose levels found in this study may also explain that no clear difference in coagulation indices was observed. Thus, a clear causal relationship between glucose and coagulation activation could not be confirmed with the present study. Results should therefore be interpreted with caution. The statistical difference found in D-dimer- and FVIII-levels may have been multiple testing results and one can argue whether these changes are biologically relevant.

That the surgical procedure activates coagulation is clearly demonstrated by the increase of D-dimer, F1 + 2 and TAT and the decrease in AT post-operatively. Our findings are in line with previous studies which assessed coagulation activation in orthopaedic surgery [10,18]. Other causes, such as bleeding or vascular damage induced by surgery are more likely to have influenced these coagulation parameters than the relatively modest increase in glucose.

Our study has several limitations. First, one may debate the dose escalation and treatment duration used in this study. In diabetes patients treated with GLP-1, dose escalation from the starting dose (0.6 mg/day) to 1.2 mg/day is applied at least after one week of GLP-1 treatment, partly in order to reduce the risk of gastrointestinal side effects. In addition, steady-state pharmacokinetics for liraglutide is reached after three days

Table 3
Peri-operative glucose and coagulation indices at all time-points (placebo group). All data is presented as median (25th–75th percentile). The statistical change across the three time periods per laboratory assessment was determined by the Friedman Test.

	Pre-operative ($n = 17$)	2 hrs post-operative ($n = 16$)	Day 3 post-operative ($n = 16$)	P value
Glucose (mmol/L)	5.8 (5.2–6.0)	6.3 (5.8–6.9)[†]	5.8 (5.5–6.2)	0.003
F1 + 2 (pMol/L)	271 (207–308)	963 (810–1326)[‡]	436 (287–572)[‡]	<0.001
TAT (µg/L)	4.2 (3.6–5.8)	38.9 (24.5–54.6)[‡]	11.1 (8.6–14.8)[*]	<0.001
PAP (µg/L)	595 (401–675)	1692 (1104–2889)[†]	667 (623–753)[*]	<0.001
D-dimer (mg/L FEU)	0.7 (0.5–1.1)	11.9 (10.2–17.3)[‡]	2.0 (1.6–2.4)[†]	<0.001
FVIII (%)	163 (124–187)	132 (118–215)	235 (207–271)[†]	0.001
vWF (%)	128 (104–158)	113 (94–181)	232 (189–250)[‡]	<0.001
AT (%)	114 (104–122)	97 (84–101)[‡]	101 (98–112)[†]	<0.001
PAI-1 (ng/mL)	10.3 (6.2–15.7)	8.7 (4.9–18.0)	9.4 (4.9–11.4)	0.41

[*]$P < 0.05$, [†]$P < 0.01$, [‡]$P < 0.001$ compared to pre-operative levels, in post-hoc analysis. F1 + 2: prothrombin fragment 1 + 2; TAT: thrombin–antithrombin complex; PAP: plasmin alpha2–antiplasmin complex; vWF: von Willebrand factor; AT: antithrombin; PAI-1: plasminogen activator inhibitor-1.

of treatment [19]. Since no clinical trial data for liraglutide used for a perioperative blood glucose lowering strategy were available, we considered that the proof-of-principle dosing regimen designed for the current study was a good compromise between titrating too fast, which was likely to result in many side effects, and underdosing, which was likely to give suboptimal glucose lowering. Starting liraglutide earlier before surgery did not seem attractive, as these patients would not be hyperglycaemic before surgery.

Second, the placebo group consisted of a non-significantly larger number of female subjects compared to the liraglutide group, despite of the randomisation procedure. In order to assess any effect modification by sex, analyses were also performed for each gender separately. There could perhaps be a minimally larger effect in glucose lowering in females (difference in median glucose 0.4 mmol/L, $P = 0.02$) than in males (difference in median glucose 0.3 mmol/L, $P = 0.26$). It should be noted that comparisons for each gender separately were based on a very small sample size. So this difference should be interpreted cautiously, since it could be the result of random error or confounding.

Third, all laboratory assessments were performed when patients were already on treatment. Therefore, we were not able to include baseline values without treatment as covariate in our analyses. As all subjects who were participating in this trial were non-diabetic, glucose values were expected to be in normal range and taking a fasting baseline sample before hospital admission was not feasible.

Finally, the use of dabigatran as thromboprophylaxis may have influenced the levels of several coagulation markers when patients did receive thromboprophylaxis [20]. However, all subjects in our trial received identical anticoagulant therapy, so dabigatran would have affected both groups similarly.

5. Conclusion

The use of the human GLP-1 analogue liraglutide in non-diabetic and prediabetic patients undergoing elective hip surgery moderately reduced post-operative blood glucose levels but did not change coagulation activation.

Competing interests

JHDV is a consultant for and on the speaker's bureau of Novo Nordisk. The other authors state that they have no conflicts of interest.

Author contributions

MS participated in patient recruitment and acquisition of the data, performed the statistical analysis, contributed to the interpretation of study data and prepared the draft paper, JH contributed in the design of the study and the interpretation of study data, RP contributed to the organization and conduct of the study, JK contributed to the organization and conduct of the study, JM contributed to the laboratory assessments and interpretation of study data, JH participated in the design of the study and contributed to the interpretation of study data, and JHDV participated in the design of the study, contributed to the interpretation of study data and helped to draft the manuscript. All authors read and approved the final manuscript.

Transparency document

The Transparency document associated with this article can be found, in the online version.

Acknowledgements

References

[1] W.H. Geerts, D. Bergqvist, G.F. Pineo, J.A. Heit, C.M. Samama, M.R. Lassen, C.W. Colwell, P. American College of Chest, Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), Chest 133 (2008) 381S–453S.
[2] J. Januel, G. Chen, C. Ruffieux, et al., Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review, JAMA 307 (2012) 294–303.
[3] R.H. White, M.C. Henderson, Risk factors for venous thromboembolism after total hip and knee replacement surgery, Curr. Opin. Pulm. Med. 8 (2002) 365–371.
[4] D.M. Cohn, J. Hermanides, J.H. DeVries, P.W. Kamphuisen, S. Kuhls, M. Homering, J.B. Hoekstra, A.W. Lensing, H.R. Buller, Stress-induced hyperglycaemia and venous thromboembolism following total hip or total knee arthroplasty: analysis from the RECORD trials, Thromb. Haemost. 107 (2012) 225–231.
[5] K.M. Dungan, S.S. Braithwaite, J.C. Preiser, Stress hyperglycaemia, Lancet 373 (2009) 1798–1807.
[6] B.A. Lemkes, J. Hermanides, J.H. Devries, F. Holleman, J.C. Meijers, J.B. Hoekstra, Hyperglycemia: a prothrombotic factor? J. Thromb. Haemost. 8 (2010) 1663–1669.
[7] A. Ceriello, D. Giugliano, A. Quatraro, P. Dello Russo, R. Torella, Blood glucose may condition factor VII levels in diabetic and normal subjects, Diabetologia 31 (1988) 889–891.
[8] M. Nieuwdorp, T.W. van Haeften, M.C. Gouverneur, H.L. Mooij, M.H. van Lieshout, M. Levi, J.C. Meijers, F. Holleman, J.B. Hoekstra, H. Vink, J.J. Kastelein, E.S. Stroes, Loss of endothelial glycocalyx during acute hyperglycemia coincides with endothelial dysfunction and coagulation activation in vivo, Diabetes 55 (2006) 480–486.
[9] M.E. Stegenga, S.N. van der Crabben, R.M. Blumer, M. Levi, J.C. Meijers, M.J. Serlie, M.W. Tanck, H.P. Sauerwein, T. van der Poll, Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia, Blood 112 (2008) 82–89.
[10] J. Hermanides, R. Huijgen, C.P. Henny, N.H. Mohammad, J.B. Hoekstra, M.M. Levi, J.H. DeVries, Hip surgery sequentially induces stress hyperglycaemia and activates coagulation, Neth. J. Med. 67 (2009) 226–229.
[11] P.J. Grant, Beneficial effects of metformin on haemostasis and vascular function in man, Diabetes Metab. 29 (2003) 6S44-52.
[12] G. Derosa, A.F. Cicero, A. Gaddi, P.D. Ragonesi, M.N. Piccinni, E. Fogari, S. Salvadeo, L. Ciccarelli, R. Fogari, A comparison of the effects of pioglitazone and rosiglitazone combined with glimepiride on prothrombotic state in type 2 diabetic patients with the metabolic syndrome, Diabetes Res. Clin. Pract. 69 (2005) 5–13.
[13] J. Hermanides, R.J. Bosman, T.M. Vriesendorp, R. Dotsch, F.R. Rosendaal, D.F. Zandstra, J.B. Hoekstra, J.H. DeVries, Hypoglycemia is associated with intensive care unit mortality, Crit. Care Med. 38 (2010) 1430–1434.
[14] D.J. Drucker, M.A. Nauck, The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes, The Lancet 368 (2006) 1696–1705.
[15] J.E. Richards, J. Hutchinson, K. Mukherjee, A.A. Jahangir, H.R. Mir, J.M. Evans, A.M. Perdue, W.T. Obremskey, M.K. Sethi, A.K. May, Stress hyperglycemia and surgical site infection in stable nondiabetic adults with orthopedic injuries, J Trauma Acute Care Surg 76 (2014) 1070–1075.
[16] L.H. Eberhart, J. Graf, A.M. Morin, T. Stief, M. Kalder, R. Lattermann, T. Schricker, Randomised controlled trial of the effect of oral premedication with dexamethasone on hyperglycaemic response to abdominal hysterectomy, Eur. J. Anaesthesiol. 28 (2011) 195–201.
[17] E.W. Karlson, L.A. Mandl, G.N. Aweh, O. Sangha, M.H. Liang, F. Grodstein, Total hip replacement due to osteoarthritis: the importance of age, obesity, and other modifiable risk factors, Am. J. Med. 114 (2003) 93–98.
[18] B.S. Oberweis, G. Cuff, A. Rosenberg, L. Pardo, M.A. Nardi, Y. Guo, E. Dweck, M. Marshall, D. Steiger, S. Stuchin, J.S. Berger, Platelet aggregation and coagulation factors in orthopedic surgery, J. Thromb. Thrombolysis 38 (2014) 430–438.
[19] E. Watson, D.M. Jonker, L.V. Jacobsen, S.H. Ingwersen, Population pharmacokinetics of liraglutide, a once-daily human glucagon-like peptide-1 analog, in healthy volunteers and subjects with type 2 diabetes, and comparison to twice-daily exenatide, J. Clin. Pharmacol. 50 (2010) 886–894.
[20] L. Green, A.S. Lawrie, R. Patel, R.C.M. Stephens, I.J. Mackie, A. Chitolie, F.S. Haddad, S.J. Machin, The effect of total hip/knee replacement surgery and prophylactic dabigatran on thrombin generation and coagulation parameters, Thromb. Res. 130 (2012) 775–779.