MEDIZINISCHE UNIVERSITÄT WIEN

Homocysteine in bariatric patients following laparoscopic roux-en-Y gastric bypass surgery
Department of surgery
Medical university of Vienna
An exploratory study in 708 consecutive patients.

EK1143/2013

Marcus Poglitsch, MD

Associate professor Gerhard Prager, MD

Department of surgery (head of department: Univ. Prof. Raimund Jakesz, MD),

Medical University of Vienna

Translation of the original study protocol document approved by the local ethics committee in 2014.

Table of content

1 Background

Hyperhomocysteinaemia defined as serum levels above 15 µmol/l is associated with numerous risks. There is an elevated risk in suffering from cardiovascular events (myocardial infarction, stroke, acute limb ischemia, deep veinous thrombosis) who are today's number one cause of death in the industrialized world (1). Furthermore, Homocysteine was found to be a mediator in dementia, Alzheimer's disease (2), osteoporosis induced pathological fractures (3) and diabetic retinopathia (4). The role of homocysteine in metabolic diseases is indisputable. Obesity is also associated closely with cardiovascular disease events, therefore it is necessary to provide a systematically analysis of changes in homocysteine levels following weight loss surgery.

Changes in homocysteine levels following bariatric surgery remain controversially discussed. Where some authors found postoperatively lower values (5, 6), others reported elevated values (7-10). Even some found no difference at all between preoperative and postoperative values of homocysteine (11-13). Some of these studies used outdated bariatric surgery procedures (7, 9, 13).

In literature the postoperative changes of homocysteine after bariatric surgery remain unrevealed. Therefore, we designed this survey to assess timeline changes of homocysteine with a long-time and high follow-up. This could be of importance to postoperative prophylaxis of cardiovascular disease events.

For homocysteine being only a surrogate parameter for cardiovascular events, we decided to reveal changes in homocysteine being of clinical relevance via assessing the actual cardiovascular disease events (stroke, myocardial infarction, deep veinous thrombosis, ...).

2 Outcome

The primary outcome is to assess timeline changes of the peri and postoperative values of homocysteine in µmol/l via the CMIA (chemiluminescent microparticle immunoassay) through study completion. Secondary outcomes include

demographic parameters like weight, height, folate, and vitamin B12. Furthermore, for determing clinical relevance we assessed the postoperative newly-onset number of cardiovascular events.

3 Patients

All patients received laparoscopic roux-en-Y gastric bypass at the department of surgery at the medical university of vienna over a six year period. All patients met the criteria for bariatric surgery: BMI of above 40 kg/m^2 without comorbidities or BMI of above 35 kg/m^2 with comorbidities including diabetes mellitus, arterial hypertonia, hyperlipidaemia, obstructive sleep apnea syndrome, arthrosis and others. Minimal age was 18 years and highest age was 75 years for inclusion. Both female and male participants were eligible.

4 Parameters

4.1 Primary outcome

Homocysteine in µmol/l assessed by CMIA technique at the timepoints peoperatively, 3, 6, 9, 12, 18, 24, 36, 48, 60, 72, 84 and 96 months postoperatively. Timeframe: through study completion.

4.2 Secondary outcomes

Secondary outcome measurements include folate, vitamin B12 being well known to have impact on homocysteine metabolism. Furthermore, all standard laboratory parameters and demographic data will be assessed also. The postoperative incidence of newly-onset cardiovascular disease events will be reported.

5 Methods

Retrospective analysis of existing records of the department of surgery, medical university of vienna will be performed. To extract laboratory values out of the database the Archimed software will be utilized.

To reveal clinical relevance of changes in homocysteine values we will perform postal screening utilizing a questionnaire in all 708 participants. In the same step the informed consent form will be sent to each patient and they will be questioned if they have experienced any cardiovascular disease event after surgery (see IC form and questionnaire). An encrypted form of these lists is only available to the principal investigator and the study nurses.

Finally, the data will be compared to two state wide databases (AKIM and Webokra) to verify cardiovascular events.

6 Statistics

Descriptives

Case number strategy: the number of participants include all patients undergoing roux-en-Y gastric bypass consecutively over a six year period. We expect 708 cases. For this study being only exploratory we forwent a formal Power analysis.

To reveal statistical relevant postoperative changes of homocysteine we performed paired t-tests between preoperatively. Pearson's or Spearman's Correlations will be performed to reveal the influence of folate and vitamin B12 on the homocysteine metabolism.

The results of the postal screening section will be evaluated descriptively and compared to general incidences of cardiovascular disease events.

7 Data privacy protection

All patients will be numbered continously and anonymized for further evaluation. Only authorized personnel will be able to access original names and data.

Furthermore, data will be stored and evaluated on personal computers at the medical university of Vienna with restricted access.

8 Risk-benefit analysis

The included participants have no direkt benefit of the survey. The proposed study is only a retrospective evaluation of preexistant data, therefore, no risk is anticipated. The only relevant risk being emerging of sensitive health data will be minimized by anonymous evaluation and restricted access to the data. Results of this study can be used as a basis of generating further hypothesis of other surveys.

9 References

1. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA. 1995 Oct 4;274(13):1049-57.
2. Loscalzo J. Homocysteine and dementias. N Engl J Med. 2002 Feb 14;346(7):466-8.
3. Herrmann M, Peter Schmidt J, Umanskaya N, Wagner A, Taban-Shomal O, Widmann T, et al. The role of hyperhomocysteinemia as well as folate, vitamin B(6) and B(12) deficiencies in osteoporosis: a systematic review. Clin Chem Lab Med. 2007;45(12):1621-32.
4. Agullo-Ortuno MT, Albaladejo MD, Parra S, Rodriguez-Manotas M, Fenollar M, Ruiz-Espejo F, et al. Plasmatic homocysteine concentration and its relationship with complications associated to diabetes mellitus. Clin Chim Acta. 2002 Dec;326(1-2):105-12.
5. Williams DB, Hagedorn JC, Lawson EH, Galanko JA, Safadi BY, Curet MJ, et al. Gastric bypass reduces biochemical cardiac risk factors. Surg Obes Relat Dis. 2007 Jan-Feb;3(1):8-13.
6. Woodard GA, Peraza J, Bravo S, Toplosky L, Hernandez-Boussard T, Morton JM. One year improvements in cardiovascular risk factors: a comparative trial of laparoscopic Roux-en-Y gastric bypass vs. adjustable gastric banding. Obes Surg. [Comparative Study Research Support, Non-U.S. Gov't]. 2010 May;20(5):578-82.
7. Borson-Chazot F, Harthe C, Teboul F, Labrousse F, Gaume C, Guadagnino L, et al. Occurrence of hyperhomocysteinemia 1 year after gastroplasty for severe obesity. J Clin Endocrinol Metab. 1999 Feb;84(2):541-5.
8. Dixon JB, Dixon ME, O'Brien PE. Elevated homocysteine levels with weight loss after Lap-Band surgery: higher folate and vitamin B12 levels required to maintain homocysteine level. Int J Obes Relat Metab Disord. 2001 Feb;25(2):219-27.
9. Sheu WH, Wu HS, Wang CW, Wan CJ, Lee WJ. Elevated plasma homocysteine concentrations six months after gastroplasty in morbidly obese subjects. Intern Med. [Research Support, Non-U.S. Gov't]. 2001 Jul;40(7):584-8.
10. Toh SY, Zarshenas N, Jorgensen J. Prevalence of nutrient deficiencies in bariatric patients. Nutrition. 2009 Nov-Dec;25(11-12):1150-6.
11. Gomez-Ambrosi J, Pastor C, Salvador J, Silva C, Rotellar F, Gil MJ, et al. Influence of waist circumference on the metabolic risk associated with impaired fasting glucose: effect of

weight loss after gastric bypass. Obes Surg. [Research Support, Non-U.S. Gov't]. 2007 May;17(5):585-91.
12. Ledoux S, Coupaye M, Bogard C, Clerici C, Msika S. Determinants of hyperhomocysteinemia after gastric bypass surgery in obese subjects. Obes Surg. 2011 Jan;21(1):78-86.
13. Sledzinski T, Goyke E, Smolenski RT, Sledzinski Z, Swierczynski J. Decrease in serum protein carbonyl groups concentration and maintained hyperhomocysteinemia in patients undergoing bariatric surgery. Obes Surg. [Research Support, Non-U.S. Gov't]. 2009 Mar;19(3):321-6.