THESIS TOPIC

Subject N° (to be completed by the ED):   FUNDING:  □ Requested  □ Acquired  Funding origin: Doctoral School contest

Thesis title: C – UA – Impact of preconceptional bariatric surgery on bone metabolism

3 keywords:  Bariatric surgery  Bone metabolism  Bone fragility

Unit / team: GEROM UPRES EA 4658

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Socio-economic and scientific context (approximately 10 lines):

Obesity is a major public health problem in the world. Predictions for 2025 estimate that 18% of men and 21% of women will be obese, and that 6% of men and 9% of women will be morbidly obese with a body mass index (BMI) greater than 40. The primary treatment of obesity consists of therapeutic education of the patient (dietary follow-up, physical activity and psychological care). However, the high failure rate of therapeutic education has led to a clear increase in bariatric surgery in patients with a BMI of 40 Kg/m2 (or 35 Kg/m2 with comorbidity). This increase in popularity of bariatric surgery can be explained by an overall amelioration of metabolic profile. However, a growing body of evidences suggests a deleterious effect of bariatric surgery on bone metabolism with an increased risk of fracture. Presently the mechanism for this higher bone fragility is unknown. Furthermore, 80% of bariatric surgeries are conducted in women of childbearing age. Pregnancy and lactation act on the skeleton by inducing bone resorption to release bone calcium. This higher bone resorption is physiologically reversible, however, whether this is true after bariatric surgery remains to be investigated. The bone consequences of bariatric surgery on descendence are presently unknown. This is of interest as bone fragility after 65 years old is partly due to in utero life.

Working hypothesis and aims (approximately 8 lines):

Previous studies have attempted to look at bariatric surgery in animal models but without pregnancy. However, the popularity of bariatric surgery is important in women of childbearing age. This PhD project will be divided in two arms. The first arm will focus on the bone consequences of two different bariatric surgery procedures (sleeve gastrectomy and gastric bypass) performed in female animals in order to investigate the consequences of pregnancy and lactation on bone health of mothers. The validation of some biomarkers in humans will also be performed due to the presence of several bariatric surgery cohorts in women at the University Hospital of Angers.

As in utero malnutrition is a risk factor for bone fragility over 65 years old in humans, the consequence of bariatric surgery, performed in mother, on offspring required investigations. A follow-up of offspring will be performed by bone densitometry over a 12 months period. The goal of this study would be to detect early the sign of bone fragility as a proof-of-concept. Finally, administration of nutritional factors could also be envisaged in order to revert bone fragility after bariatric surgery.

Main milestones of the thesis (approximately 12 lines):

The main milestones of this PhD project would be to develop and maintain the preclinical model of bariatric surgery in female animals in order to replicate the bone consequences observed in humans. The second milestone would be to study overtime the development of a bone fragility and at sacrifice to collect several bone anatomical pieces to further understand the mechanisms leading to bone fragility. The third milestone would be to investigate whether bone fragility develop in male and female offspring over a 12-month period and hence to investigate the cause of bone fragility/no bone fragility in this model. Finally, the fourth milestone would be to administer nutritional factors that could revert bone fragility.

This is expected that during his/her PhD, the candidate will be able to present his/her work at national and international meeting and that the project will be sound enough to lead to 3 publications (mother study, offspring study, interventional study) in high impact factor peer-reviewed journals.

Scientific and technical skills required by the candidate (2 lines):

The candidate will need to demonstrate project management skills and organization. Previous experience in bone biology would be a plus but training can be dispensed on-site. The candidate will have to handle animals and as such experience with animal handling is required.
3 publications from the team related to the topic (last 5 years):


- MANSUR S.A., MIECZKOWSKA A., FLATT P.R., CHAPPARD D., IRWIN N., MABILLEAU G. The GLP-1 receptor agonist exenatide ameliorates bone composition and tissue material properties in high fat fed diabetic mice, Frontiers in Endocrinology, 2019, 10: 51


National and international collaborations:
The supervisor has numerous national and international on-going collaborations that are listed below:

- Inserm UMR-S 1063 Oxidative stress and metabolic pathologies (Dr S. Le Lay), University of Angers
- CNRS UMR 6015-Inserm UMR 1083 Cardiovascular and mitochondrial physiopathology (Dr C. Fassot), University of Angers
- UPRES EA 3859 Hemodynamic, fibrosis and liver tumour (Dr F. Schmitt), University of Angers
- Inserm UMR-S 1229 Regenerative Medicine and Skeleton (Prof V. Geoffroy, Dr S. Beck), University of Nantes
- CNRS UMR 8251 Regulation of glycemia by central nervous system (Prof C. Magnan), University Paris 7
- Diabetes Research Group (Prof P.R. Flatt), University of Ulster, UK
- Endocrinology Research Division (Prof J. J. Holst), University of Copenhagen
- Ludwig Boltzmann Institute of Osteology (Dr S. Blouin), Vienna (Austria)
- Department of Morphology (Prof C. Behets-Wydemans), UC Louvain, Belgium