Title: Metabolic surgery and cardiovascular outcomes in patients with severe obesity

Background and Aims:

Obesity is linked to an enhanced risk of cardiovascular disease and mortality. Long-term weight loss maintenance with prevention and remission of hypertension, type 2 diabetes and dyslipidemia following metabolic surgery has been shown, with a reduction in cardiovascular disease risk. Metabolic surgery has been shown to increase life expectancy in individuals with elevated cardiovascular risk. Metabolic surgery is a surgical treatment primarily for extremely obese patients. The types of metabolic surgery are sleeve gastrectomy (SG), laparoscopic adjustable gastric band (LAGB), Roux-en-Y gastric bypass (RYGP), biliopancreatic diversion/duodenal switch (BPD/DS) and one anastomosis gastric bypass/mini gastric bypass (OAGB/MGB). In the early stages, metabolic surgery might prevent or slow atherogenesis and cardiovascular outcomes by breaking the vicious circle between endothelial dysfunction and inflammation but also in later stages preventing plaque destabilization.

During this fellowship, we managed to prepare a database inclusive of approximately 1300 patients having a BMI greater than 40 kg/m2 or a BMI between 35-40 kg/m2 and two comorbidities who were referred to an outpatient clinic for metabolic surgery (sleeve gastrectomy (SG) or Roux en-Y gastric bypass (RYGB) between 2015 to 2021. All clinical, radiological, and laboratory findings of patients were recorded at baseline as well as different post-surgery follow-up time-points.

Besides setting up the aforementioned database, our main objectives of studies during the fellowship course were:

1. The predictive performance of noninvasive factors for liver fibrosis in patients with severe

obesity.

2. The impact of metabolic surgery on cardiovascular outcomes in patients with severe obesity.

Project number 1:

Predictive performance of noninvasive factors for liver fibrosis using machine learning algorithms

Liver fibrosis due to metabolic derangement is a burden on global health. However, data regarding the predictive performance of the noninvasive factors for liver fibrosis are scarce. Thus, the objective of this study was to evaluate the association between these factors and liver fibrosis using a machine learning algorithm. We conducted a retrospective cohort study that included 1005 patients who underwent metabolic surgery at the outpatient clinic in Mashhad, Iran. Patients were classified into two groups: the fibrosis and the non-fibrosis group. Out of the 24-selected variables, the area under the curve (AUC) characteristics of liver fibrosis diagnosed by liver stiffness measurement (LSM) using 2-D shear wave elastography were high for six variables including (hemoglobin, fasting blood sugar, skeletal muscle mass, alanine transaminase, triglyceride, and aspartate transaminase) with LR (0.73, 95% CI: 0.65, 0.81) and SVM (0.72, 59% CI: 0.64, 0.80) and highest sensitivity for SVM (0.83, 95% CI: 0.72, 0.91) and NB (0.66, 95% CI: 0.53, 0.77), respectively. The predictive performance of noninvasive factors of liver fibrosis was significantly higher for six variables with high application and accuracy in the diagnosis and prognosis of liver fibrosis.

Project number 2:

Diagnostic value of non-invasive liver function tests in liver fibrosis and changes in these parameters post metabolic surgery

Over the past few years, attempts have been made in uncovering non-invasive investigative techniques for determination of liver fibrosis which include serological markers, diagnostic scoring, and imaging modalities. Although these methods are safer, less expensive, and more readily available, they do not have the same diagnostic capacity when compared to a liver biopsy. There remains a need to find an investigative method encompassing all the above qualities for determination of liver fibrosis. The aim of this study was to ascertain the diagnostic accuracy of non-invasive liver function tests in liver fibrosis and assess the changes in them after metabolic surgery. 1005 individuals with severe obesity who were referred for metabolic surgery were analyzed. Hepatic indexes including AAR, APRI, NFS and Fibrosis–4 (FIB4) was checked. Furthermore, all participants underwent two-dimensional shear wave elastography (2D–SWE). All investigations were repeated (6-8) months after metabolic surgery. The receiver operating characteristic (ROC) curve as well as area under the ROC curve were utilized to determine the optimal cut-off values for baseline study parameters. AST/ALT (AAR) was the most sensitive (79%) pre-operative non-invasive serological marker for detecting liver fibrosis, whereas NAFLD Fibrosis Score (NFS) was the most specific (84%). Regression analysis from both, adjusted and unadjusted models, showed that baseline AAR was a predictor of post-operative liver status in terms of hepatic fibrosis. The authors recommend using both investigations in conjunction with elastography to increase the likelihood of detecting liver fibrosis.

Project number 3:

The effect of metabolic surgery on circulating levels of oxidized low-density lipoproteins is apparently independent of changes in body mass index: a systematic review and meta-analysis

Obesity is related to dyslipidemia, and increased circulating oxidated LDL (ox-LDL) concentrations that may predispose to atherosclerosis. Metabolic surgery may lower the risk of cardiovascular mortality. Elevated plasma ox-LDL have been associated with atherogenesis and atherosclerotic cardiovascular disease (ASCVD) events. The aim of this meta-analysis was to investigate the impact of metabolic surgery on pro-atherogenic circulating ox-LDL levels in patients with severe obesity. Four databases were systematically searched from inception to May 1st, 2021. Also, to clarify the heterogeneity of studies with regard to treatment duration, research design and the demographic features, a random-effects model and the generic inverse variance weighting approach were utilized. To determine the association with the estimated effect size, a random-effect meta-regression approach was performed. Finally, a meta-regression analysis was conducted to explore the influence of respectively baseline and changes in body mass index (BMI), baseline ox-LDL and post-surgery follow up period with the estimated effect size of surgery on ox-LDL levels. Meta-analysis of 11 studies including 470 subjects showed a significant decline in circulating ox-LDL following metabolic surgery (SMD: -0.971, 95% CI: -1.317, -0.626, p<0.001, I^2: 89.43%). The results of meta-regression did not show any significant association between the changes in ox-LDL after metabolic surgery and baseline BMI, duration of follow-up or baseline ox-LDL values. However, there was a significant association between ox-LDL alteration and percentage of BMI change. Metabolic surgery in patients who had severe obesity causes a decrease of circulating ox-LDL, that was apparently dependent in BMI changes.

Project number 4:

Impact of metabolic surgery on circulating PCSK9 levels as marker of cardiovascular disease risk: a meta-analysis

Metabolic surgery for severely obese patients, has proven to be the most effective treatment choice. In addition to other metabolic effects, cardiovascular outcomes are improved following metabolic surgery. PCSK9 plasma concentration have been demonstrated to predict cardiovascular (CVD) risk. This systematic review and meta-analysis focuses on PCSK9 changes in obese patients following metabolic surgery. A systematic literature search in four databases was performed. Studies were evaluated regarding heterogeneity in design, populations under investigation, and treatment duration using random-effects model and the generic inverse variance weighting approach. A random-effect meta-regression approach was used to investigate the association with the estimated effect size. The results of meta-analysis on 4 trials including 260 individuals demonstrated a remarkable decline of PCSK9 after metabolic surgery (WMD: -57.341ng/ml, 95% CI: -87.969, -26.714, $p<0.001$; I2:96.25%). Consistently, a significant decrease of LDL-C after metabolic surgery (WMD: -22.573mg/dl, 95% CI: -27.571, -17.574, $p<0.001$; I2:86.35%) was observed. PCSK9 is reduced significantly after metabolic surgery. The decrease of PCSK9 might be utilized as an independent surrogate marker of improvement of ASCVD risk after metabolic surgery.

Project number 5:

The effect of metabolic surgery on circulating levels of lipoprotein(a): a meta-analysis

Obesity, especially severe obesity, is strongly related to a higher risk of atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality. Metabolic surgery is a durable and

effective weight loss therapy for people with severe obesity and weight-related co-morbid conditions. Elevated plasma levels of lipoprotein (a) [Lp(a)] are causally associated with ASCVD. The aim of the present meta-analysis was to analyze whether metabolic surgery impacts Lp(a) concentrations. A literature search was performed from inception to May 1st, 2021. A random-effects model and the generic inverse variance weighting method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration, and the characteristics of the studied populations. A random-effect meta-regression model was used to explore the association with an estimated effect size. Meta-analysis of 13 studies including 1,551 patients showed a significant decrease of circulating Lp(a) after metabolic surgery (SMD: -0.438, 95% CI: -0.702, -0.174, p<0.001, I^2: 94.05%). The results of the meta-regression did not indicate any significant association between the changes in Lp(a) and duration of follow-up from surgery, reduction in body mass index, or baseline Lp(a) concentration. The reduction in circulating Lp(a) was robust in the leave-one-out sensitivity analysis. Metabolic surgery significantly decreases circulating Lp(a) concentrations. This decrease may positively impact ASCVD in patients with obesity.

Project number 6:

Effect of Metabolic Surgery on Flow-Mediated Vasodilation as a Measure of Endothelial Function: A Systematic Review and Meta-Analysis

Flow mediated vasodilation (FMD) is a marker of endothelial function and its decline is related to increased cardiovascular risk. This systematic review and meta-analysis evaluated the impact of Metabolic surgery on FMD. A systematic literature search in PubMed, Scopus, Embase, and Web of Science was performed to 1 May 2021. All types of metabolic surgery were considered, with the inclusion that FMD had to have been tested before and after the surgical procedure. A meta-

analysis and a systematic review of 23 studies (n = 891 individuals) demonstrated improvement in FMD following metabolic surgery (weighted mean difference (WMD): 5.867, 95% CI: 4.481, 7.252, p < 0.001; I2: 96.70). There was an improvement in FMD for up to 6 months following metabolic surgery in a meta-analysis from 7 trials that included 356 subjects (WMD: 5.248, 95% CI: 2.361, 8.135, p < 0.001; I2: 98.18). The meta-analysis from 9 trials (n = 414 subjects) showed an improvement in FMD 6 to 12 months after metabolic surgery (WMD: 5.451, 95% CI: 3.316, 7.587, p < 0.001; I2: 94.18). The meta-analysis from 10 trials (n = 414 subjects) demonstrated an improvement in FMD 12 months after Metabolic surgery (WMD: 2.401, 95% CI: 0.944, 3.859, p = 0.001; I2: 88.35). Random-effects meta-regression did not show any association between the alteration in FMD and percent body mass index (BMI) change, or changes in blood pressure; however, there was an association between the changes in FMD and the duration of follow-up (slope: −0.106; 95% CI: −0.205, −0.008; p = 0.033) with greater changes in FMD after 12 months. Metabolic surgery significantly improved FMD that increased with time, and the resultant improvement in endothelial function was independent of weight loss or a reduction in blood pressure.

Project number 7:

The Effect of Metabolic Surgery on Circulating Levels of Monocyte Chemoattractant Protein-1: A Systematic Review and Meta-Analysis

MCP-1 (monocyte chemoattractant protein) plays an important role in early phases of atherogenesis as well as in plaque destabilization which causes cardiovascular events playing an important role in low-grade inflammation. Obesity and, particularly extreme obesity, is a pivotal risk factor for atherosclerosis and many other diseases. In the early stages, metabolic surgery might

stop or slow atherogenesis by suppressing inflammation but also in later stages preventing plaque destabilization. The aim of this meta-analysis was to provide an answer whether metabolic surgery has a significant effect on circulating MCP-1 level or not. A systematic literature search in PubMed, Scopus, Embase, and Web of Science was performed from inception to January 1st, 2022. To investigate the relationship with the estimated effect size, a random-effect meta-regression model was used. Meta-analysis of 25 studies with 927 subjects included demonstrated a significant decrease of MCP-1 concentration after metabolic surgery. The data of meta-regression did not indicate any association between the alterations in body mass index (BMI) and absolute difference in MCP-1 levels but a linear relationship between the changes in MCP-1 and length of follow up was proven. Metabolic surgery significantly decreases MCP-1 concentration but there was no association between the changes in BMI and absolute difference in MCP-1 levels before and after the surgery.

Publications:

- Jamialahmadi T, Reiner Ž, Alidadi M, Kroh M, Cardenia V, Xu S, Al-Rasadi K, Santos RD, Sahebkar A. The Effect of Bariatric Surgery on Circulating Levels of Oxidized Low-Density Lipoproteins Is Apparently Independent of Changes in Body Mass Index: A Systematic Review and Meta-Analysis. Oxid Med Cell Longev. 2021 Dec 6;2021:4136071. doi: 10.1155/2021/4136071. PMID: 34912496; PMCID: PMC8668329.

- Jamialahmadi T, Alidadi M, Atkin SL, Kroh M, Almahmeed W, Moallem SA, Al-Rasadi K, Rodriguez JH, Santos RD, Ruscica M, Sahebkar A. Effect of Bariatric Surgery on Flow-Mediated Vasodilation as a Measure of Endothelial Function: A Systematic Review and

Meta-Analysis. J Clin Med. 2022 Jul 13;11(14):4054. doi: 10.3390/jcm11144054. PMID: 35887817; PMCID: PMC9323618.

➢ Jamialahmadi T, Reiner Ž, Alidadi M, Kroh M, Almahmeed W, Ruscica M, Sirtori C, Rizzo M, Santos RD, Sahebkar A. The Effect of Bariatric Surgery on Circulating Levels of Lipoprotein (a): A Meta-analysis. Biomed Res Int. 2022 Aug 17;2022:8435133. doi: 10.1155/2022/8435133. PMID: 36033567; PMCID: PMC9402303.

➢ Jamialahmadi T, Banach M, Almahmeed W, Kesharwani P, Sahebkar A. Impact of bariatric surgery on circulating PCSK9 levels as a marker of cardiovascular disease risk: a meta-analysis. Arch Med Sci. 2022 Aug 8;18(5):1372-1377. doi: 10.5114/aoms/152685. PMID: 36160336; PMCID: PMC9479707.

Yours sincerely
Tannaz Jamialahmadi, MD, PhD,

Postdoctoral Research Fellow
Mashhad University of Medical Sciences (MUMS)
Mashhad, IRAN
P.O. Box: 9177948954
Phone: 0098 51 31801271
Email: jamiat981@mums.ac.ir   and   jamiat931@gmail.com

Scopus link: https://www.scopus.com/authid/detail.uri?origin=resultslist&authorId=57208751391&zone=
Google Scholar: https://scholar.google.com/citations?user=-guYGugAAAAJ&hl=en&oi=sra

RE: The Wael Al-Mahmeed & IAS Research Training Grants and Fellowships

Endorsement:

I am in agreement with the above summary of Dr. Jamialahmadi's academic accomplishments as listed above.

Matthew Kroh, MD, FACS, FASMBS, FASGE

Vice Chair, Innovation and Technology, Digestive Disease Institute

Division Chief, Advanced Laparoscopic Surgery and Surgical Endoscopy

Professor of Surgery, Cleveland Clinic Lerner College of Medicine

Herewith, I confirm this report.

Amirhossein Sahebkar, PharmD, PhD

Mashhad University of Medical Sciences, Mashhad, Iran