Endothelial function in obesity and effects of bariatric and metabolic surgery

Authors
Elijah Sanches, MD[1]; Besir Topal, MD[2]; Monika Proczko, MD[3]; Pieter S. Stepaniak PhD[4]; Rich Severin PT, DPT, CCS[5,6]; Shane A. Phillips, MD, PhD[7], Ahmad Sabbahi PT, PhD, MA, CCS[5,7]; Juan Pujol Rafols, MD[8]; Sjaak Pouwels, MD, PhD[9]

Affiliations
1. Department of Surgery, Haaglanden Medical Center, The Hague, The Netherlands
2. Department of Cardiothoracic Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
3. Department of General, Endocrine and Transplant Surgery, University Medical Center, Gdansk University, Gdansk, Poland
4. Department of Operating Rooms, Catharina Hospital, Eindhoven, The Netherlands
5. Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, IL, USA;
6. Doctor of Physical Therapy Program, Robbins College of Health and Human Sciences, Baylor University, Waco, TX, USA
7. Department of Physical Therapy, Integrative Physiologic Laboratory, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, IL, USA
8. Department of Surgery, Clinica Mi Tres Torres, Barcelona, Spain
9. Department of Intensive Care Medicine, Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands

Table 1. Methods for the assessment of endothelial (dys) function [15,51,52].

	CAG	Forearm Perfusion technique	FMD	RH-PAT
Vascular bed	Coronary	Peripheral	Peripheral	Peripheral
Trigger	Infusion of endothelial dependent vasodilator	Infusion of endothelial dependent vasodilator	Reactive hyperemia	Reactive hyperemia
Measurement	Vessel diameter Blood flow	Plethysmogram	Vessel diameter	Plethysmogram
Invasive	Yes	Yes	No	No
Predictive for CVE	Yes	Yes	Yes	Yes
Reversible	Yes	Yes	Yes	Yes
Adjustment by control vessel	Yes	Yes	No	Yes
Operator independent	?	?	?	Yes
Easily operated	No	No	No	Yes
Expensive?	Yes	No	No	?

Abbreviations: CAG = coronary angiography, FMD = Flow-mediated dilatation; RH-PAT = reactive hyperemia- peripheral arterial tonometry, CVE = cardiovascular events.

Background
Due to the lifestyle changes and the on-going urbanization waves there is obesity pandemic. The visceral fatty tissue of patients with obesity, in comparison with subcutaneous fat, has more gene expression related to inflammation, oxidative stress, cytokine production, and angiogenesis. The abovementioned leads to a decrease in arteriolar function and also an impaired endothelial vasodilatation and eventually endothelial dysfunction.

Methods
This review aims to provide an overview of the pathophysiology of obesity and endothelial dysfunction and the effects after bariatric and metabolic surgery and the consequences of surgery for the endothelial function. In this review, we focussed and searched for literature in Pubmed and The Cochrane library (from the earliest date of each database until February 2020) regarding endothelial function, obesity, and effects of bariatric and metabolic surgery.

Conclusion
Within cardiovascular research, the endothelium and its function have a prominent role and it is the responsibility of the researchers to unravel the pathophysiological mechanisms and potential new targets for treatment of cardiovascular diseases.

Article highlights

- The visceral fatty tissue of patients with obesity, in comparison with subcutaneous fat, has more gene expression related to inflammation, oxidative stress, cytokine production, and angiogenesis.
- This leads to a decrease in arteriolar function and also an impaired endothelial vasodilatation and eventually endothelial dysfunction.
- Obesity and endothelial dysfunction are a multifactorial complex pathophysiological process that might be influenced by weight reduction after bariatric surgery.
- Endothelial function tests can possibly be used to identify patients at risk for cardiovascular complications after (bariatric) surgery.

❖ The essence of a healthy endothelium lies in the balance between vasodilators/vasoconstrictors and pro- and anticoagulation factors. This balance of these factors is necessary for optimal physiological functioning of the endothelium and imbalance leads to endothelial dysfunction. The presence of endothelial dysfunction may eventually lead to various cardiovascular comorbidities such as peripheral arterial disease, cerebral vascular disease, coronary artery disease.

❖ Dysfunction of endothelium is characterized by one or more of following aspects: reduced production and bioavailability of NO, impaired endothelium-dependent vasodilatation, impaired fibrinolytic capacity, hemodynamic dysregulation, enhanced expression of adhesion molecules and inflammatory genes, increased generation of reactive oxygen species (ROS) and enhanced permeability of vascular endothelium. This leads to functional and structural alterations of the endothelium.

❖ There is a significant body of evidence available that links endothelial dysfunction and resultant atherosclerosis to insulin-resistant states in obesity and diabetes (both type 1 and type 2).

❖ When considering cardiovascular (CV) risk factors such as hypertension, hypercholesterolemia, and insulin resistance (all usually present in the context of obesity) the resulting phenotype is typically a reduction in NO bioavailability and impaired endothelial function which then contributes to deteriorating CV function. Inflammation is closely associated with obesity. As adipose tissue expands there is an increase in immune cell infiltration that initiates the inflammatory response . Studies have shown increases in tumor necrosis factor-alpha (TNF-α), expression of ET-1, and reactive oxygen species (ROS). High level of ROS is well known to impair normal endothelial function.

❖ In a study conducted by Brethauer et al., there was a follow-up of 6 months after RYGB surgery and they showed an improvement of endothelial function compared to preoperative.

❖ The plasma levels of GLP-1 increase rapidly after RYGB, but the same increase in GLP-1 does not happen with the same weight loss after dietary restriction, so this observation raised the hypothesis that these changes in GLP-1 levels could lead to the rapid changes and metabolic improvements (only) after RYGB. The improvement in insulin resistance after bariatric surgery takes place within days, before any substantial weight loss. The coronary microvascular dysfunction (CMVD) also ameliorates after bariatric surgery.

❖ Cardiac morbidity and mortality also improve after bariatric and metabolic surgery. In the pivotal studies, there is a reduction of 29% in the adjusted hazard ratio for death after a follow-up period of 10.9 years. There was in reduction of 40% in death rate of all causes, 92% in death by diabetes, and 56% in death by coronary artery disease.

KEYWORDS
Endothelial function;bariatric surgery; metabolic surgery; cardiac remodeling;postoperative complications; cardiovascular remodeling