## The role of obesity and adipokines in coronary microvascular dysfunction: a systematic review and meta-analysis

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**Background:** Patients with obesity present structural and functional changes in the heart and in the coronary circulation, which ultimately leads to an increased risk of cardiovascular disease. Obesity is associated with a low chronic state of inflammation which seems to be linked to a compromised coronary vasoreactivity, which is shown to be a forerunner and a long-term predictor of clinically relevant cardiovascular events.

**Methods:** A systematic review was performed by searching PubMed, Embase and Cochrane Library database. Selection criteria were applied leading to the inclusion of studies of any level of evidence published in peer-reviewed journals reporting clinical or preclinical results. Relative data were extracted and critically analysed. PRISMA guidelines were applied and risk of bias was assessed, as well as the methodological quality of the included studies. After this assessment, we excluded all the articles with serious risk of bias and/or low quality. Meta-analysis was conducted on the data collected regarding coronary blood flow (CFR) and hyperemic myocardial blood flow (MBF), while for the other parameters a descriptive analysis was performed.

**Results:** After applying the described criteria, we included 15 articles on human and animal literature assessed as medium or high quality. The data of 1399 patients were examined, 456 of which with obesity (BMI  $\ge$  30). A pooled effect size analysis shows that coronary flow reserve (CFR) is significantly reduced in patients with obesity [Random Effect (RE): -47.7%, 95% confidence interval (CI) -80.2% – -15.2%; n = 422]. Increased BMI is associated with reduced CFR. The same trend is found evaluating pharmacological induced stress MBF, which was reduced in patients with obesity [RE: -47.8%, 95% CI -73.7% – -21.8%; n = 409]. Nevertheless, MBF at rest did not show a significant difference in patients with obesity from our analysis [RE: 15%, 95% CI -24% - 53%; n = 409]. Pro-inflammatory adipokines secretion, as leptin and CRP, seems to correlate with a significant decrease of stress-induced MBF and reduced CFR.

**Conclusions:** Obesity is associated with a significant higher risk of coronary microvascular disfunction, which is reflected by diminished CFR and stress MBF. Systemic inflammation and the imbalance of adipokines related to obesity has been closely linked to a blunt coronary flow. CMD is a pre-clinical heart conditions that often remains undiagnosed. Further evidence is required to clear out the role of Obesity from a molecular point of view on the coronary endothelium.