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

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Abstract

Introduction: This systematic review and meta-analysis focuses on PCSK9 changes in obese patients following bariatric surgery.

Methods: A systematic literature search in four databases was performed. Comprehensive Meta-Analysis (CMA) V2 software used to conduct the meta-analysis. Studies were evaluated regarding heterogeneity in design, populations under investigation, and treatment duration using a random-effects model and the generic inverse variance weighting approach. A random-effects meta-regression approach was used to investigate the association with the estimated effect size.

Results: The results of the meta-analysis on 4 trials including 260 individuals demonstrated a remarkable decline of PCSK9 after bariatric surgery (WMD = –57.34 ng/ml, 95% CI: –87.97, –26.71, \( p < 0.001 \); \( I^2 = 96.25\% \)). Consistently, a significant decrease of LDL-C after bariatric surgery (WMD = –22.57 mg/dl, 95% CI: –27.5, –17.574, \( p < 0.001 \); \( I^2 = 86.35\% \)) was observed.

Conclusions: PCSK9 is reduced significantly after bariatric surgery. The decrease of PCSK9 might be utilized as an independent surrogate marker of improvement of atherosclerotic cardiovascular disease risk after bariatric surgery.

Key words: bariatric surgery, low-density lipoprotein-cholesterol, obesity, meta-analysis, PCSK9.

Obesity is an increasing morbid condition with epidemic features associated with cardiovascular risk factors [1]. Currently, bariatric surgery for severely obese patients has proven to be the most effective treatment...
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PCSK9 is a key regulator of low-density lipoprotein-cholesterol (LDL-C) via enhancing LDL receptor internalization and endosomal degradation. PCSK9 plasma levels have been demonstrated to predict cardiovascular (CVD) risk [5–8]. Interestingly, some studies have found a correlation between PCSK9 concentrations and fat mass [9]. Although caloric restriction lowers PCSK9 concentration in adults [10], bariatric surgery has recently been found to lower plasma LDL-C as well as PCSK9 levels simultaneously [11]. However, the magnitude of such a reduction is not known and there has been no meta-analysis evaluating the extent of improvement varies depending on the surgical approach utilized [4].

Quality assessment. The Newcastle-Ottawa Scale (NOS) was utilized to estimate the quality of the studies included in this meta-analysis [12, 13]. Three aspects of each qualified study are considered for this scale: (1) the selection of the patients in the studies (4 items), (2) the comparability of the studied populations (one item) and (3) the outcome of interest (3 items).

Quantitative data synthesis. The meta-analysis was conducted by Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [14]. The weighted mean differences (WMDs) with relevant CIs were determined for continuous outcomes. From each group sample sizes, means, and standard deviations were obtained for each relevant outcome to calculate WMDs. Overall estimate of effect size was measured by a random effects meta-analysis. To account for the heterogeneity of studies with regard to study design, characteristics of the populations under investigation and treatment duration, a random-effects model (using the Der-Simonian-Laird method) and the generic inverse variance weighting approach were utilized [15]. A sensitivity analysis employing the leave-one-out

| Study, year     | Study design            | Follow-up | Treatment          | Control                 | Clinical result                                      | P-value | Patients         | No. of patients |
|-----------------|-------------------------|-----------|--------------------|-------------------------|------------------------------------------------------|---------|------------------|-----------------|
| Zenti et al.,   | Non-randomized          | 6 months  | Bariatric surgery  | Nonobese healthy        | Significant decrease in PCSK9 values                 | < 0.003 | Morbidly obese subjects | 20              |
| 2020 [16]       | interventional study    |           |                    | controls                |                                                      |         |                  |                 |
| Blanchard et al.| Prospective study       | 6 months  | SG/RYGB            | –                       | Significant change in PCSK9 values                   | < 0.0001| Morbidly obese subjects | 156             |
| 2020 [9]        |                         |           |                    |                         |                                                      |         |                  |                 |
| Ghanim et al.,  | Prospective study       | 6 months  | RYGB               | –                       | Significant change in PCSK9 values                   | Not mentioned | Morbidly obese subjects | 15              |
| 2018 [5]        |                         |           |                    |                         |                                                      |         |                  |                 |
| Boyer et al.,   | Randomized interventional study | 24 h 5 days | 6 months | BPD-DS | Severe obesity patients | Significant decrease in PCSK9 values | < 0.003 | Morbidly obese subjects | 69              |
| 2015 [11]       |                         |           |                    |                         |                                                      |         |                  |                 |
approach (i.e., deleting one study each time and repeating the analysis) was applied to analyze the effect of each study on the overall effect size.

Results. Among 90 published studies identified in the systematic database search, 34 were directly related to the topic of this study. Among them, 30 studies were excluded after careful evaluation (20 studies were reviews, 7 studies did not match the inclusion criteria and 3 studies did not report sufficient data). Therefore, 4 studies which evaluated PCSK9 after bariatric surgery were included (Table I) [16]. Figure 1 depicts the process of study selection.

Quality assessment of included studies. All the selected studies showed representativeness of the exposed cohorts, but most of them were distinguished by a lack of selection of the non-exposed cohort. Given that most of the studies did not include a non-exposed group, they were not assessed for comparability and adequacy of follow-up of cohorts. Finally, all included studies met the assessment of outcome. Quality assessment of the selected studies is presented in Table II.

Effect of bariatric surgery on PCSK9 and LDL-C. The random-effects meta-analysis of 4 studies including 260 subjects demonstrated a significant decrease of plasma PCSK9 levels after bariatric surgery (WMD = –57.341 ng/ml, 95% CI: –87.969, –26.714, \( p < 0.001; I^2 = 96.25\% \)) (Figure 2 A). The reduction in PCSK9 was robust in the leave-one-out sensitivity analysis. Consistently, a significant decrease of LDL-C after bariatric surgery (WMD = –22.573 mg/dl, 95% CI: –27.571, –17.574, \( p < 0.001; I^2 = 86.35\% \)) was observed (Figure 2 B). The reductions in PCSK9 and LDL-C were robust in the leave-one-out sensitivity analysis (Figures 3 A, B).

Meta-regression. Random-effects meta-regression was used to analyze the association between baseline BMI and the PCSK9-reducing effect of bariatric surgery. The results suggested a significant association between the changes in PCSK9 and baseline BMI (slope: 8.232; 95% CI: 5.622, 10.842; \( p < 0.001 \)). The results must be interpreted with caution owing to the limited number of included studies.

Publication bias. Evaluation for bias using Egger's test (intercept = –5.206, standard error = 0.858; 95% CI = –8.899, –1.513, \( t = 6.066, df = 2 \), two-tailed \( p = 0.026 \)) suggested publication bias, while Begg's test (Kendall's tau with continuity correction = –0.166, \( z = 0.339 \), two-tailed \( p\text{-value} = 0.734 \)) suggested that there was no publication bias in the meta-analysis demonstrating bariatric surgery's impact on PCSK9. Trim and fill correction identified one potentially “missing” study. In accordance with the “fail-safe N” test, 2961 missing

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Table II. Quality assessment of included studies

| Study               | Selection | Comparability | Outcome          |
|---------------------|-----------|---------------|------------------|
|                     | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstrate that the focal outcome was not existent at the start | Comparability of cohorts | Assessment of outcome | Long enough follow-up | Adequacy of follow-up |
| Zenti et al. 2020   | *         | *             | *                | *                  | *                  | *                  | *                  | *                |
| Blanchard et al. 2020 | *        | –             | *                | *                  | *                  | *                  | *                  | *                |
| Ghanim et al. 2018  | *         | –             | *                | –                  | *                  | *                  | *                  | *                |
| Boyer et al. 2015   | *         | *             | *                | *                  | *                  | *                  | *                  | *                |
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### A

| Study name          | Difference in means (95% CI) | Difference in means and 95% CI |
|---------------------|------------------------------|--------------------------------|
| Zenti et al. 2020   | –90.000 (–120.118 to –59.882) | –113.751 to –66.249, Z = –7.427, p < 0.001 |
| Blanchard et al. 2020 | –60.000 (–78.641 to –41.359)  | –93.796 to –26.204, Z = –5.697, p < 0.001 |
| Ghanim et al. 2018  | –61.000 (–78.641 to –43.359)  | –94.035 to –29.965, Z = –9.992, p < 0.001 |
| Boyer et al. 2015   | –23.350 (–32.797 to –13.903)  | –32.897 to –13.794, Z = –83.603, p < 0.001 |

### B

| Study name          | Difference in means (95% CI) | Difference in means and 95% CI |
|---------------------|------------------------------|--------------------------------|
| Zenti et al. 2020   | –16.700 (–28.262 to –5.138)  | –32.715 to –1.183, Z = –2.044, p = 0.041 |
| Blanchard et al. 2020 | –15.000 (–20.342 to –9.658)  | –20.964 to –4.136, Z = –5.503, p < 0.001 |
| Ghanim et al. 2018  | –25.000 (–30.597 to –19.403) | –31.964 to –13.136, Z = –16.137, p < 0.001 |
| Boyer et al. 2015   | –27.110 (–37.571 to –16.649) | –37.971 to –15.849, Z = –61.697, p < 0.001 |

### Discussion

This meta-analysis indicated a significant decrease of circulating PCSK9 levels after bariatric surgery. This is the first meta-analysis evaluating the impacts of bariatric surgery on PCSK9 as a regulator of plasma cholesterol levels. This finding is consistent with other reports suggesting a positive impact of bariatric surgery on cardiovascular risk factors [17–20]. The observed drop in circulating PCSK9 levels could be attributed to long-term weight loss caused by the bariatric procedure as well as sustained decreases in total food intake [11]. Total weight loss after bariatric surgery was found to be inversely associated with PCSK9 alterations [9]. It suggests
that following bariatric surgery, PCSK9 levels were significantly decreased throughout chronic and significant weight loss. However, a recent study indicated that enhancing nutritional quality and physical activity did not result in reductions in circulating PCSK9 levels, implying that modest weight loss is not enough to reduce plasma PCSK9 concentration [21]. Furthermore, reduced PCSK9 levels in the chronic period may potentially be explained by better function and regulation of adipose tissue, as well as adipokine secretion following bariatric surgery. It was recently found that leptin and resistin may modulate PCSK9 and LDL-C levels [22]. Previous research also revealed that in response to bariatric surgery-induced weight loss and insulin sensitivity, adipose tissue plays an undetected role in PCSK9 homeostasis. Thus, it is feasible to speculate that physiological insulin levels may influence expression of hepatic PCSK9 and its circulating levels [16]. Alternatively, it is possible that the observed alterations in plasma PCSK9 levels are attributable to a change in metabolism of bile acids. Certainly, after Roux-en-Y gastric bypass (RYGB), bile acids in plasma have been shown to be significantly elevated in morbidly obese patients [23]. Increased bile acid concentrations can result in reduced PCSK9, as bile acids reduce hepatic mRNA and protein expression of PCSK9, an effect that is likely mediated by the activation of farnesoid X receptor [24].

Despite the novelty of this study, limitations include the small number of overall studies, restricting the generalizability of the findings. Moreover, in most of the studies there was no differentiation of free and total PCSK9. Finally, the included studies lacked control groups with other methods of weight loss to allow a direct comparison between different weight loss approaches with respect to their impact on plasma PCSK9 levels.

In conclusion, our findings imply that bariatric surgery is related to lower circulating levels of PCSK9. This finding may partly explain the improvement in lipid profile and cardiovascular risk that occurs following surgery. More research is needed to better understand the mechanisms underlying the influence of bariatric surgery on PCSK9 concentration, as well as to determine the clinical impact of the weight loss procedure on PCSK9 function [25–28].

Conflict of interest

The authors declare no conflict of interest.

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