The effect of *Helicobacter pylori* eradication on C-reactive protein: results from a meta-analysis

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Abstract

Introduction: *Helicobacter pylori* is a bacterium that causes chronic gastroduodenal infection and affects various systemic diseases. An increase in the blood level of C-reactive protein (CRP; a systemic inflammatory marker), at a low-grade chronic inflammation level, is observed in cases of infection. However, the effect of *H. pylori* eradication on CRP remains undetermined. Therefore, we aimed to evaluate the circulating CRP levels in eradicated patients through a meta-analysis.
Material and methods: The PubMed database was searched from its inception to June 2020. Studies that described the CRP levels following *H. pylori* eradication were collected. A random-effects meta-analysis was then performed using inverse variance with standardized mean difference.
Results: A total of 10 eligible studies (642 subjects in total) were available. The median age in the studies was 49.9 years. The CRP level was 6.0 (median) mg/l before *H. pylori* eradication and 5.8 (median) mg/l after eradication. From the results of the overall meta-analysis, there was found to be a significant reduction in the CRP levels with *H. pylori* eradication (standardized mean difference: −0.64; 95% confidence interval: −1.02 to −0.27). The result was not similarly confirmed in a subanalysis of the available randomized controlled trials.
Conclusions: Weak evidence exists regarding the effects of *H. pylori* eradication on CRP levels. Further research is called for.

Key words: anti-bacterial therapy, C-reactive protein, *Helicobacter pylori*, inflammation.

Introduction

The bacterium *Helicobacter pylori* causes gastroduodenal inflammation [1]. *H. pylori* infection is present in 28–84% of populations around the world [2]. The precancerous lesions of chronic gastritis are well known to be caused by *H. pylori* infection [3–5]. *H. pylori* eradication using a regimen containing anti-bacterial agents is useful not only for healing gastroduodenal ulcers but also for preventing gastric cancer [6].

C-reactive protein (CRP), produced in the liver and released into blood, is a representative marker reflecting systemic inflammation [7]. This protein is increased not only in acute but also in chronic diseases, and its slight change in chronic diseases at a low-grade subclinical level has pathophysiological relevance [7–9]. In *H. pylori* infection, a low-grade chronic increase in circulating inflammatory markers, especially CRP, is

observed [10]. Such chronic inflammation is also known to initiate and exacerbate various systemic pathologies [11]. *H. pylori* infection is indicatively related to other gastric and even extra-gastric diseases, including gastric mucosa-associated lymphoid tissue lymphoma, functional dyspepsia, idiopathic thrombocytopenic purpura, iron deficiency anemia, chronic urticaria, metabolic disorder, ischemic heart disease, cognitive impairment, and neurodegeneration [6, 12–16].

The clinical manifestations of some diseases may be improved after *H. pylori* eradication in relation to the CRP levels [4–6, 17, 18]. As the CRP levels are typically low in such inflammatory states, changes in them may be overlooked. The effect of *H. pylori* eradication on CRP remains undetermined; accordingly, the present study was designed to evaluate the effect of *H. pylori* eradication on circulating CRP levels through a meta-analysis.

Material and methods

The relevant literature was searched using the PubMed database from its inception to June 3, 2020. The following keywords were used to search: ("Helicobacter pylori"[Mesh] OR "Helicobacter pylori"[tiab] OR "H. pylori"[tiab]) AND ("C-Reactive Protein"[Mesh] OR "c-reactive protein"[tiab] OR "CRP"[tiab]) AND ("eradicat*"[tiab]). Studies that focused on the effect of *H. pylori* eradication on CRP were included. Non-English-language and non-adult studies were excluded.

First, all candidate articles searched were independently screened according to the title and abstract. Original articles that did not focus on *H. pylori* and CRP were excluded. Second, the full text of potentially relevant abstracts was evaluated for eligibility. Original articles that did not focus on *H. pylori* and CRP were further excluded. When the researchers' opinions matched, the articles were considered eligible. The agreement between the two researchers was determined by the κ value. The eligibility was judged based on the two researchers' opinions. Third, summary tables of the respective articles were extracted and created.

The risk of bias was independently assessed using Risk of Bias (RoB) 2 [19] for randomized studies and the Newcastle-Ottawa Quality Assessment Scale (NOS) [20] for non-randomized studies. RoB 2 was assessed as described in the Cochrane handbook for the following six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each domain was classified into one of three categories (high risk, low risk, some concerns). The NOS assigns a maximum of 9 points to studies of the highest

quality according to three quality parameters: selection, comparability and outcome; high score means better quality. Any disagreement of the assessment by the two researchers was resolved by discussion.

The standardized mean difference (SMD) with the 95% confidence interval (CI) of the mean change in the CRP levels after *H. pylori* eradication was calculated as described in the Cochrane handbook [21]. The meta-analysis was performed by comparing each individual case before and after eradication, regardless of study design, because the CRP levels differ among individuals. Similar analyses were performed in earlier studies [22–24]. The statistical heterogeneity was evaluated by visual inspection of the forest plots and calculating the I^2 statistic (I^2 values of 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: may represent considerable heterogeneity) [21]. When there was substantial heterogeneity ($I^2 > 50\%$), the potential reason for the heterogeneity was assessed using a subgroup analysis. The potential publication bias was assessed by visual inspection of the funnel plot [21]. The meta-analysis was performed with a random-effects model using the genetic inverse method in the Review Manager 5.4 software program of RevMan 2020.

Results

Figure 1 shows the process of selection of articles that reported the effect of *H. pylori* eradication on CRP. After the first step, a total of 44 records were searched, and 15 articles were considered candidates (inter-reader agreement, κ = 0.894). At the second step, four articles were excluded because these articles did not meet the criteria. Eleven studies were then identified in quantitative synthesis (inter-reader agreement, κ = 1.0) [25–35]. Finally, 10 studies (total of 642 subjects) were meta-analyzed, as 1 article [30] did not report important measures, such as the standard deviation, range, or standard error of the CRP levels.

Table I shows the summary of the reviewed studies. Four studies were reported from the Middle East (Turkey [27], Iran [32], Egypt [33, 35]), 4 from Europe (Spain [25, 34], Italy [26], the Netherlands [29]), 1 from the United States [31] and 1 from Korea [28]. The study design consisted of 2 randomized controlled trials (RCTs), 2 cohort studies, 2 case-controlled studies and 4 before-after studies. The age reported in the reviewed studies was 49.9 (median (range: 44.7–56.0)) years. The CRP level was 6.0 (median (range: 0.0028–310)) mg/l before *H. pylori* eradication and 5.8 (median (range: 0.0026–100)) mg/l after it. The periods of eradication ranged from 7 to 14 days. The
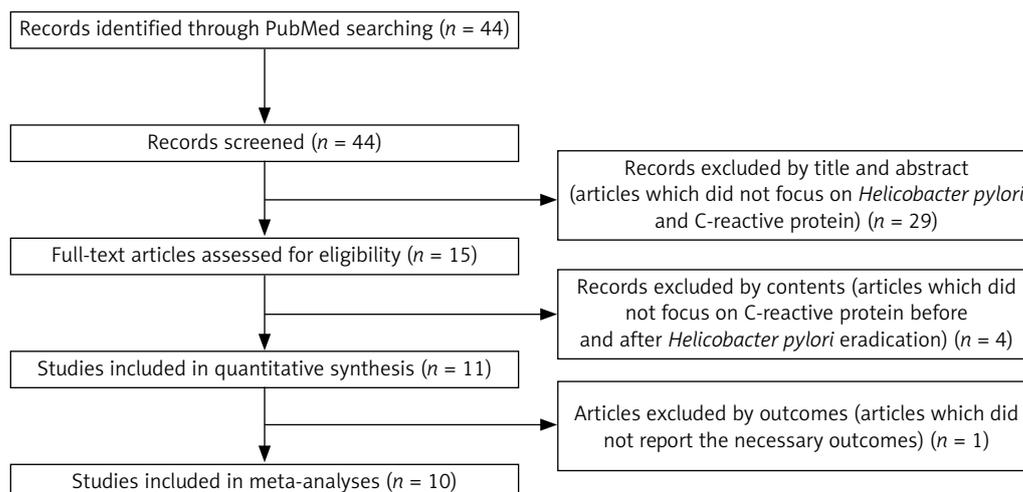
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Figure 1. Flow chart of article selection

H. pylori eradication rate was 96.4% (median (range: 73.3–100%)). The follow-up period, meaning the interval period to examined CRP levels before and after eradication, was 3 (median (range: 1.5–24)) months.

Tables II and III show the quality scores for the reviewed randomized and non-randomized studies, respectively. The overall risks of bias in 2 RCTs were classified into some concerns due to unclear random sequence generation and reporting bias. The quality assessment of 8 non-RCTs were moderate scores in the range of 5–6. Regarding publication bias, the funnel plot appeared to be asymmetric, with some missingness at the lower right portion of the plot, suggesting possible publication bias (Supplementary Figure S1).

The CRP levels were reduced after *H. pylori* eradication not only in healthy subjects [34] but also in subjects with diabetes mellitus [25], rheumatoid arthritis [26], non-alcoholic hepatitis [33], and cirrhosis [35]. From the results of the overall meta-analysis, *H. pylori* eradication was associated with reduced CRP levels (SMD = –0.64; 95% CI: –1.02 to –0.27; I^2 = 89%, Figure 2). In a subgroup analysis by study designs, the reduction of CRP in the eradicated patients was not found in the group of RCTs, while it was found in the group of before-after studies (Figure 3).

In additional subgroup analysis by comorbidity (such as glucose intolerance/diabetes, rheumatoid arthritis, chronic liver disease), *H. pylori* eradication reduced the CRP levels in both patients with and without comorbidities (Supplementary Figure S2). In a subgroup analysis by country (which can reflect ethnicity), *H. pylori* eradication reduced the CRP levels in patients in Europe and the Middle East, while this seemed to be an insufficient analysis because there was only one report in the United States or Asia (Korea) (Supplementary Figure S3). In a subgroup analysis by the follow-up period,

H. pylori eradication reduced the CRP levels more in patients with ≥ 3-month periods relative to those with < 3-month periods (Supplementary Figure S4).

Discussion

The overall meta-analysis revealed that *H. pylori* eradication was associated with reduced CRP levels. However, the result was not similarly supported by a subgroup of the RCTs, which meant that the evidence as regards the effects of *H. pylori* eradication on the reduction of CRP levels was weak. As a systemically low-grade inflammation, as expressed by the CRP level, is related to the development and progression of various diseases [11], the present study findings would promote our understanding of the pathophysiology.

Although the present study does not mention the etiological mechanisms responsible for the relationship between CRP and *H. pylori* eradication, several potential factors involved have been assumed. The mucosal response to *H. pylori* infection induces the production of cytokines (e.g. interleukin-6, tumor necrosis factor-γ) on CRP, mainly in the liver hepatocytes [36, 37]. *H. pylori* eradication suppresses the cytokine production, which can reduce the CRP level [38]. The microbiome is a possible contributor as the diverse microbiome is thought to modulate inflammation and the host's immune system favorably [39–41]. A microbiome lacking in the diversity due to infection can induce metabolic endotoxemia with an increased CRP level [40, 41]. The anti-biotic therapies against *H. pylori* infection alter the microbiome, leading to a reduction in *H. pylori*-induced inflammation [42, 43].

Furthermore, the clinical manifestations of some chronic diseases may be improved in association with the reduced CRP levels [17, 18]. While it is not fully clarified whether CRP is the

Table I. Summary of characteristics of the reviewed studies

Authors [ref no.]	Year	Design	Country	Comorbidities	Subject no.	Age [years]	Therapy [days]	Follow-up [months]	Eradication rate (%)	C-reactive protein [mg/l]	
										Before eradication	After eradication
De Luis [25]	1999	Before-after study	Spain	Type 1 diabetes mellitus	22	45.1	10	3	73.3	4.8 ±0.7	3.3 ±0.4
Zentilin [26]	2002	Before-after study	Italy	Rheumatoid arthritis	28	56	7	24	96.4	310 (180–1220)[a]	100 (30–400)[a]
Kanbay [27]	2005	Before-after study	Turkey	–	57	49.9	14	2	100	85 ±28	77 ±27
Park [28]	2005	Case-control study	Korea	–	29	44.7	7	12	100	–	0.2 ±1.3[b]
Steen [29]	2009	Randomized controlled trial	Netherlands	Rheumatoid arthritis	55	–	–	12	–	6.0 (2.7–16)[b]	5.8 (2.5–9.3)[a]
Siddiqui [31]	2009	Before-after study	USA	–	46	55.8	14	2	93.5	30 ±29	11.4 ±14.2
Kachuei [32]	2016	Randomized controlled trial	Iran	Prediabetes	26	52.3	14	1.5	88.5	1.1 ±0.2	1.1 ±0.2
Abdel-Razik [33]	2018	Cohort study	Egypt	Non-alcoholic fatty liver disease	127	49.8	14	3	78.9	0.0031 ±0.002	0.0026 ±0.002
Cornejo-Pareja [34]	2019	Case-control study	Spain	Healthy	40	47.0	10	3	97.5	41 ±4	36 ±3
Abdel-Razik [35]	2020	Cohort study	Iran	Cirrhosis	212	53	14	3	78.5	0.0028 ±0.002	0.0028 ±0.005

No. – number. C-reactive protein: mean ± standard deviation, [a]range, [b]change level.

etiological agent of inflammation or a simple indicator/marker related to inflammation [11, 44], the pathophysiology of chronic diseases appears to be generally improved in a relatively long period. When the subanalysis by the follow-up period of eradicated patients was conducted, the CRP levels were more reduced in the patients with a longer follow-up period (as shown in (Supplementary Figure S4). Future work on the relationship of CRP and clinical manifestations with the period after *H. pylori* eradication may shed light on the etiological mechanisms.

The present study had some strengths. First, the CRP levels were analyzed before and after *H. pylori* eradication among the same individuals. Accordingly, the individual characteristics were not likely to have had a large effect on the results. Second, the duplicate assessments were performed for the eligibility, risk of bias and data abstraction in the review process.

There were some study limitations. First, circulating CRP levels can be associated with age, gender, ethnicity, lifestyle and comorbidity [45], although few within-person variations of CRP are revealed at the year-to-year level [46]. The subanalysis by comorbidity and country did not reveal a clear difference in the results (as shown in (Supplementary Figures S2 and S3), while the other factors of age, gender and lifestyle were not collected in the original studies used in the present meta-analysis. Second, there was a small number of original studies (especially RCTs) with not very large numbers of participants and some different follow-up periods; thus, the present study integrated the different study designs, which might undermine the meta-analysis. Third, although the measurement methods of CRP could differ across studies, many studies did not describe the methods. Thus, we did not conduct a subanalysis according to the methods, but we assumed that the studies usually did not change the methods of measuring the CRP levels before and after eradication. Fourth, the funnel plot asymmetry to detect publication bias in the literature might slightly overestimate the effect sizes. The present study findings must be carefully interpreted with these limitations, which will be addressed as the next challenge.

In conclusion, the overall meta-analysis demonstrated that *H. pylori* eradication was associated with reduced CRP levels; however, the result was not supported by a subgroup of the RCTs. Weak evidence exists regarding the effects of *H. pylori* eradication on CRP levels. Further research is warranted.

Conflict of interest

The authors declare no conflict of interest.

Table II. Quality scores for the reviewed randomized studies

Authors [ref no.]	Risk of bias 2 tool assessment					
	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
Steen [29]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Kachuei [32]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns

No. – number.

Study or subgroup	Std. mean difference	SE	Weight (%)	Std. mean difference IV, random, 95% CI	Std. mean difference IV, random, 95% CI
De Luis 1999	−2.5839	0.4174	7.6	−2.58 (−3.40, −1.77)	
P. Zentilin 2002	−1.756	0.3179	8.9	−1.76 (−2.38, −1.13)	
Park 2005	0.02	0.24	10.0	0.02 (−0.45, 0.49)	
Kanbay 2005	−0.2889	0.1883	10.6	−0.29 (−0.66, 0.08)	
Steen 2009	−0.0181	0.1907	10.6	−0.02 (−0.39, 0.36)	
Siddiqui 2009	−0.8295	0.2177	10.3	−0.83 (−1.26, −0.40)	
Kachuei 2016	0.0938	0.2775	9.5	0.09 (−0.45, 0.64)	
Abdel-Razik 2018	−0.2922	0.1262	11.3	−0.29 (−0.54, −0.04)	
Cornejo-Pareja 2019	−1.4006	0.2508	9.8	−1.40 (−1.89, −0.91)	
Abdel-Razik 2020	−0.1	0.0972	11.5	−0.10 (−0.29, 0.09)	
Total (95% CI)			**100.0**	**−0.64 (−1.02, −0.27)**	

Heterogeneity: $t^2 = 0.31$; $\chi^2 = 85.50$, d$f = 9$ ($p < 0.00001$); $I^2 = 89\%$
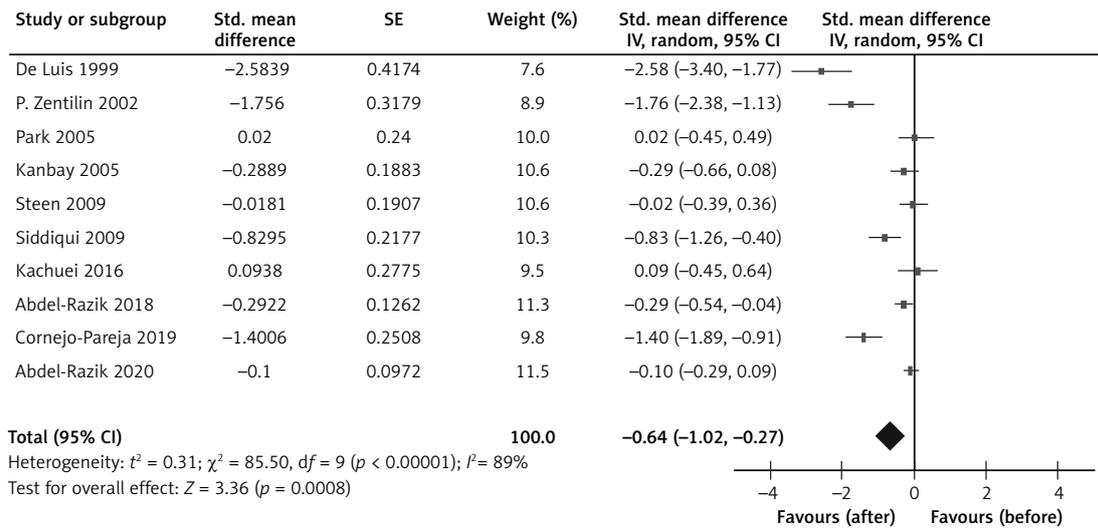Test for overall effect: $Z = 3.36$ ($p = 0.0008$)

Favours (after)　Favours (before)

Figure 2. Forest plot of the change in the C-reactive protein level after *Helicobacter pylori* eradication

Study or subgroup	Std. mean difference	SE	Weight (%)	Std. mean difference IV, random, 95% CI	Std. mean difference IV, random, 95% CI
1.4.1. Randomized controlled trial					
Steen 2009	−0.0181	0.1907	10.6	−0.02 (−0.39, 0.36)	
Kachuei 2016	0.0938	0.2775	9.5	0.09 (−0.45, 0.64)	
Subtotal (95% CI)			**20.1**	**0.02 (−0.29, 0.33)**	
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.11$, d$f = 1$ ($p = 0.74$), $I^2 = 0\%$					
Test for overall effect: $Z = 0.11$ ($p = 0.91$)					
1.4.2. Cohort study					
Abdel-Razik 2018	−0.2922	0.1262	11.3	−0.29 (−0.54, −0.04)	
Abdel-Razik 2020	−0.1	0.0972	11.5	−0.10 (−0.29, 0.09)	
Subtotal (95% CI)			**22.8**	**−0.18 (−0.36, 0.01)**	
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 1.46$, d$f = 1$ ($p = 0.23$), $I^2 = 31\%$					
Test for overall effect: $Z = 1.89$ ($p = 0.06$)					
1.4.3. Case-control study					
Park 2005	0.02	0.24	10.0	0.02 (−0.45, 0.49)	
Cornejo-Pareja 2019	−1.4006	0.2508	9.8	−1.40 (−1.89, −0.91)	
Subtotal (95% CI)			**19.8**	**−0.69 (−2.08, 0.70)**	
Heterogeneity: $\tau^2 = 0.95$; $\chi^2 = 16.75$, d$f = 1$ ($p < 0.0001$); $I^2 = 94\%$					
Test for overall effect: $Z = 0.97$ ($p = 0.33$)					
1.4.4. Before-after study					
De Luis 1999	−2.5839	0.4174	7.6	−2.58 (−3.40, −1.77)	
P. Zentilin 2002	−1.756	0.3179	8.9	−1.76 (−2.38, −1.13)	
Kanbay 2005	−0.2889	0.1883	10.6	−0.29 (−0.66, 0.08)	
Siddiqui 2009	−0.8295	0.2177	10.3	−0.83 (−1.26, −0.40)	
Subtotal (95% CI)			**37.4**	**−1.31 (−2.18, −0.43)**	
Heterogeneity: $\tau^2 = 0.71$; $\chi^2 = 34.16$, d$f = 3$ ($p < 0.00001$); $I^2 = 91\%$					
Test for overall effect: $Z = 2.93$ ($p = 0.003$)					
Total (95% CI)			**100.0**	**−0.64 (−1.02, −0.27)**	

Heterogeneity: $\tau^2 = 0.31$; $\chi^2 = 85.50$, d$f = 9$ ($p < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 3.36$ ($p = 0.0008$)
Test for subgroup differences: $\chi^2 = 8.46$, d$f = 3$ ($p = 0.04$), $I^2 = 64.5\%$
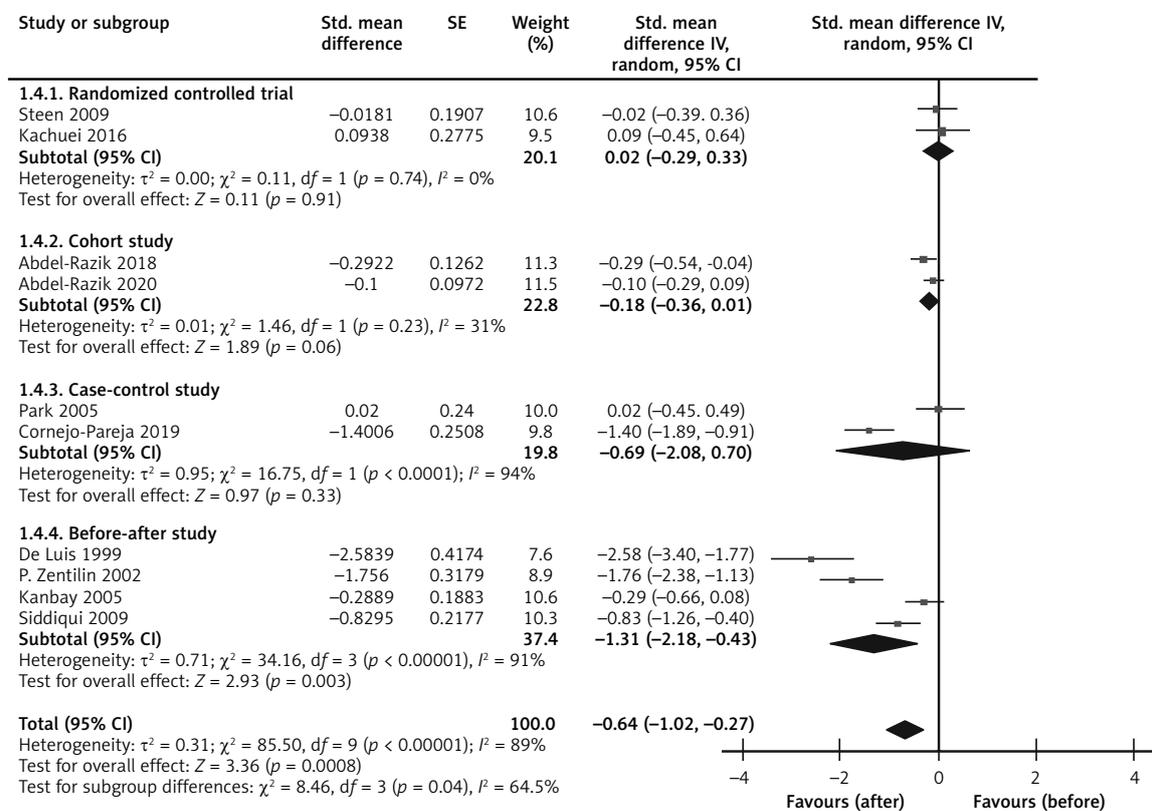
Favours (after)　Favours (before)

Figure 3. Subgroup analysis by study designs

Table III. Quality scores for the reviewed non-randomized studies

Authors [ref no.]	Newcastle-Ottawa Quality Assessment Scale								Total Score
	Selection				Comparability	Outcome			
	Representatives of the exposed cohort/adequate case definition (0, 1)	Selection of the non-exposed cohort/representative of cases (0, 1)	Ascertainment of exposure/selection of controls (0, 1)	Demonstration that outcome of interest was not present at start of study/definition of controls (0,1)	Comparability on the basis of design or analysis (0, 1, 2)	Assessment of outcome/exposure (0, 1)	Was follow-up long enough for outcomes to occur? (0, 1)	Adequacy of follow-up of cohorts (0, 1)	
De Luis [25]	1	1	1	0	0	1	0	1	5
Zentilin [26]	1	1	1	0	0	1	1	1	6
Kanbay [27]	1	1	1	0	0	1	0	1	5
Park [28]	1	1	1	0	0	1	1	0	5
Siddiqui [31]	1	1	1	0	0	1	0	1	5
Abdel-Razik [33]	1	1	1	0	0	1	0	1	5
Cornejo-Pareja [34]	1	1	1	0	0	1	0	1	5
Abdel-Razik [35]	1	1	1	0	0	1	0	1	5

No. – number.

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