


META-ANALYSIS

The effect of micronutrients on postpartum pelvic organ prolapse patients

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Article Info	ABSTRACT
<p>Received Mar 19, 2023 Revised Jun 2, 2023 Accepted Jun 16, 2023 Published Aug 1, 2023</p> <p>*Corresponding author: Rahajeng rahajeng.fk@ub.ac.id</p> <p>Keywords: Pelvic Organ Prolapse Micronutrient Vitamin D Type-1 collagen MMP-1 Maternal Health</p> <p>This is an open access article under the CC BY-NC-SA license (https://creativecommons.org/licenses/by-nc-sa/4.0/)</p> 	<p>Objective: Pelvic Organ Prolapse (POP) is when pelvic tissues sink into the vagina due to weakened ligaments or muscles. POP is common globally. Adequate nutrition, including Vitamin D, is vital for prevention. Vitamin D maintains bone and muscle health, regulates MMP-9 to control collagen, essential for pelvic support. Increased MMPs lead to collagen breakdown and POP. Recognizing vitamin D's role in collagen and POP is crucial for prevention. This study aimed to determine definitive association between vitamin D, collagen type I and MMP-1 in POP patients.</p> <p>Materials and Methods: Our search yielded 1375 studies, of which 7 were included in the present investigation. Two studies addressed the micronutrient status of vitamin D, four investigated the micronutrient status of type 1 collagen, and two studied the micronutrient status of MMP-1 in postpartum POP patients.</p> <p>Results: The results showed that the mean of vitamin D levels from POP group was substantially decreased compared to a those of healthy women in the control group (95% confidence interval (CI), -3.64; -3.44 and p <0.05). There was a decrease of collagen I protein in POP (95% CI, -3.26; -2.45. p <0.05). Additionally, MMP-1 expression increased in POP patient (95% CI. 1.48-2.23, p <0.05)</p> <p>Conclusion: Micronutrient status was severely compromised in POP group compared to control subjects.</p>

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Highlights:

1. Serum vitamin D levels were significantly different between POP and in healthy women.
2. Micronutrient MMP-1 expression is increased in POP patients.

INTRODUCTION

Pelvic organ prolapse (POP), known as a common gynecologic disorder, is defined as the descent of the pelvic structures into the vagina due to the loss of ligament or muscle support.¹ It is one of a disease that remarkably affects women's quality of life.² Pelvic organ prolapse is highly prevalence disease with unknown primary cause which affects up to 50% of parous women in both developing and developed countries.³ POPs are also subcategorized by descending

compartment. Cystocele is described as anterior wall herniation, rectocele means a descent of the posterior vaginal wall and vaginal vault prolapse is described as descent of the uterus, cervix, or apex of vagina.⁴ Nutrition require in POP disease is an important topic to discuss. Baseline characteristics of the average daily intake of energy and nutrients are considered as the percentage of the recommended postpartum intake. ECLIPSES study in Spain recommended adequate intake (above 80% of the RDA) during postpartum is about 82.6% for energy component, 80.6% for protein,

99.5% for carbohydrate, 88,7 for vitamin C, 95.1% for vitamin B2 and 170.8% for vitamin B12, while the intake is far from RDA recommendation which about below 35% is vitamin D, iron and folate.⁵

Vitamin D is important micronutrient for skeletal integrity and muscle function. In postmenopausal women, vitamin D deficiency and POP are often found together.^{6,7} Vitamin D downregulates matrix metalloproteinase-9 (MMP-9), reduces collagen breakdown and improves organization of collagen.⁸ Collagen, especially collagen type I, helps maintain supportive function of the pelvic floor. Abnormality in collagen anabolic activity that cause changes in collagen content and structure may be involved in the pathogenesis or development of POP.⁹ Expression of MMP-1, MMP-2 and MMP-9 was found to be associated in more collagen breakdown, losing collagen integrity and increase in POP patients.¹⁰ This study aims to determine definitive association between vitamin D, collagen type I and MMP-1 in POP patients.

MATERIALS AND METHODS

Articles were searched using three electronic databases: PubMed, Google Scholar, and Cochrane. Searches were performed using keywords appropriate to the clinical question and the Boolean operators 'AND' and 'OR' were used to search for items in three databases.

Articles identified by the search were further excluded based on inclusion and exclusion criteria. The inclusion criteria for this article search were articles in English, interventional meta-analytical studies, proportion of micronutrient requirements in POPs, and study subjects. The exclusion criteria were observational studies,

studies without meta-analytical data, repeatedly published literature sources, data extracted from reviews or abstracts, and reported results only in mean ± standard deviation of score coloring. Seven relevant articles were obtained after sorting using the above inclusion and exclusion criteria.

All authors participated in summarizing and systematically evaluating the evidence using standard abstraction forms. The team tested the screening and abstract forms on several articles before starting the abstract and review process. Screening and data collection forms were revised by the team. Data were entered from the included studies and analyzed for data heterogeneity using Review Manager 5.4. We concluded that the data showed heterogeneity when the p-value was less than 1. 0.05 at high I2. A forest plot showing the mean difference for each included study, which was used to ascertain the overall effect of the included studies, with a CI of 95%. This study had been granted ethical clearance issued by the Health Research Ethical Committee Faculty of Medicine Universitas Brawijaya, Malang, Indonesia. No. 04/UN10.F08/PN/2023.

RESULTS AND DISCUSSION

Our search yielded 1375 studies and 7 of which were included in our study. Two studies discussed the micronutrient status of vitamin D, four studies discussed the micronutrient status of type 1 collagen and seven studies addressed the micronutrient status of MMP-1 in postpartum POP patients. The flowchart literature through the assessment process for this review update is shown in Figure 1.

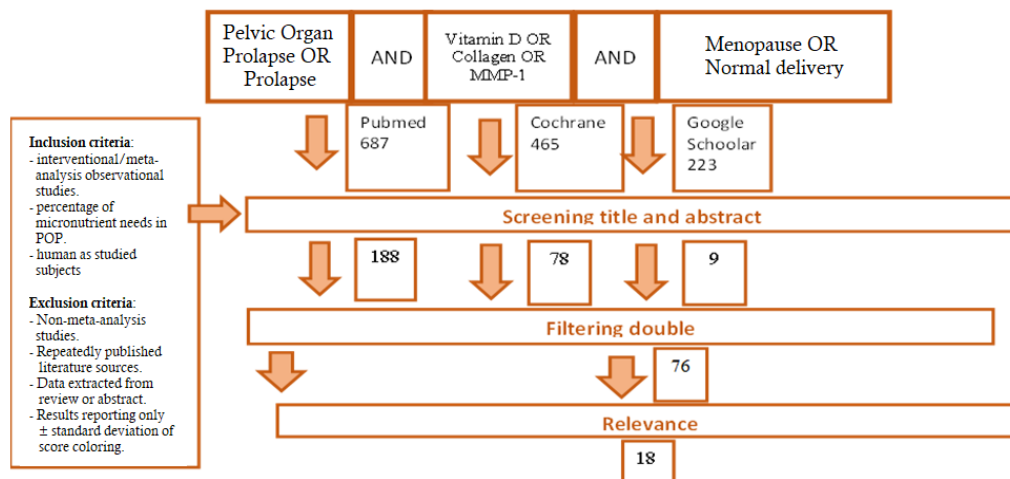


Figure 1. Flowchart of included studies.

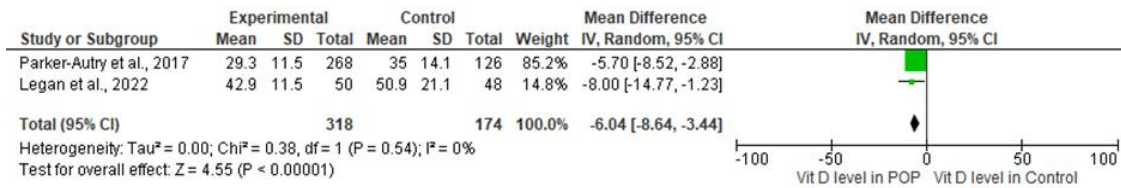


Figure 2. Vitamin D status and pelvic floor disease in forest plot analysis.

The effect of micronutrient vitamin D on Pelvic Organ Prolapse

The heterogeneity among the included studies was found in low level (I²=0%, p >0.05). The findings showed that mean serum vitamin D levels were significantly different between POP and in healthy women in control group (95% confidence interval (CI), (-8.64; -3.44) and p <0.05) (Figure 2).^{11,12}

Legan et al., (2022), in a cross-sectional study, found that vitamin D levels in POP patient had decreased as compared to control or normal patient. In this study, 66% of POP patients were found with vitamin D deficient of lower than 25-30 nmol/L. Based on prolapse stages, the participants did not significantly differ in the incidence of vitamin D deficiency. But in bivariate analyses, there was relationship between POP grade (0 to 4) and vitamin D levels, with the relationship showing a significant, moderately high negative correlation.¹²

In a retrospective cohort study by Parker-Autry et al. (2017), POP patients had reduced vitamin D level compared to healthy women. Among women in the pelvic floor dysfunction group, 48% had adequate amount of vitamin D levels and 52% had vitamin D deficiency. Mean serum 25(OH)D levels in the adequate and deficient group were 38.4 ± 7.6 ng/ml and 18.6 ± 7.1 ng/ml, respectively. Women with inadequate/deficient vitamin D levels were more likely to be

younger, had a higher BMI and African American ethnicity.¹¹ Kaur et al. (2017) found that mean modified vaginal health index (MVHI) improved as vitamin D levels increased.¹³ While Rahajeng et al., (2021) suggested that vitamin D has a significant positive effect on extracellular matrix expression.⁷

The effect of micronutrient collagen type I on Pelvic Organ Prolapse

Collagen type I alpha 1 is an important structural component of the vaginal epithelium and endopelvic fascia. The results showed that the expression of collagen type I was significantly different between POPs and healthy women in control group (95% confidence interval (CI), (-3.24; -2.45) and p <0.05) (Figure 3).^{9,14-16}

Han et al. (2014) hypothesized that collagen expression has an important function in POP angiogenesis. Collagen type I has been found to decrease in POP patients and causing POP. When examined microscopically, the collagen fibers showed a disordered arrangement within the tissue.⁹

Hu et al. (2017) also observed that the metabolic network of tissue collagen is highly dependent on in vivo synthesis and degradation of collagens. The decreased collagen content in POP patients may have occurred due to increased collagen degradation explained by increased of MMP components.¹⁴

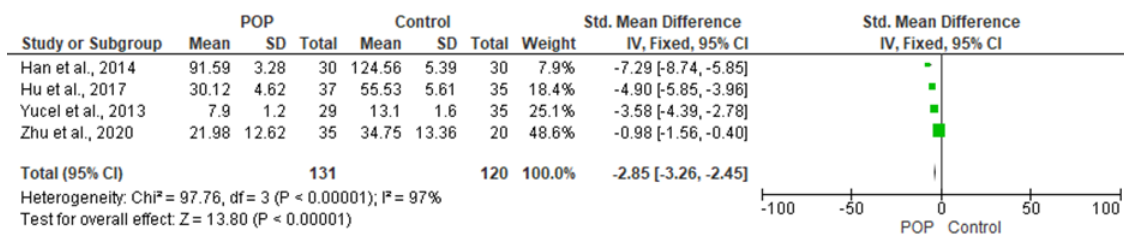


Figure 3. Collagen type I and pelvic floor disease in forest plot analysis.

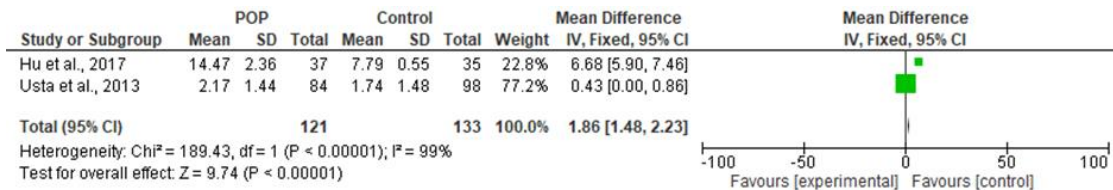


Figure 4. Relationship between MMPI status and pelvic disorder.

Yucel et al. (2013) stated that collagen is a major component of connective tissue produced by fibroblasts and plays a role in tendon resistance. In particular, collagen type I is known to impart strong mechanical forces to connective tissue compared to other collagen families. Yucel et al. (2013) also found that there was decreased expression of collagen type I in uterosacral tissue in women with POP. Tissues from POP women had significantly reduced vascular subarea of the uterosacral ligament.¹⁵

A study by Zhu et al. (2020) showed no significant change in MMP1 levels between POP and control patients, but increased expression of MMP2 and MMP9. Also, compared with those in the control group, TIMP1 and TIMP2 mRNA levels were found decreased in POP group, but without difference in the protein levels statistically. Collagen I protein expression levels were found to be decreased by histopathological examination, which explains the aberrant collagen expression involvement in POP pathophysiology.¹⁶

All studies included in this study reported that there was lower collagen type I expression in patient with POP compared to control. Because of few numbers of included study, we could not exclude the publication bias. Another publication like that of Gong and Xia (2019) also had similar findings as in our research. They observed that collagen fibril structure in POP patients was loose, disordered, discontinued and stiffer than that in control group.¹⁷ Saputra et al. (2022) had shown odds ratio having POP are 3.23 times more frequent in patients with lower collagen type I expression compared to control.¹⁸

The effect of Micronutrient Matrix Metalloproteinase (MMP-1) on Pelvic Organ Prolapse

Collagen type I, II, III and IV are major substrates for MMP-1, an interstitial collagenase enzyme that contributes to collagen degradation process.¹⁹ Hu et al. (2017) had revealed differences between MMP-1 expression in women with POP compared to women without POP. However, Usta et al. (2013) was not in agreement with Hu et al.'s study results. When the included studies' data were analyzed further, there was

a remarkable difference in MMP-1 expression level in POP women compared to control.^{14,20}

Possible explanations include age differences, environmental condition, lifestyle difference, and menopausal status that may correlate with MMP-1 expression. As shown in Figure 3, the included studies showed statistical significance, with associations varying from 1.48 to 2.23 across sub-studies. However, heterogeneity of the data was found very high (I² = 99%, p < 0.05). This was due to the limited number of studies included in this meta-analysis.^{14,20}

We hereby applied meticulous exclusion criteria in order to obtain the very finest selection of articles. However, due to a fine selection process, we may only include a limited number of studies in this systematic review. We suggest that there will be more studies in the future discussing about role of vitamin D and MMP-1 in POP.

CONCLUSION

This meta-analysis discussed the relationship between vitamin D, collagen type 1 and MMP-1 status with pelvic floor disease, revealing that micronutrient status in POP women was severely impaired compared to that in healthy women.

DISCLOSURES

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Conflict of interest

There is no conflict of interest for each involved author.

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Author Contribution

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