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Does hormone replacement therapy impact implant osseointegration in females- A systematic review and meta-analysis

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ABSTRACT

Background: This review aimed to comprehensively investigate the impact of Hormone Replacement Therapy (HRT) on implant osseointegration and bone loss. The study considered factors such as HRT type, osteoporosis, smoking, and diabetes mellitus, and analysed the available literature to provide insights into the association between HRT and implant outcomes.

Methods: Multiple databases were utilized, and studies with diverse designs and methodologies were included that examined the relationship between HRT and implant osseointegration. The selected studies were analyzed and relevant data on implant success rates, bone loss, and other correlations was extracted.

Results: The review findings indicate that HRT has a detrimental impact on implant osseointegration, as evidenced by lower implant success rates and increased bone loss in HRT-treated individuals. The odds ratio analysis further strengthens this association, with significant values of 0.59 (95% CI: 0.50–0.70) and 0.64 (95% CI: 0.54–0.76), indicating a higher likelihood of implant failure in HRT-treated patients., highlighting the need for caution when considering HRT as a treatment option in patients undergoing implant procedures. Smoking and diabetes mellitus were also found to significantly affect implant outcomes, emphasizing the importance of addressing these factors in patient management.

Conclusion: The assessments demonstrate that HRT adversely affects implant osseointegration and increases bone loss. The results suggest the importance of considering the potential negative impact of HRT on implant outcomes and the need for thorough patient evaluation and management. Further research is warranted to explore the underlying mechanisms, assess the impact of specific HRT types and dosages, and evaluate preventive strategies to mitigate the detrimental effects of HRT on implant success.

1. Introduction

HRT has been widely utilized for managing menopausal symptoms and preventing age-related conditions in postmenopausal women (National Academies of Sciences, 2020). It involves the administration of estrogen, with or without progesterone, to supplement the declining

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levels of hormones during menopause (National Academies of Sciences, 2020; Daline et al., 2023). One area impacted by HRT is the reproductive system. HRT can help regulate the menstrual cycle and alleviate common symptoms associated with menopause, such as hot flashes, night sweats, and vaginal dryness (Vigneswaran and Hamoda, 2022). ERT is often prescribed to address these specific symptoms. Another crucial area affected by HRT is bone health (Vermesan et al., 2015; Henes and Hübner, 2020). Estrogen has been found to have a protective effect on blood vessels and can help maintain cardiovascular health in premenopausal women ("The 2022 Hormone Therapy Position Statement of The North American Menopause Society", 2022; Barrera-Chaparro et al., 2023). However, the impact of HRT on cardiovascular health is complex and may vary depending on factors such as the timing of therapy initiation and individual risk factors (Amirkashani et al., 2022). Furthermore, HRT can influence the brain and nervous system. Estrogen has neuroprotective properties and may contribute to improved cognitive function and reduced risk of cognitive decline and dementia in some women (Deli et al., 2020). Research suggests that HRT may help maintain brain health and potentially mitigate age-related cognitive changes. Lastly, HRT can affect the skin and hair (Hage et al., 2022). Estrogen plays a role in maintaining skin elasticity and moisture (Hashemzadeh et al., 2021). HRT may contribute to improved skin quality by reducing dryness and wrinkles. It can also have positive effects on hair health (Al Muderis et al., 2017).

As described by Branemark, implant osseointegration refers to the direct structural and functional connection between the implant surface and the surrounding bone (Al Muderis et al., 2017). It involves the formation of a stable and biologically active interface, enabling load transmission and long-term implant stability (Liu et al., 2021; Hornung et al., 2020). Implant osseointegration is influenced by various factors, including patient demographics, systemic conditions, and lifestyle factors (Terauchi et al., 2012). Among these factors, the use of HRT has attracted attention due to its potential effects on bone metabolism and remodeling (Terauchi et al., 2012).

HRT has been shown to improve bone mineral density and reduce fracture risk in postmenopausal women (Goldštajn et al., 2023). Estrogen, the main component of HRT, plays a vital role in maintaining bone health by inhibiting bone resorption and promoting bone formation (Goldštajn et al., 2023). However, the effects of HRT on implant osseointegration specifically have not been extensively studied. Previous investigations examining the relationship between HRT and implant outcomes have yielded conflicting results (Chhikara et al., 2023; Ghadirinejad et al., 2023; Soegiantho et al., 2023; Wellington et al., 2023). Some studies suggest a detrimental impact of HRT on implant osseointegration, while others report no significant association (Giro et al., 2007, 2008; Seratiuk Flores et al., 2023). This conflicting evidence necessitates a comprehensive review of the existing literature to ascertain the true effects of HRT on implant osseointegration.

Understanding the potential detrimental effects of HRT on implant osseointegration is essential for clinicians and researchers involved in implant dentistry and orthopedic surgery. It can guide treatment decisions and aid in predicting outcomes for patients undergoing implant procedures. Additionally, the findings of this review will contribute to the existing body of knowledge and inform future research in this field. Therefore, this study aimed to provide a systematic review of the available literature, analyzing the relationship between HRT and implant osseointegration by synthesizing the findings from diverse studies and conducting a meta-analysis to validate the obtained findings.

2. Materials and methods

2.1. Review design

For this study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Page et al., 2020; Haddaway et al., 2022) was utilized to ensure a comprehensive and transparent approach to study selection, data extraction, and synthesis (Fig. 1).

2.2. PICOS protocol

In this investigation, the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework was employed to clearly define the key components of the research question and guide the study selection process. The PICOS elements are as follows:

1. Population: The population of interest for this review consisted of females who had undergone implant procedures. Specifically, the focus was on females receiving HRT as part of their treatment.
2. Intervention: The intervention of interest was HRT.
3. Comparison: The comparison group consisted of females who did not receive HRT. This group served as a reference to assess the differential effects of HRT on implant osseointegration.
4. Outcome: The primary outcome of interest was implant osseointegration. The review aimed to examine the effects of HRT on the success rates and bone integration surrounding implants in females.
5. Study design: Only clinical, cohort-based studies were selected for inclusion.

2.3. Database protocol

For this review, a comprehensive search strategy was implemented across seven different online databases. The search strategy aimed to identify relevant studies using Boolean operators (AND, OR) and Medical Subject Headings (MeSH) keywords. In each database, a combination of MeSH terms and keywords related to HRT, implant osseointegration, and females was employed. The search terms were connected using Boolean operators to create a comprehensive search query.

2.4. Selection protocol

Inclusion criteria comprised cohort-based clinical studies with female participants who had received dental implants, investigating the effect of HRT on implant osseointegration as a primary outcome measure. Exclusion criteria excluded animal and in vitro studies, reviews, case reports, and studies lacking essential HRT and hormone data disclosure. These criteria aimed to focus on relevant, longitudinal human studies to explore the direct relationship between HRT and dental implant outcomes in females.

2.5. Assessment of bias

For this review, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016; McGuinness and Higgins, 2020) was utilized to assess the risk of bias in the included studies (Fig. 2).

2.6. Statistical protocol

The meta-analysis protocol used for the review involved the utilization of RevMan 5 software to perform the analysis. The FE model was selected to generate forest plots representing the OR of HRT effects on implant bone loss and osseointegration. Additionally, the protocol aimed to investigate the role of other factors, apart from HRT, that influence osseointegration. To begin the meta-analysis, the relevant data extracted from the included studies were entered into RevMan 5. The extracted data included the number of events (e.g., implant failures) and the sample sizes for both the HRT and control groups. These data were used to calculate the OR estimates and their corresponding 95 % CI. The FE model was employed assuming that the true effect size is the same across all included studies.

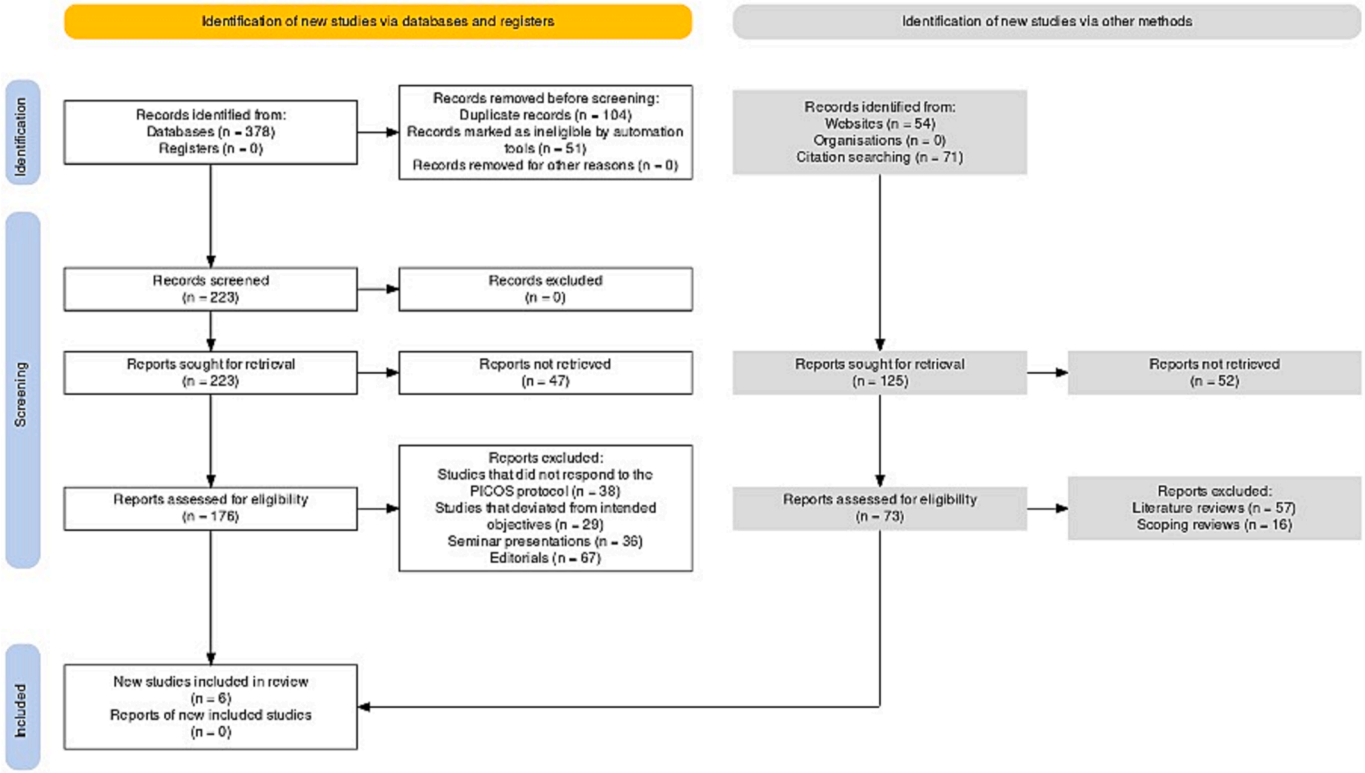

Fig. 1. Prisma Flowchart.

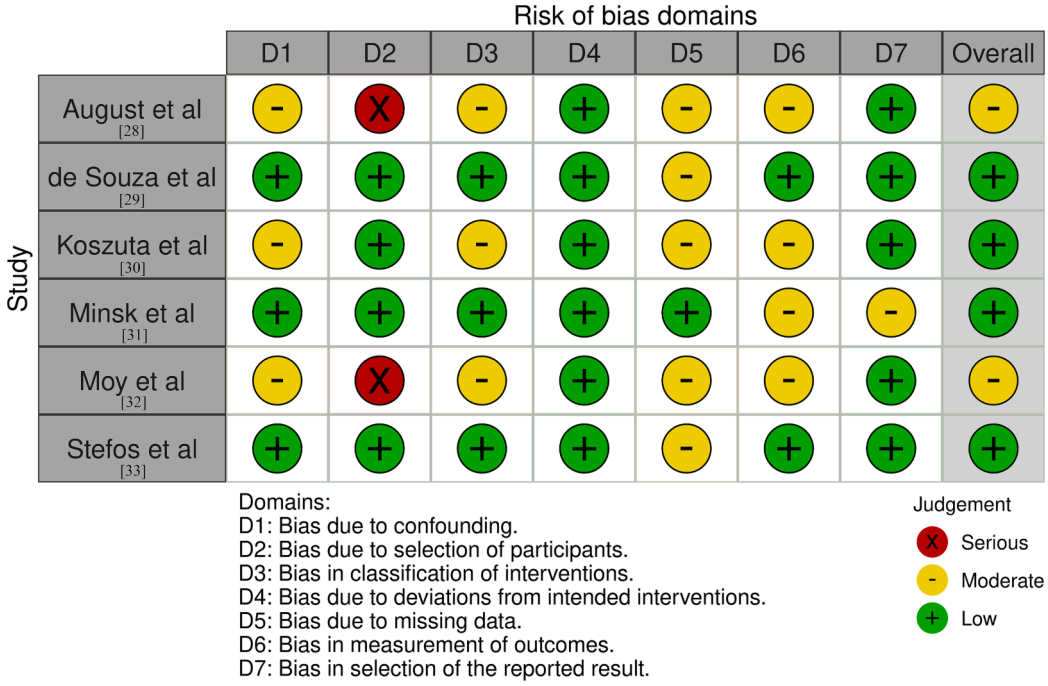

Fig. 2. Risk of Bias.

3. Results

An initial comprehensive search yielded a total of 378 records. Duplicate records were then meticulously removed, resulting in the exclusion of 104 records. Additionally, automated tools marked 51 records as ineligible at this stage. No records were removed for other reasons during this initial phase. To further enrich the search, the study identification process extended to websites, citation searching, and other methods. Specifically, 54 records were identified from websites, while 71 records were found through citation searching, contributing to a total of 125 records sought for retrieval. Unfortunately, 47 records were not retrieved, leaving 78 records for screening. Subsequently, the identification of new studies continued via other methods, resulting in 52 records not being retrieved out of 125 sought for retrieval. Reports

assessed for eligibility numbered 176, and thorough evaluation led to the exclusion of studies that did not adhere to the PICOS protocol (38 studies), those that deviated from the intended objectives (29 studies), seminar presentations (36 studies), and editorials (67 studies). Among the reports assessed for eligibility, 73 studies remained, after excluding literature reviews (57 studies) and scoping reviews (16 studies). In the final phase of the study selection process, six studies (August et al., 2001; de Souza et al., 2013; Koszuta et al., 2015; Zou et al., 2023; Lázaro-Abdulkarim et al., 2022; Stefos et al., 2022) met all the eligibility criteria and were included in the review.

Table 1 presents the demographic characteristics of the participants in the 6 studies (August et al., 2001; de Souza et al., 2013; Koszuta et al., 2015; Zou et al., 2023; Lázaro-Abdulkarim et al., 2022; Stefos et al., 2022) selected for the review. The table includes information on the year of publication, region of the study, sample size (n), and the mean age of the participants. The studies were conducted in different regions and spanned a range of years. The sample sizes varied across the studies, ranging from 71 to 677 participants. The mean ages of the participants also showed variation, with values ranging from 44.8 to 64.1 years. On an overall basis, the selected studies comprised a diverse range of sample sizes and mean ages, reflecting different populations and age distributions. This diversity in demographics allows for a broader understanding of the impact of the investigated factors on the outcomes assessed in the studies. The table also includes information on the study protocol, type of HRT used, groups assessed, total number of implants, follow-up period, other correlations observed, and the inferences drawn from the observations. The studies employed different protocols, including retrospective and prospective designs, to investigate the effects of HRT on implant success rates. Estrogen was the most commonly used HRT type in the studies, although one study did not specify the type of HRT used. The HRT group and control group were assessed in each study to compare the outcomes. The total number of implants varied across the studies, with ranges from 287 to 811 implants. The follow-up periods also varied, with durations ranging from 6 to 105 months. These differences in sample sizes and follow-up periods reflect the heterogeneity of the selected studies (August et al., 2001; de Souza et al., 2013; Koszuta et al., 2015; Zou et al., 2023; Lázaro-Abdulkarim et al., 2022; Stefos et al., 2022).

The forest plot presented in Fig. 3 demonstrated a significant association between HRT and a detrimental impact on implant osseointegration. The overall OR, which represents the odds of experiencing noticeable bone loss with HRT relative to the control group, was calculated as 0.64. The 95 % CI for this OR ranged from 0.54 to 0.76, indicating the detrimental effect of HRT on implant osseointegration. The heterogeneity across the studies was assessed using the Chi^2 statistic and the I^2 statistic. The Chi^2 value of 4.83 with 5 degrees of freedom resulted in a p-value of 0.44, suggesting that the studies were not significantly different from each other. Additionally, an I^2 value of 0 % indicated no observed heterogeneity. Also, the test for the overall effect was highly significant, with a Z-score of 5.15 and a p-value less than 0.00001. This meant that the observed detrimental effect of HRT on implant osseointegration was not due to chance, reinforcing the conclusion that HRT significantly increased the risk of bone loss surrounding implants.

The forest plot displayed in Fig. 4 illustrates the OR representing the impact of HRT on bone loss surrounding implants. The overall OR was 0.59 with a 95 % CI of 0.50 to 0.70, indicating a significant increase in bone loss associated with HRT. The heterogeneity of the studies, as indicated by a Chi^2 value of 6.74 with 5 degrees of freedom ($p = 0.24$), and an I^2 statistic of 26 %, had suggested a moderate level of variability among the study results. The test for the overall effect had been highly significant, with a Z-score of 6.12 and a p-value less than 0.00001. This had suggested that the observed increase in bone loss associated with HRT was statistically significant.

The forest plot displayed in Fig. 5 provides an overview of OR representing the impact of DM, osteoporosis, and smoking on implant

Table 1
Selected papers and the assessment of their demographic variables.

Study ID	Year	Region	Sample size (n)	Mean age (in years)	Protocol	HRT type	Groups assessed	Total implants (n)	Follow-up period (in months)	Other correlations observed	Inference observed
August et al (August et al., 2001 Nov)	2001	USA	243	64.1	Retrospective	Estrogen	HRT group (n = 75), CG (n = 168)	811 (241 in the HRT group)	Unspecified	Osteoporosis affected implant success rates significantly	13 % of the HRT implants saw failure, compared to 6 % in the CG
de Souza et al (de Souza et al., 2013 May)	2013	Brazil	126	50.3	Retrospective	Unspecified	HRT group (n = 13), CG (n = 180)	722 (61 in the HRT group)	12–105 (range)	Osteoporosis and DM did not affect implant success rates significantly	42 % of the HRT implants saw failure, compared to 28 % in the CG
Koszuta et al (Koszuta et al., 2015 Sep)	2015	Poland	71	44.8	Prospective	Estrogen	HRT group (n = 20), CG (n = 51)	Unspecified	6	None	Significant bone loss was assessed in the HRT group (85 %) as compared to the CG (15 %)
Minsk et al (Zou et al., 2023 Jun 29)	1998	Unspecified	116	> 50	Retrospective	Estrogen	HRT group (n = 25), CG (n = 91)	450 (71 in the HRT group)	Unspecified	Smoking affected implant success rates significantly	11 % of the HRT implants saw failure, compared to 7 % in the CG
Moy et al (Lázaro-Abdulkarim et al., 2022)	2003	USA	677	58	Retrospective	Estrogen	HRT group (n = 161), CG (n = 304)	287	Unspecified	Smoking and DM affected implant success rates significantly	27 % of the HRT implants saw failure, compared to 16 % in the CG
Stefos et al (Stefos et al., 2022)	2022	Greece	100	63.62	Case-cohort	Unspecified	HRT group (n = 31), CG (n = 69)	Unspecified	Unspecified	Smoking and osteoporosis affected implant success rates significantly	19 % of the HRT implants saw failure, compared to 27 % in the CG

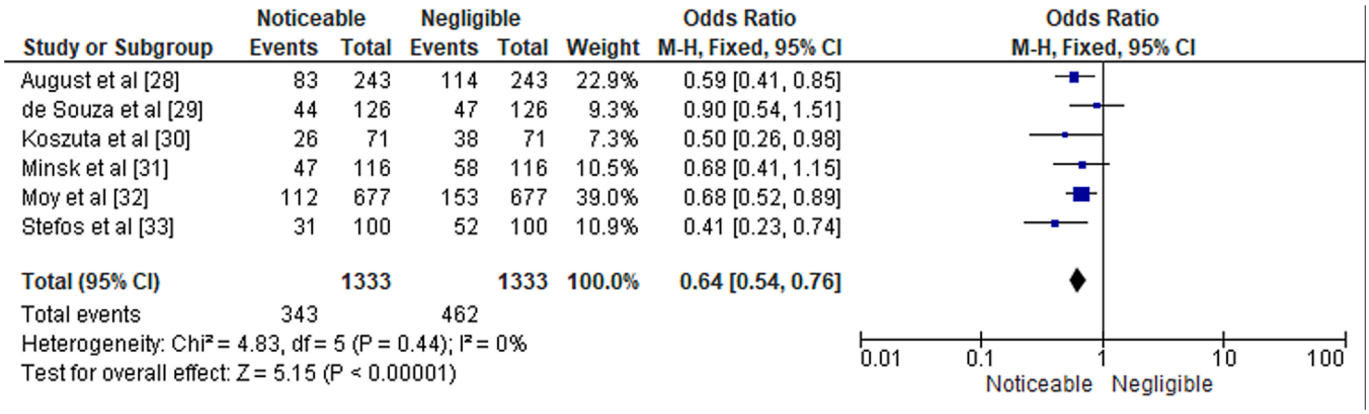

Fig. 3. Forest plot of analysis of the OR demonstrating the detrimental impact of HRT on implant osseointegration across a selection of studies.

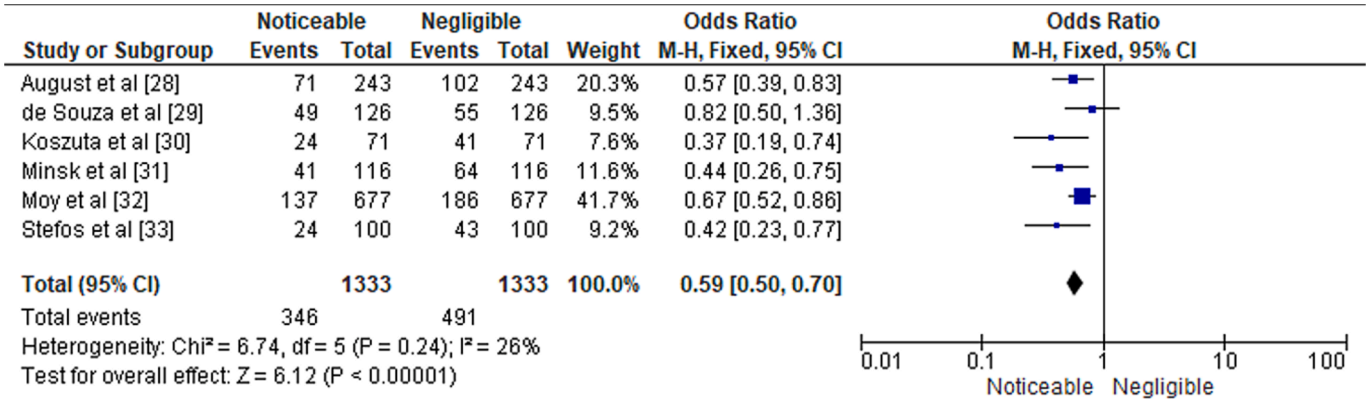

Fig. 4. Illustrates the or representing the impact of hrt on bone loss surrounding implants in a selection of studies.

osseointegration in the selected studies. The findings indicate a detrimental effect of these factors on implant osseointegration, leading to reduced levels of osseointegration. For DM, an overall OR of 0.59 had been observed with a 95 % CI of 0.47 to 0.75. Heterogeneity had been high ($I^2 = 75$ %) and the test for the overall effect had been significant ($Z = 4.35$, $P < 0.0001$). For osteoporosis, the overall OR had been 0.56 with a 95 % CI of 0.42 to 0.75. The heterogeneity had been moderate ($I^2 = 55$ %) and the test for the overall effect had also been significant ($Z = 3.83$, $P = 0.0001$). For smoking, the overall OR had been 0.62 with a 95 % CI of 0.48 to 0.80. The heterogeneity had been low ($I^2 = 31$ %) and the test for the overall effect had been significant ($Z = 3.65$, $P = 0.0003$). The total combined effects from all subgroups had yielded an OR of 0.59 with a 95 % CI of 0.51 to 0.69. The heterogeneity had been moderate ($I^2 = 40$ %) and the test for overall effect had been highly significant ($Z = 6.83$, $P < 0.00001$). The test for subgroup differences had not been significant ($Chi^2 = 0.27$, $df = 2$, $P = 0.87$, $I^2 = 0$ %), indicating no significant differences between effects observed in the DM, osteoporosis, and smoking subgroups.

4. Discussion

Several correlations were observed in relation to HRT and implant outcomes. Osteoporosis was found to significantly affect implant success rates in two studies, leading to a higher rate of implant failure in the HRT group compared to the control group. In one study, significant bone loss was observed in the HRT group compared to the control group. Smoking was identified as a significant factor affecting implant success rates in two studies, with a higher rate of implant failure in the HRT group compared to the control group. Additionally, DM was found to significantly impact implant success rates in one study, with a higher failure rate in the HRT group compared to the control group. The inferences drawn from the observations highlight the overall impact of HRT on implant outcomes. In some studies, HRT was associated with a higher rate of implant failure compared to the control group, indicating a detrimental effect. Other studies did not find a significant impact of HRT on implant success rates when considering factors such as osteoporosis and DM. However, it should be noted that the specific details of each individual study, including its methodology and sample characteristics, should be considered when interpreting the overall conclusions. Overall, the findings suggest that HRT, particularly in the presence of certain factors such as osteoporosis and smoking, may have a detrimental effect on implant success rates. However, the impact of HRT on implant outcomes is influenced by various factors, and further research is necessary to better understand the complex relationship between HRT and implant osseointegration.

The mechanistic insight through which estrogen exerts a regulatory effect on different biomarkers may partially account for the observed reduction in PPD (Lee et al., 2019) and the significant decrease in BOP observed in women receiving HRT (Minervini et al., 2023; Norderyd et al., 1993). However, contrasting findings have been reported in another study (Tarkkila et al., 2008), indicating that HRT does not reduce the number of periodontal pockets with PPD > 6 mm after a couple of years, suggesting that the reduction in PPD may be limited. The evidence regarding the impact of HRT on PPD is conflicting, and it does not appear to be influenced by the type of HRT or the duration of follow-up. It is crucial to acknowledge that periodontal parameters, both clinical and radiographic, pose challenges in terms of reproducibility due to their reliance on minute measurements in millimeters or even micrometers. Therefore, studies should meticulously describe the methods employed for reproducibility, including training and

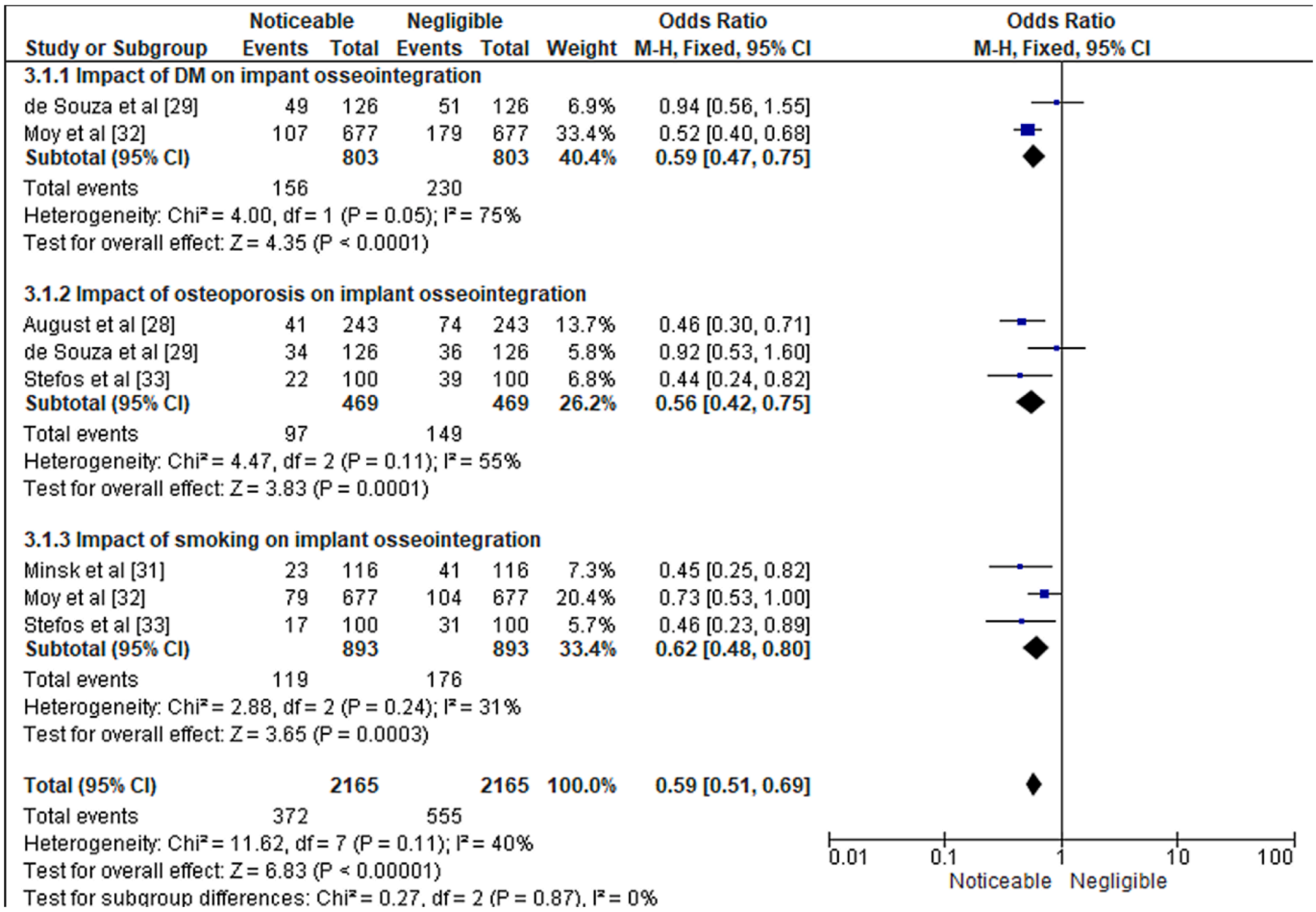

Fig. 5. Overview of or representing the impact of dm, osteoporosis, and smoking on implant osseointegration in the selected studies.

calibration, to facilitate meaningful comparisons with other studies. In contrast, BOP, being relatively easier to measure, has limited evidence suggesting its association with HRT.

Dental implant procedures have become a standard and reliable solution for the effective replacement of missing teeth, offering high success rates when placed in adequately dense and quality bone structures (Giro et al., 2007, 2008; Hua et al., 2014; Pye et al., 2009; Seratiuk Flores et al., 2023). However, there are certain factors that can influence the long-term viability of dental implants, particularly concerning the alterations in estrogen levels following menopause (Tateishi et al., 2013). The decline in estrogen levels after menopause leads to an increased recruitment, differentiation, and prolonged survival of osteoclasts, resulting in excessive bone resorption and affecting both bone healing and density (Hua et al., 2014; Almagro et al., 2013; Buencamino et al., 2009; Ikebe et al., 2009). Furthermore, various estrogen-regulated cytokines might play a critical role in bone resorption by facilitating the recruitment and maturation of osteoclast precursors post-menopause (Tateishi et al., 2013; Buencamino et al., 2009; Dvorak et al., 2011). Consequently, estrogen deficiency can contribute to osteoporosis, increasing the risk of implant failure (Hua et al., 2014; Tateishi et al., 2013). Decreased bone mass has been suggested as a potential risk factor for compromised osseointegration of dental implants (August et al., 2001; Almagro et al., 2013; Eleni and Lazaros, 2014).

The studies we selected have elucidated the relationship between estrogen deficiency and the consequential alterations in bone structure, which contribute to a decreased interface between dental implants and bone surface, thereby posing a relative risk of implant failure (Lee et al., 2019; Minervini et al., 2023; Norderyd et al., 1993). Given the positive influence of estrogen on bone mass, it was initially anticipated that HRT would enhance osseointegration. However, our findings indicate that only one study suggested a non-significant positive impact of HRT on implant loss, specifically observed in the maxilla (August et al., 2001; Minervini et al., 2023). Conversely, two studies demonstrated either a non-significant or significant negative effect when considering both jaws (Zou et al., 2023; Lázaro-Abdulkarim et al., 2022). Nevertheless, the contentious influence of decreased bone mass on implant survival necessitates further investigation (Alsaadi et al., 2008; Giro et al., 2007, 2008; Seratiuk Flores et al., 2023). It is worth noting that postmenopausal and premenopausal women exhibit similar implant failure rates, approximately 10 % and 5 %, respectively (Diz et al., 2013; Di Stasio et al., 2018; Minervini et al., 2017). Failure of dental implants may occur due to insufficient osseointegration during the initial healing phase or due to *peri*-implant tissue rupture or infection, leading to the loss of implant support—a multifactorial issue (Ikebe et al., 2009; Diz et al., 2013; Martin et al., 2010).

Concerns surrounding the use of HRT primarily revolve around potential adverse effects. Several studies mention the adverse effects of HRT, which encompasses breast and endometrial cancer, cerebrovascular and coronary diseases (Civitelli et al., 2002; Lee et al., 2019; Minervini et al., 2023; Norderyd et al., 1993). Among them, a clinical trial (Civitelli et al., 2002) reported adverse effects experienced by participants, encompassing minor effects such as headaches, vaginal bleeding, heat waves, mood changes, leg pain, and gastrointestinal irritation, as well as major effects including breast and endometrial cancer, transient ischemic attack, and ankle fracture.

This investigation, despite its valuable insights, had certain limitations that should be acknowledged. These limitations may affect the generalizability and strength of the conclusions drawn. One limitation of

this review is the inclusion of studies with different protocols and methodologies. The retrospective, prospective, and case-cohort designs used in the selected studies may introduce variations in data collection, patient selection, and follow-up periods. These differences can introduce heterogeneity and potentially affect the comparability of the results across studies. Another limitation is the variation in sample sizes and demographic characteristics among the included studies. The studies had different sample sizes, ranging from small groups to larger cohorts, which may influence the statistical power and precision of the results. Moreover, variations in age, geographic location, and other demographic variables among the study populations may introduce confounding factors and limit the generalizability of the findings to broader populations.

5. Conclusion

The findings indicate that HRT can have a detrimental impact on implant osseointegration, as evidenced by lower implant success rates and increased bone loss surrounding the implants in HRT-treated individuals. Furthermore, the review highlights the significant influence of smoking and diabetes mellitus on implant outcomes, emphasizing the need to address these factors during treatment planning and patient management. However, it is important to note the limitations of this review, such as the heterogeneity among the included studies, variations in sample sizes and demographic characteristics, limited information on specific HRT types and potential confounders, and the exclusive focus on selected factors. These limitations underscore the necessity for further research with standardized protocols, larger sample sizes, and comprehensive assessment of confounding variables to validate and expand upon these findings.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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