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CASE SERIES

Influence of Placenta Extract Intake on Periodontal Diseases and Oral Environment: A Case Series

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Background: The placenta extract is used as a dietary supplement. We aimed to investigate the effects of placenta extract on periodontal disease.

Case Presentation: In this study, placenta extract supplements were found to improve the oral environment of young and middle-aged Japanese women undergoing maintenance; after three months of taking placenta extract, bleeding upon probing was reduced. In addition, two parameters, white blood cells and protein, improved in the SillHa test, suggesting that the placenta extract contributes to the reduction of gingival inflammation through its anti-inflammatory effect. No adverse events were observed with the placenta extract.

Conclusion: Placenta extract may lead to better management, including oral rehabilitation and pharmacotherapy. However, its effect on gingival inflammation requires further investigation in a larger number of cases.

Keywords: bleeding on probing, SillHa, gingivitis, placenta extract, dentistry, periodontology

Introduction

Oral health has been reported to be associated with general health.[1] Typical diseases of the oral cavity, such as caries and periodontal disease, are the major causes of tooth loss,[2] which in turn reduces health-related quality of life.[3] In addition, periodontal disease is associated with several systemic diseases, such as cardiovascular disease and diabetes.[4]

The main cause of periodontal disease is plaque, which can usually be removed by brushing or other forms of self-care.[5] However, people with intellectual or motor disabilities are more likely to experience difficulty learning functional brushing behaviors and require support. Therefore, people with disabilities often have poor plaque control and severe periodontal disease at an early age.[6] Therefore, alternative, or complementary brushing methods must be developed for people with motor disabilities.

Placenta extract is known to have antioxidant, anti-inflammatory and wound healing promoting effects.[7–9] The active ingredient for the antioxidant effect has been identified as collagen peptide containing hydroxyproline, while the anti-inflammatory and wound-healing effects have been identified as Cyclo-trans-4-L-hydroxyprolyl-L-serine.[7–9] Placenta extracts in the oral cavity have been reported to protect pigmented gingival biopsies, reduce downtime, and reduce the severity of radiation-induced mucositis in oral cancer treatment.[10,11] These effects of placenta extracts on tissue protection and wound healing could be an alternative or complementary technique to brushing. However, there is no clinical evidence regarding the placenta extracts' effects on periodontal disease.

The details of how the placenta extract affects oral health are currently unknown. However, the clinical improvements in oral health noted above were observed when placenta extract gel was applied to the oral cavity or administered by intramuscular injection, suggesting that it acts directly on the oral cavity or indirectly via the bloodstream.[5,6] Furthermore, the fact that oral administration of placenta extract has been shown to improve skin in human studies

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suggests that oral administration is feasible.[12] In addition, oral administration is desirable in terms of adherence to the placenta extract regimen.

In the last 5 years, the number of patients with motor disabilities seen in our clinic is extremely small, less than 0.02%. Therefore, cooperation from other dental institutions is necessary to conduct research on patients with motor disabilities. However, it is difficult to obtain the cooperation of other dental institutions because there are no clinical examples of the influence of oral intake of placenta extract on periodontal disease. Therefore, we decided to conduct the study on healthy subjects to obtain clinical examples of the effects of oral intake of placenta extract on periodontal disease. Therefore, we investigated the effects of placental extract on periodontal disease in healthcare professionals undergoing dental maintenance at our clinic. We found three cases in which the use of the placenta extracts reduced bleeding upon probing and gingival inflammation. To the best of our knowledge, this case report suggests that the use of placenta extract may be a new complementary technique to effectively support maintenance.

Case Presentations

Placenta extract (generic name: JBP Placenta EQ capsules, manufactured and marketed by Japan Bio Products Co., Ltd.) was provided by Japan Bio Products Co., Ltd. In this study, in this study, Placenta extract (4 capsules, 1000 mg/day) was taken orally daily for 3 months by subjects undergoing oral maintenance. The timing of the placenta extract intake was not restricted, and subjects were instructed to take the placenta extract at regular times whenever possible. If the subject forgot to take it, he or she was instructed not to take an additional dose the next day and to record this fact. At each visit, our dental hygienist educated the subjects on brushing habits that could affect periodontal disease. Changes in periodontal disease before and after intake and one month after cessation of intake, as well as changes in the oral environment before and after intake were assessed. We measured and compared pocket probing depth (PPD) and bleeding on probing (BOP) over time. Pocket probing depth checked whether periodontal disease was caused by plaque. Bleeding on probing (BOP) checked whether periodontal disease was in an advanced or stagnant stage.[13] PPD and BOP were measured with Perio Probe number 5 (made of titanium, YDM Corporation, Tokyo, Japan). The tests were performed on five occasions: before the start of the study (day 0), 30 days after the start of the study (day 30), 60 days after the start of the study (day 60), 90 days after the start of the study (day 90), and 30 days after the end of the study (day 120). Oral environmental factors (cariogenic bacteria, acidity, buffered brain, leukocytes, proteins, and ammonia) were measured using the SillHa saliva tester (Arkray Inc., Kyoto, Japan) to quantify them.[14–16] The SillHa saliva tester can quantify the oral environment from mouth rinsing fluids. It measures six indicators of the oral environment: dental health (cariogenic bacteria, acidity, buffering capacity), gum health (leukocytes, protein), and oral cleanliness (ammonia), which are output in radar charts and other easily visualized result sheets. The tests were performed before intake (day 0) and 100 days after intake (day 100), and changes over time were compared. All tests were performed in conjunction with subject maintenance. The subjects were instructed not to brush their teeth, eat, drink, smoke, and gargle for 2 hours before the saliva tester measurement, as this could affect the results (Table 1). The SillHa analysis was performed using the software (V04.01) built into the SillHa instrument.

Table 1 Procedure Checklist for the PPD, BOP, and SillHa Saliva Test

Check	Procedure
	Did you brush your teeth 2 hours before each test?
	Did you eat and drink anything 2 hours before each test?
	Did you smoke 2 hours before each test?
	Did you gargle 2 hours before each test?

Notes: Check each of the above items as needed prior to PPD, BOP, and SillHa saliva testing. For each item, answer "Yes/No" in the leftmost box. If you answer "yes", the test will be compromised and the patient will not be allowed to undergo the test.

Abbreviations: PPD, pocket probing depth; BOP, Bleeding on probing.

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Case 1

Case 1 involved a healthy woman in her 40s with no relevant medical history. No visually detectable sarcomas were observed in the oral tissues. No periodontal disease was observed. She was not pregnant. She was not in any form of hormone treatment, nor had her hormone profile been assessed. No abnormal PPD was observed at the start of placenta extract (1000 mg/day) administration (day 0); however, mild bleeding on probing (BOP; 2.7%) was observed (Figure 1, upper left, lower row). PPD did not change from the start of placenta extract intake to 149 days of follow-up (Figure 1, upper left panel). In contrast, BOP decreased by 33% on day 37 compared to the first day of intake and remained at this level until day 120. No bleeding was observed on day 149 of follow-up (BOP, 0%) (Figure 1, bottom left). The SillHa saliva test showed a cariogenic bacteria score of 46 on day 0, which was above the average level. On day 100, it was 20, which was below the average, indicating fewer cariogenic bacteria. The acidity score was 81 on day 0, which was above the average level. It was 86 on day 100. The buffering capacity score was 15 on day 0, which was below the average level. On day 100, it was 11. The white blood cell count score was 74 on day 0, which was above the average level. On day 100, it was 47, which became the average level. The protein score was 59 on day 0, which was above average. On day 100, it was 34, which was below the average. The ammonia score was 54 on days 0, which was the average level. On day 100, it was 56, which remained the average level (Figure 2, left). No adverse events were observed during the placenta extract supplementation period.

Case 2

Case 2 involved a woman in her 20s with a history of dysmenorrhea and was taking drospirenone (Yazflex combination tablets, one tablet daily) to control menstrual pain and bleeding as part of her treatment. The patient continued receiving drospirenone during the study period. No visually detectable sarcomas were observed in the oral tissues. No periodontal disease was observed. At maintenance, there was no change in PPD from the start of the placenta extract administration (1000 mg/day) (day 0) to day 117, the last day of the study (Figure 1, top center). BOP was 2.3% at the start of the

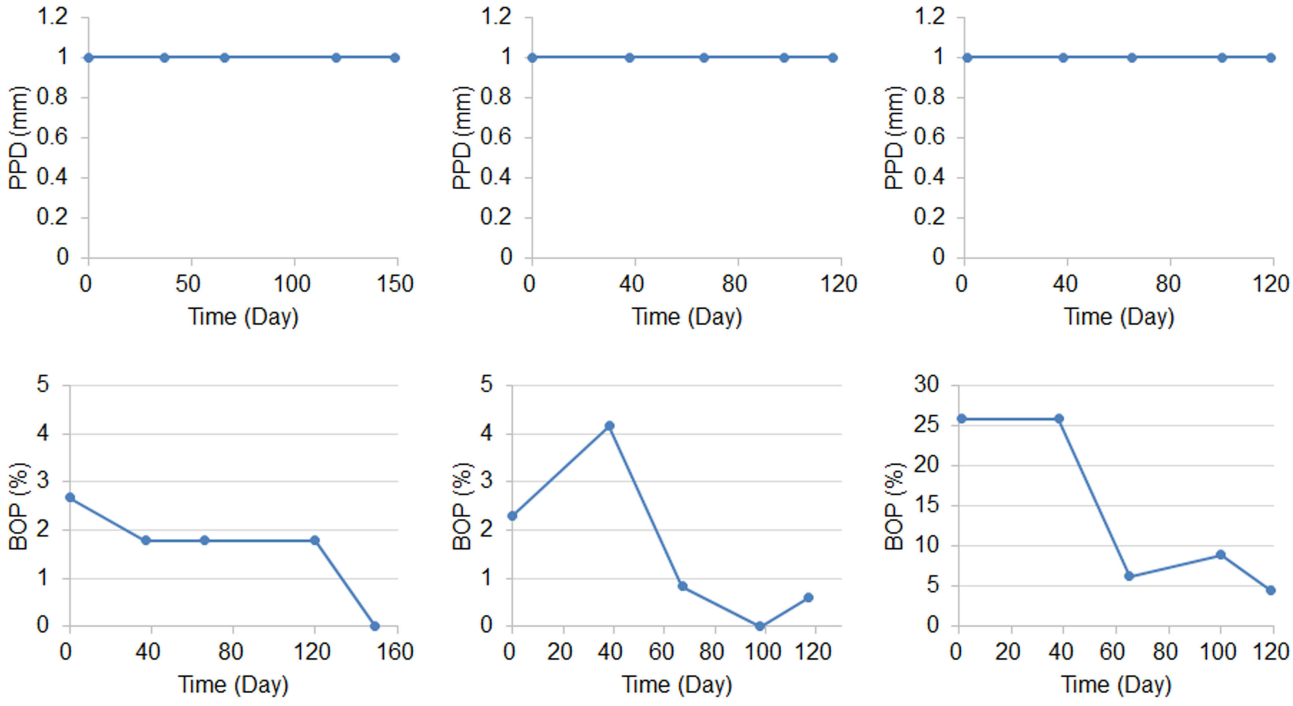

Figure 1 Comparison of the periodontal examination in three cases. Comparison of the periodontal examination in three cases. Comparison of periodontal examination parameters, including PPD (upper panel) and BOP (lower panel) between Day zero and the final examination day. Case 1: upper left, lower left; Case 2: upper center, lower center; Case 3: upper right, lower right.

Abbreviations: PPD, pocket probing depth. BOP, bleeding on probing.

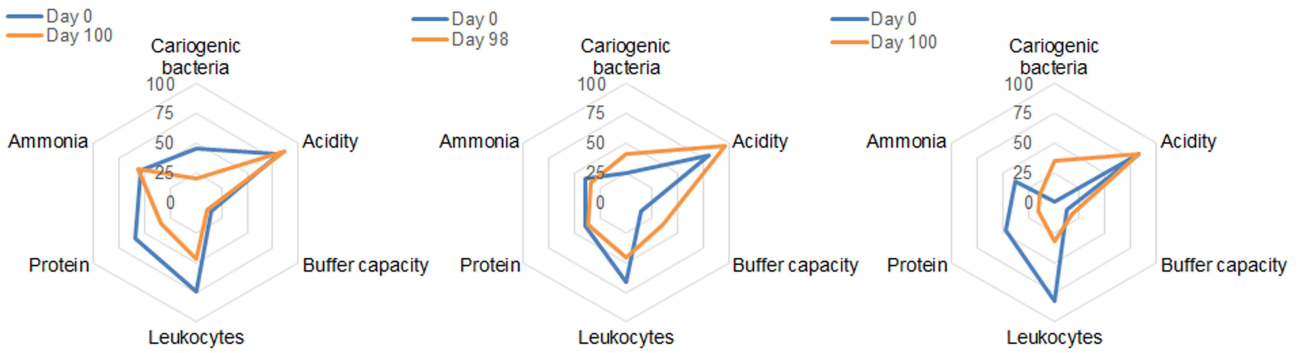

Figure 2 Comparison of the SillHa examination in three cases. Comparison of test papers for analyzing cariogenic bacteria, acidity, buffer capacity, leukocytes, proteins, and ammonia quantitative analysis on Day 0 (blue line) and the final examination day (Orange line). Case 1: left; Case 2: center; Case 3: right.

placenta extract treatment (day 0) and increased to 4.17% on day 38. The BOP then decreased to 0% on day 98, the last day of intake, and the bleeding disappeared. However, slight bleeding (0.6%) was observed at the follow-up visit on day 117 (Figure 1, bottom center). The SillHa saliva test showed a score of 25 for cariogenic bacteria on day 0, which was below the average. On day 98, it increased to 41 and became the average level. The acidity score was 80 on day 0, above the average level, and 96 points on day 98. The buffer capacity score on day 0 was 14, which was below average. On day 98, it was 36, which became the average level. The leukemia score was 66 on day 0, which was above average. On day 98, it was 46, which became an average score. The protein score was 40 on day 0, which was an average level. On day 98 it was 37, which remained average level. The ammonia score was 40 on day 0, which was below average. On day 98 it was 35, which remained below the average level (Figure 2, center). No adverse events were observed during the placenta extract supplementation period.

Case 3

Case 3 involved a woman in her 20s with no relevant medical history. No visually detectable sarcomas were observed in the oral tissues. No periodontal disease was observed. The PPD on maintenance remained unchanged from day 0 to day 118, the last day of the study (Figure 1, top right). The BOP on day 118 was 25.9% at the start of placenta extract intake (day 0) and did not change until day 38. It then decreased by 19.7% on day 65 but increased slightly by 2.7% on day 100, the last day of intake. On follow-up on day 119, the number decreased by 4.5% and was judged to be minor bleeding (Figure 1, bottom right). The SillHa saliva test showed a cariogenic bacteria score of 1 on day 0, which was below the average. On day 100, it was 35, which remained the average. The acidity score was 83 on day 0, which was above the average level. The score was also the same on day 100. The buffering capacity score was 12 on day 0, which was below the average level. On day 100, it was 18, which remained below the average. The leukemia score was 82, which was above the average. On day 100, it was 32, which became below average. The protein score was 47 on day 0, which was average level. On day 100, it was 15, which became below the average level. The ammonia score was 37 on day 0, which was below average. On day 100, it was 14, which remained below the average (Figure 2, right). No adverse events were observed during the placenta extract supplementation period.

Discussion

In the present cases, cases of oral environment improvement were observed after ingestion of horse placenta extract. To the best of our knowledge, no case has been reported to date in which supplementation with placenta extract has produced oral benefits in humans, and this case report may have provided a strong impetus to proceed with future validation studies. Other supplements that have been shown to improve gingivitis include CoQ-10, paraprobiotics, and folic acid.[17–19] The present case suggests that placenta extract may be a new option as a supplement for improving gingivitis.

PPD levels on day 0 were within the reference values, and no change in PPD levels was observed even approximately three months after the placenta extract intake, suggesting no effect on PPD. In contrast, BOP was at low risk in cases 1

and 2 and high risk in case 3. However, in all of these cases, bleeding disappeared after placenta extract intake, suggesting that placenta extract is involved in the control of gingival bleeding. Placenta extract has been reported to have anti-inflammatory effects by inhibiting the expression of inflammatory cytokines and cyclooxygenase (COX)-2 inhibition.[20,21] Placenta extract has also been reported to inhibit the secretion of inflammatory cytokines such as interleukin (IL)-6 and IL-8 in primary human gingival fibroblasts.[22] Based on the above, it is suggested that these effects contribute to resolving gingival bleeding.

In the present case, in which the oral environment was improved by taking horse placenta extract, the active ingredient of the horse placenta extract has not yet been identified. When collagen peptide, which has been suggested to promote skin wound healing, was continuously administered orally to rats modeling pressure sores, it was reported that the sum of the wound area ratio, an index of healing, to complete healing was significantly lower in the collagen peptide group than in the control group.[23] Therefore, suggesting that collagen peptide supplementation may play a beneficial role in the repair of gingival damage. On the other hand, it has been reported that administration of placenta extract to a mouse model of wound healing resulted in an accelerated reduction in wound size.[24] In addition, after eight weeks of treatment with placenta extract in patients with wounds of six weeks or longer attending a wound clinic, 67.5% of the treated group showed 50% or greater epithelialization compared to only 23.3% in the control group.[25] Furthermore, it has been shown that placenta extract also contains collagen peptides.[7,26] The effect of these identified peptides in promoting wound healing has not been verified at this time and needs to be verified in the future. However, since the placenta extract used in this study was prepared from whole placenta, including amnion, umbilical cord, and villi, it can easily be inferred that it contains a large number of unidentified collagen peptides. Therefore, the possibility that these unidentified collagen peptides contribute to wound healing cannot be excluded. In addition, cyclo-trans-4-L-hydroxyprolyl-L-serine identified from placenta extract has been shown to promote corneal epithelial wound healing in vitro and in vivo.[9] Cyclo-trans -4-L-hydroxyprolyl-L-serine is a collagen-derived substance because it is composed of hydroxyproline residue, a molecule unique to collagen. This supports the possibility that collagen-derived substances in placenta extract may contribute to wound healing. Considering the above, we speculate that the collagen peptides in the placenta extract contributed to the reduction of BOP.

SillHa's oral environment showed an overall improvement in white blood cell and protein levels after placenta extract intake in all three cases in this study. These two items are associated with gum health, particularly bleeding and inflammation of the gums, which could be the basis for lower BOP after placenta extract intake. The implication of the ammonia value in the SillHa test is the degree of oral cleanliness, and when the total number of bacteria in the oral cavity is high, the ammonia value will increase, causing halitosis.[14–16] In the three patients in this study, the ammonia level was at or below the average level before and after taking horse placenta extract. From these results, it can be concluded that the intake of horse placenta extract does not affect the total number of bacteria in the oral cavity or contributes to the inhibition of the total number of bacteria in the oral cavity. Since it has been reported that treatment of dermal keratinocytes with horse placenta extract significantly increased gene expression of the antimicrobial peptides β-defensin-1 and −2,[27] the possibility of an inhibitory effect on oral bacteria cannot be ruled out. However, since the ammonia levels in the three cases did not exceed the average level before and after the intake of horse placenta extract, it is necessary to verify in the future whether the horse placenta extract acted in an antibacterial manner in the oral cavity. Cariogenic bacteria, acidity and buffer capacity are factors related to dental health. Elevated levels of these factors indicate carious teeth or a tendency to develop carious teeth.[14–16] Cariogenic bacteria improved from the average level to the average level or remained at the average level after the intake of horse placenta extract, suggesting that the results reflected the results of ammonia, leukocytes, and protein levels. On the contrary, acidity was above the average level before and after horse placenta extract intake, suggesting that horse placenta extract had no effect on acidity. Buffer capacity was below the average level before and after the intake of horse placenta extract, suggesting that it reflects the results of acidity. However, it could be interesting to evaluate placenta extract in combination with other adjuvant therapies such as Ozone, photo biomodulation, and probiotics in order to understand their potential mutual effect on oral environment for the future research.[28–30.]

Known treatment options for periodontal disease include scaling and root planing, nonsurgical mechanical periodontal debridement, adjunctive administration of antibiotics, local antimicrobials, laser therapy, antimicrobial

photodynamic therapy, probiotics, and chlorhexidine.[31] Among these possibilities, ozone, in particular, can be administered as gaseous ozone, ozonated water, and ozonated oil, providing a broader range of options than other methods.[32–34] However, when the focus is on home treatment of periodontal patients, these are not simple and sufficient for them. In particular, it is desirable to establish more effective home treatment for periodontal patients with motor disabilities. In this study, the use of placenta extract was suggested to make some positive contributions, and it is expected that it may help to establish such a home treatment.

However, as the subjects in this study were all periodontitis patients with mild bleeding on probing and gingival inflammation, there are limitations to the interpretation of the effects of placenta extract intake in periodontitis patients. In addition, all three cases included in this study were female, and no male cases were included, which means that we could not look at gendered differences. Therefore, the possibility of selection bias in this study cannot be excluded. Furthermore, the study is a case study with only one intervention group in three cases and no control group, which limits the interpretation of the results. The evaluation may be influenced by natural changes in health status from the beginning of the study to the end of the study period and by the subjectivity of the evaluators and subjects due to the fact that the study was not blinded. To verify the efficacy of placenta extract on gingival inflammation, it is necessary to conduct a validation study such as a randomized controlled trial with a control group such as a placebo group in the future.

Conclusion

The use of placenta extract as a supplement in mild periodontitis has been reported for its potential to improve the oral environment by reducing bleeding and gingival inflammation. The effects of the placental extract observed in this report need to be further investigated by objective studies in a larger number of periodontitis cases, which may lead to better management, including oral rehabilitation and pharmacotherapy.

Ethics Approval

This study was approved and reviewed by the Ethics Committee of Medical education i design lab (ID: I24-5-1). The study procedures were conducted in accordance with the Declaration of Helsinki and its amendments (Ethical Principles for Medical research Involving Human Subjects, adopted by the 18th World Medical Association General Assembly Helsinki, Finland, June 1964, and amendments).

Informed Consent and Patient Consent for Publication

Informed consent and patient consent for publication were obtained from all participants in this study.

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