

The Effect of Vitamin B-Complex Supplement on Salivary Flow Rate, Salivary Viscosity and PH among Post-Menopausal Women: Randomised Trial

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ABSTRACT

Background: Vitamin B Supplementation could be a promising and affordable treatment option for adverse hormonal manifestations in the oral cavity for postmenopausal women in Nigeria. This study aimed to determine the effect of vitamin B-complex supplementation in improving salivary flow indices of Unstimulated Salivary Flow rate (USFR), Salivary Viscosity (SRV), and Salivary pH, among postmenopausal women.

Methods: A total of 70 postmenopausal women attending outpatient clinics of the University of Benin Teaching Hospital (UBTH) were recruited into the study and were randomized into two arms: Treatment (35) and Placebo (35). The treatment group received a vitamin B-complex supplement (370mg twice daily) and the control group received a placebo. The respondents were followed up for 4 weeks on a weekly basis. Data was analyzed using IBM SPSS version 24.0 with statistical significance set at $p < 0.05$.

Results: At the end of 4 weeks; there was a significant difference in unstimulated whole salivary flow rate (UWSFR) between the groups ($p = 0.041$) with regression analysis indicating that Vitamin B supplementation and baseline UWSFR were significant predictors of UWSFR. The unstandardized B coefficient indicated a 0.08 gm/min increase in UWSFR in the treatment group ($p = 0.023$) compared to the placebo group at recall. There was no significant effect of Vitamin B complex in improving SRV. ($B = 0.014$, $p = 0.865$) and salivary pH ($p = 0.365$).

Conclusion: Vitamin B-complex supplements over 4 weeks significantly improved USFR but did not significantly improve SRV and pH.

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INTRODUCTION

The World Health Organization defines menopause as the permanent cessation of menstruation due to loss of ovarian follicular activity (WHO Research on menopause, 1996, Mishra et al, 2021). It is the permanent cessation of menstruation and is defined as 12-month amenorrhoea after the final menstruation (WHO Research on menopause, 1996, Olowokere et

al., 2021). It usually occurs between 45 and 55 years with a mean age of 50 to 52 years (Blümel et al., 2021).

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Postmenopause is the continuous stage after menopause. Among Nigerian women, the mean menopausal age is between 48 to 50 years which implies that based on the latest population estimate, there are about 3.03% of women aged 50 years and above, translating to about 5.9 million women in Nigeria (Adewuyi & Akinade 2010; Ande et al., 2011; National Bureau of Statistics 2018). This constitutes a sizeable proportion of the population that are predisposed to the challenges attached to this milestone, as this stage in women's health is associated with problems and symptoms that could hamper healthy aging in women (Adewuyi & Akinade 2010; Ande et al., 2011).

The menopausal symptomatic reaction can be taken to be the sum of the impact of the three components: 1) the amount of oestrogen depletion and the rate at which oestrogen is withdrawn; 2) the inherited and acquired propensities to succumb or withstand the imposition of the overall aging process; and 3) the psychologic impact of aging and the individual's reaction to the emotional implications of a change of life (O'Bryant et al., 2013).

Many bodily changes occur during the postmenopausal period which manifest in the oral cavity (Zachariassen, 1993; Frutos et al., 2002; O'Bryant et al., 2013). The bodily changes may include vaginal dryness, loss of breast fullness, thinning hair, dry skin, hot flashes, chills, night sweats, sleep problems, mood changes, weight gain, and slowed metabolism (O'Bryant et al., 2013).

The changes and potential problems in the mouth that may be associated with postmenopause include burning mouth syndrome, dry mouth, altered taste sensations, menopausal gingivostomatitis, mucosal changes, periodontitis, osteoporosis, and eating disorders (Zachariassen, 1993; Frutos et al., 2002). Friedlander (2002) reported that oral problems in postmenopausal women emanate mainly from paucity of saliva, leading to xerostomia, burning mouth syndrome, increase in incidence of dental caries, dysesthesia, taste alterations, atrophic gingivitis, and periodontitis. Evidentially, postmenopausal women have lower flow rates of saliva and this reduced salivary flow rate is responsible for xerostomia among postmenopausal women (Mahesh et al., 2014). This is attributable to the diminished role of oestrogen on the oral mucosa and salivary glands due to hypoestrogenism (Leimola-Virtanen et al., 2000; Thompson et al., 2001).

Menopausal symptoms have been reported to be high among Nigerian women (Ande et al., 2011) with early symptoms like hot flashes in about half of menopausal women and late symptoms like joint pain seen in about two-thirds to three-quarters of the menopausal women. It is anticipated that oral health issues of menopause will be of high prevalence among Nigerian women. Therefore, there is a need for

Dentists, Oral Medicine practitioners, and Gynaecologists to work toward oral health management options to meet the treatment needs of perimenopausal and postmenopausal women in the reduction of their oral health problems (Hambire & Hambire, 2021).

In underserved settings like Nigeria, Hormone replacement therapy (HRT) which has been used for the treatment of menopausal symptoms for over 50 years (Yalçin et al., 2005) may be unaffordable for the generality of women. This is aside from the fact that hot flashes and night sweats are the only symptoms universally reported to respond to estrogen replacement almost immediately (Yalçin et al., 2005). Therefore, the effect of HRT in alleviating symptoms and improving oral health remains controversial (Yalçin et al., 2005; Eviö et al., 2006; Mahesh et al., 2014) which necessitates the need to search for affordable and effective options that could help alleviate menopause-related oral health issues in Nigerian women.

One alternative treatment option that seems promising in the treatment of menopause-related oral health symptoms is Vitamin B supplementation, especially as the postmenopausal stage is ranked among the risk factors for vitamin B deficiencies (WHO supplemental nutrition with dietary advice for older people affected by undernutrition, 2019). Moreover, conditions such as recurrent aphthous stomatitis, atrophic glossitis, or a painful, burning tongue, which are characterized by inflammation and defoliation of the tongue have been associated with vitamin B₁₂ and iron deficiencies (Field et al., 1995; Ehizele et al., 2009). Nutritional supplement that contains all eight B vitamins namely B₁ (thiamine), B₂ (riboflavin), B₃ (niacin), B₅ (pantothenic acid), B₆ (pyridoxine), B₇ (biotin), B₉ (folate) and B₁₂ (cobalamin), is referred to as vitamin B-complex (WHO supplemental nutrition with dietary advice for older people affected by undernutrition, 2019). The role of compounds from the group of vitamin B cannot be overestimated in the postmenopausal stage of life.

The basis of assessing the viability of Vitamin B supplementation in postmenopause in reducing oral health related to menopause is also based on the report that indicated decreased bacterial activity in the presence of thiamine, riboflavin, and pyridoxine (Balogh et al., 1960). Furthermore, supplementation with a multivitamin containing high-dose B vitamins has been associated with changes in the cortisol awakening response at 16 weeks (Camfield et al., 2013). Therefore, given the fact that salivary changes in post-menopausal Nigerian women have hardly been reported, this study aimed to determine salivary changes: Salivary Flow rate, Salivary Viscosity and Salivary pH, among Nigerian postmenopausal women and to ascertain the effect of vitamin B-

complex supplement in improving salivary flow indices.

MATERIALS AND METHODS

This study was a single-blinded, parallel randomized placebo-controlled clinical trial conducted over nine (9) months from November 2021 to July 2022. It was conducted among Postmenopausal women attending outpatient clinics of the University of Benin Teaching Hospital, Benin City who met the inclusion criteria. This clinical trial involved two equal groups where vitamin B-complex supplement (370mg twice daily) was administered to the treatment group and a placebo to a control group using purely maize starch tablet of 370 mg of the same colour as the vitamin B-complex supplement twice daily for 4 weeks. This clinical trial has been registered with the PAN AFRICAN CLINICAL TRIALS REGISTRY (PACTR) with registration number PACTR202109528354413. The protocol for this research was reviewed and approval was granted by the Research and Ethics Committee of the University of Benin Teaching Hospital, Benin City.

Exclusion and Inclusion Criteria

The Inclusion criteria included: Postmenopausal women without a history of Sjogren's syndrome or fibrosis of salivary glands; and postmenopausal women not on any drug known to cause xerostomia, examples are tricyclic antidepressants and antihistamines. Exclusion criteria included: Postmenopausal women with diabetes mellitus, Celiac disease, HIV, Crohn's disease, alcohol dependence, kidney conditions, rheumatoid arthritis, ulcerative colitis, and inflammatory bowel disease that prevent the body from properly absorbing vitamin B-complex.

Recruitment, Randomization, and Blinding

A total of 70 patients were recruited into the study and were randomized equally into the two study arms (35 each). The study participants (postmenopausal women) in this study were blinded to the knowledge of the drugs they were given.

All the respondents were followed up during the one-month interval using phone calls and text messages to remind them of their appointments and to keep up with their daily regimen. Constitution of the Vitamin B Complex used in this study: The pure samples were prepared into 370mg tablets in the Tablet Production Unit of the Faculty of Pharmacy, University of Benin. Each tablet contained Vitamin B-complex supplement pill (35mg thiamine-B1, 35mg riboflavin-B2, 35mg niacin-B3, 35mg pantothenic acid-B5, 25mg pyridoxine-B6, 10ug cobolamin-B12, 600ug folate-B9, 150ug biotin-B7). 1 pill=370mg. Participants took 1 pill twice daily for 4 weeks. This dosage did not exceed the recommended dosage as presented in the text "Tolerable Upper Intake Levels for vitamins and minerals" done by the European Food and Safety Authority (EFSA) (Jankovskis and Selga G 2021). Placebo (370mg tablet of purely maize starch twice daily) also done by the Tablet Production Unit of the Faculty of Pharmacy, University of Benin, was administered to the control group.

Procedure-Collection of Unstimulated Whole Saliva Using Spitting Method

The saliva samples were collected from the subjects under standardized conditions, between 9am and 11 am. At least one hour after breakfast with the patient being seated and leaning slightly forward. Participants were asked to rinse their mouth with tap water to remove food debris. The saliva secreted during the first one minute were swallowed; that secreted during the next five minutes were expectorated into a pre-weighed plastic tube. The timing was done using stopwatch. The saliva flow was determined gravimetrically by weighing the saliva using MH-Series Pocket Scale, with the assumption that one milligram is equal to one millimeter. Then the flow rate (ml/min) was determined by dividing the obtained weight with five. The samples were then saved for pH and Viscosity measurements.



Figure 1: MH-Series Pocket Scale



Figure 2: Simple capillary viscometer

Relative viscosity of saliva (RVS)

Measurement of relative viscosity of saliva was done using simple capillary viscometer developed by Reid and Ugwu (Reid & Ugwu, 1987) and a variant developed by Elblbesy (2014). This method has been applied severally in Nigeria, (Memeh & Reid 1988; Okonofua *et al.*, 1990; Azodo & Osahon, 2020) and has been stated to be valid and cost effective. It can easily be done as a chair side test (Azodo & Osahon, 2020) and has been acknowledged to be very appropriate in developing countries. (Elblbesy, 2014) Salivary viscosity was determined by allowing saliva to flow through a 10ml syringe and measuring the rate of flow from 2mls to 0mls. The timing was done using a stop watch and recorded in seconds. The plunger of the disposable syringe was carefully removed, creating a positive pressure, which allowed the saliva to flow through the needle end. The start off for the flow is usually above 4mls but timing start off is at 2mls as a precautionary measure. The viscosity of the liquid is determined by a comparison with a standard which is water. Distilled water was used first to established the standard before the experiment with saliva.

RVS was calculated using the following equation: $RVS = t_{saliva} / t_{water}$. Where t_{saliva} is the time of flow of 2mls of saliva and t_{water} is the time of flow of 2mls of distilled water which is the standard.

Saliva pH

Saliva pH was measured using pH litmus paper strip (NEUTRALIT®). The pH litmus paper strip was used to determine if a solution is acidic, basic or neutral. The pH was determined by dipping part of the strip into the collected saliva for 30 to 60 seconds and the colour change is matched with the color-coded scale. The number on the corresponding code indicates the pH of the saliva

Data management

Data was analyzed using IBM SPSS version 24.0. Association in the bivariate analysis was determined with chi-square statistics or Fisher exact for categorical variables and independent t-

test for continuous variables for comparison of salivary changes at baseline and Recall. Multivariate analysis in the form of logistics and linear regressions was done to determine if exposure to vitamin B complex supplement is a significant predictor of the categorical and continuous variables respectively. Statistical significance in this study was set at $p < 0.05$

RESULTS

A total of 70 post-menopausal women participated in the study, 35 in each of the treatment and control groups. There was no statistical difference in the distribution of socio-demographic characteristics between the study groups. The mean age of the participants was 60.10 ± 6.54 years. Most of the participants were married [61(87.1%)]. The overall mean age at menopause was 51.07 ± 4.00 years with that for the placebo group being 51.29 ± 4.18 and that of the treatment group being 50.88 ± 3.81 .

Analysis of Unstimulated Whole Salivary Flow rate (UWSFR) at Presentation and Recall visits between the groups

There was no significant difference in unstimulated whole salivary flow rate (UWSFR) at presentation between the placebo (0.36 ± 0.23 gm/min) and treatment (0.40 ± 0.20 gm/min) arms of the study ($p = 0.447$). However, at recall visit there was a significant difference in salivary flow rate between the groups, with salivary flow rate in the treatment group (0.46 ± 0.19 gm/min) statistically significantly higher than that in the placebo group (0.35 ± 0.23 gm/min) ($p = 0.041$). Also, there was a significant increase within the treatment group in salivary flow rate at recall ($p < 0.0001$), which was not observed in the placebo group ($p = 0.835$) as shown in Table 1. Table 2 shows the treatment group and baseline UWSFR were significant predictors of unstimulated whole salivary flow rate at recall. The unstandardized B coefficient indicates a 0.08 gm/min increase in salivary flow rate in the treatment group ($p = 0.023$) compared to the placebo group.

Table 1: Comparative analysis of Unstimulated Whole Salivary Flow rate (gm/min) between the groups

Variables	Groups		Total	F Statistic	P value
	Placebo (n=35) Mean ± SD	Treatment (n=35) Mean ± SD			
Baseline USFR	0.36 ± 0.23	0.40 ± 0.20	0.38 ± 0.22	F=0.585	0.447
Recall UWSFR	0.35 ± 0.23	0.46 ± 0.19	0.40 ± 0.22	F=4.323	0.041*
P value	0.835	<0.0001*			

Table 2: Linear Regression on Unstimulated Whole Salivary Flow rate (gm/min)

Predictors	Reference category	Unstandardized Coefficient		Standardized Beta coefficient	P value
		B	Std. Error		
Age (yrs.)	Unit increase	0.003	0.004	0.093	0.473
Duration since last menstruation (yrs.)	Unit increase	-0.003	0.005	-0.083	0.533
Baseline UWSFR (gm/min)	Unit increase	0.755	0.083	0.748	<0.0001*
Treatment	Placebo	0.08	0.035	0.182	0.023*

Model parameters: R²=0.638, p <0.000

Analysis of Saliva Relative Viscosity (SRV) at presentation and at Recall Visit between the groups

At presentation, the mean SRV in the placebo group and treatment groups were 2.01±0.45 and 2.31±0.52 respectively (Table 3). There was a significant difference in SRV between the groups at presentation (p =0.013). Within the treatment

group, there was a significant difference in viscosity from 2.31±0.52 to 2.23±0.46 (p=0.001). Table 4 showed the treatment group (p= 0.865) was not a significant predictor of SRV at recall. The table also shows that with a unit increase in baseline SRV, there was a 0.703 increase in SRV at recall.

Table 3: Comparative analysis of Saliva Relative Viscosity (SRV) between the groups

Variables	Groups		Total Mean ± SD	F Statistic	P value
	Placebo (n=35) Mean ± SD	Treatment (n=35) Mean ± SD			
Baseline SRV	2.01±0.45	2.31±0.52	2.16±0.5	F=6.523	0.013*
Recall SRV	2.02±0.45	2.23±0.46	2.12±0.46	F=3.954	0.051
P value	0.972	0.001*			

Table 4: Linear Regression on SRV at Recall Visit

Predictors	Reference category	Unstandardized Coefficient		Standardized Beta coefficient	P value
		B	Std. Error		
Age (yrs.)	Unit increase	0.004	0.01	0.052	0.706
Duration since last menstruation (yrs.)	Unit increase	2.41E-05	0.011	0	0.998
Baseline SRV	Unit increase	0.703	0.081	0.768	<0.001*
Treatment	Placebo	0.014	0.079	0.014	0.865

Model parameters: R²=0.777, p <0.0001

Analysis of pH at Presentation and Recall Visit between the groups

As shown in Table 5, The mean pH at presentation was 6.77±0.33 and 6.73±0.31 in the placebo and treatment groups respectively; there were no significant differences in pH at presentation (p =

0.574). At recall, the mean pH was 6.61±0.87 and 6.76±0.33 in the placebo and treatment groups respectively and there were no significant differences between the groups (p = 0.365). Table 6 showed the treatment group was not a significant predictor of pH at the recall visit (p=0.329).

Table 5: Comparative analysis of pH between the groups

Variables	Groups		Total Mean ± SD	F Statistic	P value
	Placebo (n=35) Mean ± SD	Treatment (n=35) Mean ± SD			
Baseline pH	6.77±0.33	6.73±0.31	6.75±0.32	F=0.319	0.574
Recall pH	6.61±0.87	6.76±0.33	6.69±0.65	F=0.831	0.365
P value	0.299	0.160			

Table 6: Linear Regression on pH at Recall Visit

Predictors	Reference category	Unstandardized Coefficient		Standardized Beta coefficient	P value
		B	Std. Error	Beta	
		Age (yrs.)	Unit increase	-	
Duration since last menstruation	Unit increase	0.032	0.022	0.292	0.147
Baseline pH	Unit increase	0.607	0.255	0.288	0.020*
Treatment	Placebo	0.157	0.159	0.118	0.329

Model parameters: R²=0.140, p=0.052

DISCUSSION

There was no statistically significant difference in the distribution of socio-demographic characteristics between the study groups. The mean age of 60.10 ± 6.54 years of the study participants is expected because menopause usually occurs in the fifth decade (Adekunle et al 2000). The mean menopausal age of 51.07±4.00 years is slightly higher than 49.8 ± 2.6 reported in a previous study in Benin City (Ade et al., 2011); 49.36 ± 5.0 years reported in Ibadan (Adeloye et al., 2021). This slight difference in the mean age of menopause may be due to the differences in the mode of recruitment of the participants in the compared studies. The increasing Body Mass Index among Nigerians (Zhu et al 2018) including menopausal women may also have contributed to the increasing mean age of menopause (Agha-Hosseini & Mirzaii-Dizgah, 2012).

The mean unstimulated whole salivary flow rate in this study at baseline was 0.38±0.22 gm/min is higher than 0.28± 0.64 mL/min reported in Turkey (Yalçın et al 2005), 0.29 ± 0.17 mL/min reported in Italy and the values reported in Iran (0.30 ± 0.02 mL/min and 0.35 ± 0.01 mL/min) (Miranda-Rius et al 2015). The differences can be ascribed to the differences in saliva collection and measurement methods among studies. Vitamin B complex supplementation resulted in a significant difference in salivary flow rate between the groups, with salivary flow rate in the Vitamin B group higher than that in the placebo group (p=0.041).

Vitamin B complex supplementation and baseline UWSFR emerged as predictors of increased unstimulated salivary flow rate in this study. The baseline UWSFR may reasonably serve as a prognostic indicator of the likelihood of an increase in unstimulated salivary flow rate with Vitamin B complex supplementation. This effect may be due to Vitamin B-complex supplementation affecting salivary flow indirectly by increasing the synthesis of the neurotransmitters. Thiamine serves as a cofactor in the biosynthesis of acetylcholine which

stimulates muscarinic and nicotinic receptors which results in an increased saliva flow (Just & Walz, 1996). Pyridoxal 5'-phosphate-dependent enzymes are involved in the transamination and decarboxylation of amino acids to amines such as dopamine and serotonin. Dopamine stimulates the secretion of the fluid component of the saliva, while serotonin is necessary to stimulate the secretion of the proteinaceous components (Azodo & Osahon, 2020).

The overall mean salivary viscosity in this study at baseline was 2.16±0.5, with baseline SRV of 2.01±0.45 in the placebo group and 2.31±0.52 in the treatment group. This baseline salivary viscosity (2.16±0.5) was far higher than 1.49 ± 0.11 reported among females aged 17 to 40 years in Benin City, Edo State (Stephens and Wand 2012). The increase in salivary viscosity with aging may be the plausible explanation of the study finding as the maximum age in that study was 40 years. (Stephens & Wand, 2012). The increased salivary viscosity signified decreased lubricator function possibly giving a false sense of dry mouth, burning sensation, and taste disturbances among participants. Vitamin B complex supplementation did not have a significant effect on salivary relative viscosity (SRV) in this study after adjusting for baseline SRV in the groups. This finding is inconsistent with the significant impact of Vitamin B supplementation on unstimulated salivary flow rate at recall, as improved UWSFR should cause a reduction in SRV. More studies involving a larger sample size might be needed to validate this finding, as intra-group comparison within the treatment group indicated that SRV was significantly reduced from a baseline value of 2.31±0.52 to 2.23±0.46; although regression analysis showed there was no statistically significant change in SRV between the groups at recall.

The mean salivary pH in this study at baseline was 6.75±0.32 with 6.77±0.33 in the placebo group and 6.73±0.31 in the treatment group which was

comparable to the salivary pH (6.75 ± 0.34) reported among postmenopausal women in Italy (Bhat et al, 2010). Although, this is lower than 6.96 ± 0.13 reported in Turkey (Yalçın et al., 2005) but higher than 5.67 ± 0.49 , 5.77 ± 0.37 and 5.98 ± 0.52 reported among menopausal women in India (Nuaimy et al., 2012; Saluja et al., 2014; Parakh et al., 2016). The differences in the salivary pH may be due to the fact the Indian study assessed stimulated saliva rather than unstimulated saliva used in this study. Alterations in the flow rate of saliva affect salivary pH by affecting the inorganic constituent of saliva, especially bicarbonate, calcium, and phosphate (Agrawal et al., 2022). Vitamin B complex supplementation did not significantly affect the salivary pH which means that if alteration in the salivary pH of menopausal women is needed, alternative therapy other than Vitamin B complex supplementation such as dieting will be needed.

Conclusion, Recommendations, and Limitations

Vitamin B-complex supplements used for 4 weeks significantly improved the unstimulated salivary flow rate but did not significantly improve salivary viscosity and pH. Based on the study findings, Vitamin B supplementation may be recommended as part of a daily regimen for post-menopausal women to increase their Salivary flow rate which may help resolve their menopausal oral symptoms such as Dry mouth and Burning sensation. However, study findings may be limited by the possibility of inconsistency in compliance with the take-home test drugs. Also based on the 4-month duration of the study only short-term benefits were thoroughly assessed but there is a need for a prolonged study on the effects of Vitamin-B supplementation to assess possible long-term benefits.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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