REVIEW

Salivary biomarkers: A boon to aid in early diagnosis of osteoporosis

Shefali Goel*, Rekha Gupta, Shubhra Gill, Poonam Kadain, Abhishek Kumar Gupta

Department of Prosthodontics, Maulana Azad Institute of Dental Sciences, Delhi, India

*Corresponding author e-mail: shefaligoel2017@gmail.com

ABSTRACT

Osteoporosis is a crippling disease, which has gripped our society and acts as a silent killer. Its early identification and treatment is the mainstay for its management. Saliva confers various merits over the conventional diagnostic aids, which are available. Ease of accessibility, with no pain experienced by the patients, accord it an edge over the current investigations. Its non-invasive nature obliviates patient's reluctance to testing. It can be easily rendered in susceptible or high-risk patients even while routine dental checkup. Pro-inflammatory cytokine like Interleukin-6 (IL6), which is encoded by the IL6 gene, plays vital role in bone remodelling and has shown increased levels in postmenopausal osteoporotic women. Increased level of salivary calcium has also been seen in postmenopausal osteoporotic women. Thus, salivary IL6 and salivary calcium are viable aids for prompt identification of postmenopausal osteoporotic women. BGLAP gene encodes osteocalcin (OC) that is secreted by osteoblasts and regulates bone remodelling. The concentration of bone biomarkers like OC and deoxy pyridinium (D-PYR) is found to be significantly correlated to serum OC and urinary D-PYR, suggesting the use of saliva as a diagnostic aid for assaying biomarkers of osteoporosis. Thus, salivary biomarkers testing in regular dental screening can aid in prompt identification of osteoporosis.

KEYWORDS: Saliva, osteoporosis, biomarkers, early diagnosis

Citation: Goel et al. Salivary biomarkers: A boon to aid in early diagnosis of osteoporosis. Polymorphism 2021; 6: 107-119.

INTRODUCTION

Early diagnosis of pathology augments the probability of success of the therapeutic intervention, prognosis of the condition, comfort and the survival rate of the patient. This becomes even more critical in diseases like osteoporosis, especially in postmenopausal woman where fracture might be the only clinical manifestation in the patient. Substantial morbidity and mortality risk is seen to be associated with osteoporotic fractures (Vlasiadis et al. 2008). Application of dual-energy X-ray absorptiometry (DXA) scan for bone mineral density (BMD) assessment is considered as the gold standard for osteoporosis diagnosis (Meeta et al. 2013). But DXA possess its own demerits being an expensive diagnostic modality that is not readily available and with difficulty of reproducibility (Phillipov et al. 2001) plus a static measure (Shetty et al. 2016). In addition, predisposition to osteoporosis by genetic variants might be through mechanisms independent of BMD. Thus, other diagnostic modalities are also needed that identify the condition through measurement of parameters other than BMD as can be seen with salivary biomarkers quantification (Ralston et al. 2006). Saliva testing can serve as a viable aid for early diagnosis and mass screening of osteoporosis. Serum collection is an invasive, expensive method and might cause discomfort to some patients. Use of saliva confers various merits over serum collection. Saliva collection is a non-invasive, innocuous, patient-friendly procedure, which does not require the aid of trained personnel and can even be self-collected (Vissink et al. 2008; Navazesh et al. 2008). The above makes it a favourable option for patients specially those who have a phobia for serum testing. Its non-clotting nature, ease of collection and storage makes it a cost-effective and a viable option. A major merit of this procedure is the presence of HIV inhibitors in saliva which might hamper the oral transmission, thus making saliva samples quite safe to handle (Campo et al. 2006). The above merits make it an option worth exploring as it might prove quite beneficial for regular patient's checkup and mass screenings.

Osteoporosis

Osteoporosis is characterized by poor bone microarchitecture and mass with deteriorated bone mechanical properties, which culminates into bone fragility and eventual bone fractures. WHO identifies people with BMD lesser than 2.5 standard deviations (SD) below the normal value as osteoporotic. Osteoporosis is called a "silent disease" because the progression of the condition happens without any symptom until a fracture occurs (Toronto: Osteoporosis Canada, 2008). Low trauma fragility fractures are a common manifestation of it. It primarily affects older people, particularly postmenopausal women, and is associated with 80% of fractures in people older than age 60 years (Shih et al. 1993). Imbalance of bone formation and resorption lead to the inception of osteoporosis with increased osteoclastic resorption being the main culprit (Davis et al. 1998). Family and twin studies render quality evidence that indicates that 50% and 85% peak bone mass variance is genetically determined in accordance to age and skeletal site of the patient (Smith et al. 1973; Pocock et al. 1987; Krall et al. 1993; Gueguen et al. 1995). Other key determinants for fracture risk in osteoporosis like bone turnover markers (Hunter et al. 2001), femoral neck geometry (Arden et al. 1996), muscle strength (Arden et al. 1997), body mass index (Kaprio et al. 1995), bone's quantitative ultrasound (Arden et al. 1996) have also been found to be significantly genetically influenced. Irrespective of BMD several studies have reported positive family fracture history as risk factor for osteoporosis. This signifies testing of people with positive family history should be undertaken (Cummings et al. 1995; Torgerson et al. 1996).

Postmenopausal woman

Postmenopausal women constitute a major proportion of people that are highly susceptible to

osteoporosis (Schneider et al. 1997; Reddy et al. 2016). They experience more bone loss due to hormonal alterations (Civitelli et al. 2002). Oestrogen plays a major role in the regulation and maintenance of skeletal bone growth and mass (Sano et al. 1995). In women oestrogen deficiency has been reported as the major causative agent for osteoporosis (Khosla et al. 1997; Garcı´a-Pe´ rez et al. 2003;). In woman, menopausal age has been seen to be genetically determined (Sneider et al. 1998). Numerous theories have been proposed to delineate increased bone turnover rate seen post menopause. However, activation of osteoclasts by the direct action of oestradiol is the most accepted one (Parfitt et al. 2001). Estrogen's direct action is seen in the gut where it influences the physiologic calcium absorption. In addition, oestrogen deficiency might lead to increased serum calcium level by inducing active calcium resorption by triggering the release of parathormone (Nagler et al. 2005). Positive association has been found between osteoporosis and ESR1 alleles in a study conducted on Japanese women (Sano et al. 1995). Previous literature points towards an association between menopause and decreased BMD (Calciolari et al. 2015). High BMD values were seen in postmenopausal women having a combination of VDR "bb" genotypes and ESR1 PvuII "PP" (Willing et al. 1998). Rabiei et al. in their study found that more delayed the testing in postmenopausal woman, less effective may be testing result by tools like salivary markers (Rabiei et al. 2012). Thus post the age of 50 years osteoporosis screening is necessary for proper management of the condition and patient's wellbeing (Lim et al. 2009).

Saliva collection

Both stimulated and unstimulated saliva may be used as the test sample. Methods like swabbing, draining, spitting and suction may be utilized but literature identifies draining method in which dripped off saliva from the lower lip is collected and spitting method in which exporated saliva is collected in a test tube are the more desirable ones (Reddy et al. 2016; Yamuna et al. 2017; Pereira et al. 2018). Regardless of the method used its imperative for the patients to rinse their oral cavity with water to clean out the presence of any contaminant that might have been present before the sample collection (Yoshizawa et al. 2013).

Salivary biomarkers

National Institutes of Health (NIH) has construed biomarker as an indicator that can be measured and evaluated objectively which aids in gaining insight to normal and pathologic functioning of the body and response of the body to therapeutic intervention (Silberring et al. 2010). Highly permeable nature of the salivary glands enables absorption of biomarkers from the circulation, thus making it an important diagnostic aid that might reflect the health status of an individual (Holsinger et al. 2007; Drobitch et al. 1992; Haeckel et al. 1993; Jusko et al. 1993). Saliva serves as a rich source for transcriptome, proteome, epigenome, metabolome and microbiome (Ai et al. 2010; Ai et al. 2012; Kawas et al. 2012). Various bone turnover markers can be found in the saliva like calcium, phosphorus and alkaline phosphatase (Rabiei et al. 2012; Reddy et al. 2016). Research can be found in the literature that has endeavoured to find the scope of using these salivary biomarkers as bone biomarkers. Salivary biomarkers have been utilized for diagnosis of multitudes of conditions ranging from cancers, dental caries, periodontal diseases, Sjogren syndrome to oral lesions like leukoplakia, candidiasis and risk of jaw fracture, diabetes, infections like mumps, measles (Reddy et al. 2016; Burbelo et al. 2012). Thus, it seems like a promising avenue which could be explored to aid in early diagnosis of osteoporosis (Reddy et al. 2016).

(i) Osteocalcin (OC)

Serum osteocalcin, also identified by the name of bone GLA protein, is a 49 amino acid protein secreted by osteoblasts (Delmas et al. 1995). It is a major noncollagenous protein present in the mineralised tissues. Post secretion it is mainly

incorporated into the bone matrix with a fraction of it released into the circulation where it can be detected by the immunoassay (Lian et al. 1988). Chromosome1q25-q31 has been identified in relation to the BGLAP, OC gene (Puchacz et al. 1989). Morrison et al. reported an association between osteocalcin level and 3_ region of VDR that has been affected by polymorphisms (Morrison et al. 1992). Osteocalcin is also seen to play a role in osteoclast precursors' recruitment and differentiation (Glowacki et al. 1991; Chenu et al. 1994). Reduced hydroxyapatite crystal synthesis may lead to the presence of free OC crystals which might expound increased levels of OC in osteoporotic postmenopausal women (Civitelli et al. 2009). Conflicting literature is present regarding association between OC levels and vitamin D receptor gene variants (on chromosome 11) (Morrison et al. 1992; McClure et al. 1997; Garnero et al. 1995; Garnero et al. 1996; Tsai et al. 1996). Study by Mitchell et el elucidated that chromosome 16 and 20 might harbour the serum OC influencing genes. CDMP1(Cartilage-derived morphogenetic protein) present on chromosome 20 has been mapped to the region of 20q11.2 region and is speculated to be involved in the formation of bone (Braxton et al. 2000). CDMP1, which has been found to be closely associated to bone morphogenetic proteins 5-7, is encoded by CDMP1 (Chang et al. 1994). Increased serum OC levels are seen in ailments associated with accelerated bone loss (Ross et al. 1998) and increased bone turnover (Puchacz et al. 1989; Delmas et al. 1995; Price et al. 1980; Clarke et al. 1995). Thus, serum OC can be used as a biomarker of bone turnover.

In the study by Johnson et al in ovx sheep, significant correlation has been observed between salivary and urinary / serum levels of deoxypyridinium, osteocalcin and IL-6. Salivary biomarker concentrations were found to be only slightly lower than their serum/ urine counterparts (Johnson et al. 2002).

(ii) Deoxypyridinium

90% bone organic matrix is composed of type I collagen (Narayanan et al. 1983). It has mainly two mature crosslinks, Pyridinium (PYR) and deoxypyridinium (D-PYR) (Last et al. 1990) which have gained recognition as bone resorption markers (Blumsohn et al. 1994; Eriksen et al. 1993; Eastell et al. 1993). Urinary D-PYR and serum OC has been seen as reliable indicators of bone resorption (Kelm et al. 1992; Seyedin et al. 1993). Use of above markers has been clinically validated in osteoporosis both for diagnosis and treatment efficacy (McLaren et al. 1992; Seibel et al. 1994). D-PYR has been found to be a more reliable bone marker than OC for postmenopausal osteoporosis (Yilmaz et al. 1999). Roger et al predicted that salivary OC and D-PYR could both be used to identify both osteopenia and osteoporosis in human subjects as its positive correlation was seen with calcaneal T scores (Biswas et al. 2018). Above literature signifies that both salivary OC and D-PYR can be predictably used for the diagnosis of osteoporosis.

(iii) Interleukin-6 (IL6)

IL6 is a pro inflammatory and bone resorbing cytokine which has been found to be associated with decreased ovarian function in menopause. IL6 is encoded by the IL6 gene and osteoblasts secrete IL-6 to stimulate osteoclast formation (Ferguson et al. 1988). During menopausal transition the cytokines misbalance plays a role in osteoporosis pathogenesis and progression in postmenopausal women (Desai et al. 2012). IL6 hampers osteoblasts proliferation and may have an indirect action on RANKL-L which may promote osteoclastogenesis (Abdel et al. 2013). In metabolic bone disease IL-6 has been found to be increased (Manolagas et al. 1995; Pacifici et al. 1996; Manolagas et al. 1995). Al-Daghri et al demonstrated in their study that IL6 contributes to increased bone loss in postmenopausal women (Al-Daghri et al. 2014). Increased IL-6 concentration in serum (Girasole et al. 1992), bone marrow (Manolagas et al. 1995; Jilka et al. 1992)

and gingiva (Johnson et al. 1997) are result of oestrogen deficiency seen in postmenopausal woman. Few studies elucidated increased salivary IL6 level in osteoporotic postmenopausal women (Jacobs et al. 1996; Krejci 1996; Wactawski et al. 1996). Desai et al also reported negative correlation of IL6 with oestrogen and BMD (Loza et al. 1996). In a cross-sectional study involving woman with pre and post menopause, in postmenopausal woman significant correlation has been found between metacarpal and alveolar BMD and increased salivary IL-6 level (Streckfus et al. 1997). Thus, salivary IL6 can be used for diagnosis of osteoporosis as a valid biomarker with high sensitivity, specificity and accuracy as concluded by Jabber et al (Jabber et al. 2015).

(iv) Salivary calcium

Homeostasis of serum calcium is maintained by binding between vitamin D active metabolites and vitamin D receptor (VDR), that mediates genes regulation through heterodimer formation with retinoic X receptor (RXR) (Kristjansson et al. 1993). This indicates that bone defects that result through VDR deficiency are mediated through calcium and phosphorus mal-absorption rather than 1,25-(OH)2D3 signalling absence in the bone tissue. Association of intestinal calcium absorption has been seen with BsmI VDR polymorphism (Dawson-Hughes et al. 1995; Gennari et al. 1997) and FokI polymorphism (Ames et al. 1999; Abrams et al. 2005).

In a study it was found that the only electrolyte that is not affected by salivary flow rate is calcium (Sevo'n et al. 2008; Agha-Hosseini et al. 2007; Agha-Hosseini et al. 2009). In another study conducted by Sewon L et al., reported that increased salivary calcium might reflect decreased skeletal bone density (Sewón et al. 2004). Naik et al demonstrated that postmenopausal osteoporotic woman had increased salivary calcium level compared to their normal counterparts (Biswas et al. 2018). Rabiei et al found a positive correlation between salivary calcium and osteoporosis as in osteoporotic woman increased salivary calcium concentration was seen in the study. They identified 6.1 mg/dl calcium level as the cut-off limit for salivary calcium, above which the value may serve as a risk indicator in postmenopausal females. The study concluded the application of salivary calcium as a diagnostic aid and also nullified the need for bone densitometry (Rabiei et al. 2012). Sewon L et al conducted a longitudinal study in which he found that salivary calcium decreased in stimulated saliva in menopausal women after initiation of hormone replacement therapy. Thus, they concur that there might be other factors in addition to salivary flow that may regulate/modify salivary calcium concentration (Sewón et al. 2000). However according to Moghadam et al. no correlation exists between low BMD and salivary calcium. This might be attributed to the inclusion of patients of different age group in the study and variable study design (Moghadam et al. 2016). As observed in the study by Nagler and Hershkovich, elderly population have significantly higher salivary calcium levels than the younger population. It was also seen that increased serum calcium level also reflects as increased salivary calcium level (Nagler et al. 2005). Similar findings pertaining to salivary calcium level have been seen in other studies (Sewón et al. 2000; Saha et al. 2017; Agha-Hosseini et al. 2012). In few studies significant negative correlation has been seen between salivary calcium and BMD score, salivary calcium and oestrogen level (wasti et al. 2020; Singh et al. 2016). Thus substantiating that salivary calcium can aid in diagnosis of osteoporosis.

(v) Miscellaneous biomarkers

One study found elevated level of salivary alkaline phosphatase and calcium in osteoporotic edentulous patients (Saha et al. 2017) while another study found no remarkable difference in salivary phosphorus levels between non-osteoporotic and osteoporotic individuals (Ross et al. 2000). In the study by Reddy S et al, in osteoporotic patients increased level of salivary alkaline phosphatase and salivary calcium has

been found (Reddy et al. 2016). Bairwa et al found positive correlation between serum and salivary calcium but only a weak association between serum and salivary alkaline phosphatase (Bairwa et al. 2019).

Osteoporosis and oral cavity

In contrast to the general population in patients with osteoporosis, significant oral changes can be seen. A positive correlation has been noticed between BMD of important osteoporotic sites like the femoral neck, forearm, lumbar spine and mandible (Calciolari et al. 2015; Leite et al. 2010; Makker et al. 2012). Oral changes include decreased BMD of mandible (Mohammad et al. 1994; Kribbs et al. 1989) and condyle (Tanaka et al. 2000), increased number of extracted teeth (Groen et al. 1968; Baxter and Fattore et al. 1993; VonWowern et al. 1994; Taguchi et al. 1995; Kribbs et al. 1990; Danielle et al. 1994), exaggerated residual ridge resorption (Pocock et al. 1987; Atwood et al. 1971; VonWowern et al. 1992; Hirai et al. 1993; Klemetti et al. 1993). Other studies also identify an association between decreased alveolar heights and reduced skeletal BMD and clinical attachment loss (Kribbs et al. 1989; VonWowern et al. 1994; Taguchi et al. 1995; Kribbs et al. 1990; Jeffcoat et al. 1993; Jacobs et al. 1996; Loza et al. 1996; Krejci et al. 1996; Wactawski et al. 1996; Mohammad et al. 1996; Hildebolt et al. 1997; Grossi et al. 1998; Payne et al. 1997; Talbot and Craig 1998; Payne et al. 1999; Zachariasen et al. 1999; Ronderos et al. 2000). Since oestrogen receptors can be seen in salivary glands, oral mucosa, fibroblasts, and osteoblasts (Leimola-Virtanen et al. 2000; Vaananen and Harkonen et al. 1996), thus alteration in oestrogen concentration might affect the oral cavity (Leimola-Virtanen et al. 2000). Gingival connective tissue metabolism has been found to be influenced by oestrogen deficiency that might lead to periodontitis (Johnson et al. 1997). Speculated pathogenesis which occur post oestrogen deficiency involves the stimulated synthesis of matrix metalloproteinases (MMP-2, MMP-8, and MMP-13 (Golub et al. 1999) nitric acid (Damoulis et al. 1994) and pro bone resorption cytokines (Payne et al. 1997; Streckfus et al. 1997). This might aid to explain the oral effect of osteoporosis in postmenopausal women. For postmenopausal woman with periodontitis history, oestrogen deficiency and osteoporosis may act as risk factor for alveolar bone height loss (Payne et al. 1999). This association has been reported in multitudes of studies in which strong link has been visible between patient's oestrogen status, periodontal disease (Norderyd et al. 1993; Reinhardt et al. 1999) and decreased alveolar bone BMD (Streckfus et al. 1997). Increased salivary osteocalcin concentration is associated with improved periodontal health (Bullon et al. 2007). Thus the above provide ample scientific evidence to support the regular dental screening of postmenopausal woman as it may aid in early osteoporosis diagnosis.

Effect on dental treatment

Proper identification and diagnosis of osteoporosis also augment the success of dental treatment. Treatments like implant procedure, bone grafting may be compromised due to improper osseointegration due to poor quality of bone which is seen in case of osteoporosis (Jiun-NongLinetal. et al. 2017). Inadequate diagnosis of the condition may lead to accidental jaw fractures during dental procedures like extractions of teeth, implant placement, hamper the periodontal status of teeth and may lead to its eventual loss and may also aid in the failure of implants (Giro et al. 2015; Chin- wei et al. 2016). A greater attachment loss was seen in osteoporotic women in a study conducted by Wowern et al (Wowern et al. 1994). As ascertain in literature impact on alveolar bone and periodontal tissues might occur leading to eventual tooth loss (L´opez et al. 2015; Savi´cPavi˘cin et al. 2017; Singh et al. 2014).There is proper evidence to substantiate the claim that jawbones are directly affected by the effect of

osteoporosis, thus resulting in bone resorption and reduced bone density (Reddy et al. 2016).

Osteoporosis has been identified as a major causative agent of residual ridge resorption with poor dietary calcium intake and increased phosphorus consumption augmenting the disease progression (Mercier et al. 1981). Alteration in alveolar BMD have been found to precede and be more severe than the changes in other sites bone tissue (Johnson et al. 2002). Thus early response of alveolar BMD occurs to oestrogen deficiency and early identification of alveolar BMD might aid in the diagnosis of this increased bone loss timely.

This indicates the vital role a dentist can play in prompt identification of osteoporosis with the aid of salivary biomarkers and intraoral radiography like bitewing x-ray.

Table 1. Association between Salivary biomarkers and Osteoporosis

	Genetic origin	Function	Salivary counterpart
Osteocalcin (OC)	Chromosome1q25-q31 has been identified in relation to the BGLAP gene	Involved in Osteoclast precursors recruitment and differentiation	Significant correlation has been observed between salivary and urinary / serum levels of OC, D-PYR and IL-6
Deoxypyridinium (D-PYR)	It is one of the mature crosslinks of type I collagen	Serve as bone resorption marker	Salivary OC and D-PYR can both be used to identify both osteopenia and osteoporosis in human subjects
Interleukin-6 (IL6)	IL6 is encoded by the IL6 gene	It is a pro inflammatory and bone resorbing cytokine. It is involved in osteoporosis pathogenesis and progression in postmenopausal women.	Increased salivary IL6 level has been found in osteoporotic postmenopausal women
	Intestinal calcium absorption has been seen with BsmI VDR polymorphism and FokI polymorphism	Adequate calcium level is vital for prevention of osteoporosis development	Postmenopausal osteoporotic woman has increased salivary calcium level

Conclusion and future prospective

There is ample evidence in the literature which encourage exploration of salivary biomarkers application for identification of osteoporosis. Dentists can play a vital role in its implementation

as a routine screening test in normal dental checkups.

As with any method, this mode of testing might also have its shortcomings, which might need to be overcome. For instance, biomarkers concentration might be influenced by the altered salivary flow rate due to certain systemic conditions or radiation and mode of collection (Gupta et al. 2011; Malamund et al. 2006). It must also be considered that the biomarkers, which are being investigated, may have reduced concentration in saliva with respect to serum (Miller 1994).

Despite its demerits, this mode of testing possesses various merits which makes it a worthwhile option, which needs further research. More studies need to be carried out to explore and evaluate various salivary biomarkers that can be utilized for early osteoporosis testing and validate their use.

Acknowledgements

The authors are thankful to the host institute and library.

Conflict of interest statement

The authors declare that no competing or conflict of interest exists.

Author's Contributions

All authors have contributed equally. All authors have read and approved the final version of the manuscript.

Source of Funding

No specific funding was received for this study.

Declaration of originality

The data/text presented in this manuscript is original and has not been copied from other source without appropriate citation.

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