SUMMARY Paramedian insertion of orthodontic mini-implants is increasingly used to anchor molar distalizers. The aim of this review was to systematically examine the available measurements of vertical palatal bone height (VBH). PUBMED, MEDLINE and the Cochrane Controlled Trials Register were searched using specific search terms. Hand searches of bibliographies of articles were also performed to identify studies measuring VBH or bone thickness in the human palate. Sixteen studies were included, arising from 19 published articles. Repeat presentations were excluded. Ten of the 11 computed tomogram (CT)-based studies presented data from 956 orthodontic patients on average VBH and its variation at a range of palatal sites. Individual data were not available, and pooling of data was not feasible because of heterogeneity of subjects, different measurement sites, different CT methods and their associated software. The compilation of data did indicate that the region 3–4 mm behind the incisive foramen and 3–9 mm lateral to the midpalatal suture should normally provide sufficient VBH to anchor molar distalizers. The risks of unwanted effects during distalization should be small, but the limitations listed above and the small numbers of studies available impair the precision of the estimates and do not allow the results to be generalized. Paramedian anchorage in the anterior palate can be recommended for molar distalization but, given the great inter-individual variability of the palatal bone height, it must be preceded by reliable CT-based imaging in patients identified by routine investigations as being at risk.

Introduction

For the last half century, orthodontic mini-implants (OMIs) have been part of the orthodontist’s armamentarium for moving teeth (Favero et al., 2002). Nowadays, intraoral OMIs are increasingly used for anchoring orthodontic appliances, not only because they obviate the problems of loss of anchorage due to reciprocal forces (Higuchi and Slack, 1991) but also because they get patients to comply with wearing extra-oral appliances by decreasing overall treatment time (Heymann and Tulloch, 2006). The first feasible OMI for anchoring molar distalization appliances was the Orthosystem (Cousley, 2005; Thomas et al., 2006; Wehrbein et al., 1996). This shortened implant was inserted in the midpalatal suture (Kyang et al., 2003; Lee et al., 2004; Arcuri et al., 2007). However, the bulk of orthodontic casework is in children and adolescents for whom anchorage in the midpalatal suture carries the putative risk of disturbing maxillary growth (Asscherickx et al., 2005).

The age at which the midpalatal suture ossifies and transverse palatal growth ceases is extremely variable. Melsen (1975) found obliterations of the suture already in 16 year old females and 18 year old males, but Stockmann et al. (2009) found ossifications in only half of the material investigated in 15 to 20 year olds. In the study by Knaup et al. (2004), earliest ossification of the midpalatal suture was found in a 21 year-old male, whereas the oldest unossified midpalatal suture was in a 54 year-old male. Schlegel et al. (2002) observed complete ossification in only 40 per cent of patients aged between 23 and 30. Thus, paramedian palatal sites are increasingly used in clinical practice for anchoring molar distalizers (Bernhart et al., 2001).

However, vertical bone height (VBH) in the paramedian palatal region is very variable, and it is not feasible in everyday orthodontic practice to obtain precise information on the available palatal VBH and bone volume in individual patients (King et al., 2006). The patient’s age, clinical examination, orthopantomography, or routine cephalograms are all inadequate for the purpose (Crismani et al., 2005, Wehrbein et al., 1999). Lateral radiographs have shown midsagittal implants projecting somewhat above the radiologically visible cranial border of the palate without causing a demonstrable perforation into the nasal cavity. It has been suggested that the real VBH in the midsagittal part of the anterior and mid-section of the palate is probably 2 mm greater than indicated on cephalograms (Wehrbein et al., 1999) and that routine lateral cephalometry done before orthodontic procedures reflects the minimum rather than the maximum bone height (Crismani et al., 2005).
CT-based methods, CT or cone beam computed tomography (CBCT), can give reliable estimates of VBH as measured anatomically or histologically in autopsy specimens. Because of the radiation dose and the expense, CT-based methods are only indicated when lateral cephalometry suggests a marginal quantity of bone (Jung et al., 2011). When available and appropriate, they can be valuable diagnostic procedures before placing paramedian OMI s in growing patients.

Several histological and radiological investigations of palatal VBH have been carried out to determine where OMI s can be screwed securely into the palate while carrying the smallest risk of penetrating into the nasal cavity. We have reviewed these studies and, where feasible, have compiled the available CT-based measurements of VBH in orthodontic patients to determine the safest palatal area for anchorage.

Methods

PUBMED and Cochrane Controlled Trials Register were searched from 1 January 1995 to 31 January 2012 for ‘palatal bone height’ OR ‘palatal bone volume’ OR ‘palatal cortical bone thickness’ OR ‘palatal mini-implant anchorage’. MEDLINE (Multifield Search) was searched for ‘palate’ AND ‘bone height’ OR ‘bone volume’ OR ‘cortical bone thickness’ OR ‘mini-implant anchorage’. Hand searches were also conducted to capture literature not stored electronically (e.g. theses). No methodological filter was applied. Based on the data from titles and abstracts of the retrieved studies, two authors (HW and JV) independently selected articles that met the following inclusion criteria: (i) studies on human subjects, language restriction to European languages and (ii) studies measuring VBH or bone thickness in the palate. Studies examining palatal sites unsuitable to anchor molar distalizers were excluded.

The reference lists of these articles were perused and references related to VBH or bone thickness were followed up. Any disagreement between the authors on eligibility for inclusion were resolved by discussion. From the identified articles, authors HW and JV independently extracted data referring to number of males and females, mean age and age range, method of measuring the palatal bone height, number of sites studied, medio-lateral (ML) and antero-posterior (AP) co-ordinates of those sites, the CT technique and associated software, the reference line used, the site of the maximum VBH and its height and, study-specific particularities. Where there were disagreements, authors (CV and SC) arbitrated.

Our interest in the studies was primarily in the measurements of palatal VBH. The quality of these measurements depends on the quality of the technology that was used to make them. Meta-analytical tests for heterogeneity were not applicable, because there were not enough repeated measurements at a sufficient number of palatal sites.

Results

Of 924 citations screened, 19 reports met the inclusion criteria (Baumgaertel, 2009; Bernhart et al., 2000; Gahleitner et al., 2004; Gracco et al., 2006; Gracco et al., 2007; Gracco et al., 2008; Henriksen et al., 2003; Jung et al., 2011; Kang et al., 2007; King et al., 2007; Kyung, 2004; Lai et al., 2010; Moon et al., 2010; Stockmann et al., 2009; Taghizadeh, 2010; Wehrbein et al., 1999; Wehrbein, 2008; Wehrbein, 2009; Zou et al., 2009). Of these, two (Gracco et al., 2006; Gracco et al., 2007) were of material published elsewhere (Gracco et al., 2008), the duplicated studies were excluded; for another, which had an abstract in English, the main text was in Korean (Kyung, 2004) and we were unable to obtain a translation. Of the remaining 16 reports, 4 used three-dimensional CBCT and 6 used CT—5 for measuring the bone height and one for bone density; some details of these are presented in Table 1. The remaining 6 studies are listed in Table 2; 3 studies present details of histological investigations in cadavers (Stockmann et al., 2009; Wehrbein, 2008; Wehrbein, 2009) of which one investigated only the midpalatal suture (Stockmann et al., 2009); 3 studies used two-dimensional orthopantomography equipped with a cephalostat (Henriksen et al., 2003; Jung et al., 2011; Wehrbein et al., 1999)—of which one compared lateral radiography and CBCT measurements in an area within the median plane rather than a set of particular sites (Jung et al., 2011).

Palatal bone height

The study that compared measurements on autopsy material with corresponding measurements using CBCT and CT (Jung et al., 2011) justifies the confidence that is placed on the imaging techniques. The CBCT and CT measurements showed a great variation in even the average values reported for palatal VBH in the paramedian region; male patients tended to show higher values than females in some, but not all, studies, and VBH tended to decrease rather than increase with age (Taghizadeh, 2010) (Table 1 and 2). There was no consistency between studies as to the age ranges that were used to designate age groups (children, adolescents, adults), nor in AP and ML co-ordinates of the palatal sites selected for measurements.

For 9 of the 10 studies displayed in Table 1, the point or area of the palate with the greatest VBH and its value are indicated. Table 3 gives more details about the adult data from five studies (Baumgaertel, 2009; Gracco et al., 2008; Kang et al., 2007; Lai et al., 2010; Taghizadeh, 2010), showing the average VBHs at different AP distances from the incisive foramen and ML distances from the midpalatal suture. The points in the different studies at which the average VBH is at least 5 mm are highlighted. There is a strip of adequate VBH adjacent to the midpalatal suture for most of the palatal length, but further away from the midpalatal suture, adequate bone height is only found anteriorly. Figure 1 illustrates this as a three-dimensional plot for the palatal measurements of
Table 1  Some characteristics of the studies that measured vertical bone height (VBH) of the patients, computerized tomography (CT) or cone beam CT (CBCT), antero-posterior (AP) and medio-lateral (ML) distances of the palatal sites, software and reference lines used, site of maximum VBH and its height and particularities in individual studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gracco et al., 2008</th>
<th>Gahtleimer et al., 2004</th>
<th>Bernhart et al., 2000</th>
<th>Lai et al., 2010</th>
<th>Kang et al., 2007</th>
<th>Moon et al., 2010</th>
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<td>No (male:female)</td>
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<td>18:20, not stated</td>
<td>34:38, not stated</td>
<td>11:21, 26</td>
<td>4:18, not stated</td>
<td>11:23, 24</td>
</tr>
<tr>
<td>Mean age (ys)</td>
<td>10-15, CBCT</td>
<td>12-49, CT</td>
<td>13-48, CT</td>
<td>18-35, CBCT</td>
<td>18-35, CT</td>
<td>18-35, CT</td>
</tr>
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<td>12 (both sides)</td>
<td>32 both sides</td>
<td>20 (left side)</td>
<td>80 (both sides)</td>
<td>90 (both sides)</td>
</tr>
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<td>3, 6, 9, 12</td>
<td>0, 3, 6, 9, 12</td>
<td>3, 6, 9, 12, 3, 6, 9, 12</td>
<td>3, 6, 9, 12, 15, 18, 21, 24</td>
</tr>
<tr>
<td>Sites</td>
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<td>3, 6, 9, 12</td>
<td>Easy Vision work, Philips, Best, NL</td>
<td>3:3</td>
<td>3:6</td>
<td>3:6</td>
</tr>
<tr>
<td>Interval ML (mm)</td>
<td>27</td>
<td>3, 6, 9</td>
<td>Easy Vision work, Philips, Best, NL</td>
<td>28:54</td>
<td>23-35</td>
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<td>34:38</td>
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<td>90 (both sides)</td>
</tr>
<tr>
<td>Software</td>
<td>Newtom 3G, ImageWorks, Elmsford, NY 10523 USA</td>
<td>3:6</td>
<td>Easy Vision work, Philips, Best, NL</td>
<td>34:38</td>
<td>90 (both sides)</td>
<td>90 (both sides)</td>
</tr>
<tr>
<td>Reference line</td>
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<td>Easy Vision work, Philips, Best, NL</td>
<td>34:38</td>
<td>90 (both sides)</td>
<td>90 (both sides)</td>
</tr>
<tr>
<td>Site of max VBH (AP: ML)</td>
<td>Incisive foramen (if) to end of hard palate</td>
<td>Incisive foramen (if) to posterior nasal spine</td>
<td>Incisive foramen (if) to posterior nasal spine</td>
<td>Incisive foramen (if) to posterior nasal spine</td>
<td>Incisive foramen (if) to posterior nasal spine</td>
<td>Incisive foramen (if) to posterior nasal spine</td>
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<td>10.2</td>
<td>6.6</td>
<td>7.9</td>
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<td>No significant difference between age groups or left and right</td>
<td>No significant difference between age groups or left and right</td>
<td>No significant difference between age groups or left and right</td>
<td>No significant difference between age groups or left and right</td>
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</tr>
</tbody>
</table>

The five studies that included adult patients. Table 4 shows: (a) the average adult VBHs; (b) the standard deviation (SD) around the averages; (c) the differences between the average VBHs and a ‘safe’ VBH of 5 mm (see discussion), expressed in units of the corresponding SD; (d) an estimate of the percentage of VBHs that are likely (given normal distributions about the average VBH) to be less than the ‘safe’ VBH (it can be seen that in some locations in some studies, that percentage can be quite appreciable); (e) the minimum VBH recorded in each study.

Bone density

Palatal sites with the greatest VBH were not necessarily those with the highest bone densities (Lai et al., 2010). In one study of tissue blocks of autopsy material, bone density (expressed as the hard tissue fraction to total bone volume) 3 mm lateral to the midpalatal suture was found to be largely higher than 50% (Moon et al., 2010). In another, it was about 70% and similar in the younger and older age groups (Wehrbein, 2009).

Discussion

Retrieval of publications relevant to the review

This review was systematic in that it attempted to identify all of the publications that might have a bearing on determining palatal VBH in the areas where one might wish to anchor OMIs for molar distalization. Given the recognized
Table 2  Some characteristics of the cadaver studies and a study in orthodontic patients investigating cephalograms (description and abbreviations see Table 1)

<table>
<thead>
<tr>
<th></th>
<th>Wehrbein 2008</th>
<th>Wehrbein 2009</th>
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<th>Wehrbein et al., 1999</th>
<th>Henriksen et al., 2003</th>
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<td>18 all</td>
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<td>15–39</td>
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<td>age range method</td>
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<td>cephalogram</td>
<td>cephalogram</td>
<td>cephalogram versus CBCT</td>
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<tr>
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<td>63 sections*</td>
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<td>1</td>
<td>18</td>
</tr>
<tr>
<td>interval ML (mm)</td>
<td>3 (both sides)</td>
<td>0,3 (both sides)</td>
<td>4 transverse lines*</td>
<td>0</td>
<td>0</td>
<td>0, 3, 6</td>
</tr>
<tr>
<td>interval AP (mm)</td>
<td>&amp; region of interest 6mm</td>
<td>&amp; region of interest 4mm</td>
<td>region of interest 4.5–5mm</td>
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<td>0</td>
<td>0</td>
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<td>Measure</td>
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<td>Technovit 9100, Siemens, Wehrheim, D</td>
<td>Ortophos C scanner, Bensheim, D &amp; not appropriate</td>
<td>first premolar line bone height</td>
<td>first premolar line bone height</td>
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<td>not appropriate</td>
<td>not appropriate</td>
<td>not appropriate</td>
<td>not appropriate</td>
<td>outer cortical layer</td>
</tr>
<tr>
<td>Reference line</td>
<td>not appropriate</td>
<td>not appropriate</td>
<td>not appropriate</td>
<td>not appropriate</td>
<td>not appropriate</td>
<td>outer cortical layer</td>
</tr>
<tr>
<td>Safe region</td>
<td>compact bone in 73%</td>
<td>hard tissue fraction vs total bone volume 69%#</td>
<td>first premolar level &amp; 5 / 4+</td>
<td>2 mm higher+</td>
<td>8.6 ± 1.3</td>
<td>first PM line</td>
</tr>
<tr>
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<td>not stated</td>
<td>4.3 ± 2.4</td>
<td>4.3 ± 2.4</td>
<td>4.3 ± 2.4</td>
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</tr>
<tr>
<td>Comment</td>
<td>*slices 5–7 µm</td>
<td>*slices 5–7 µm</td>
<td>*through canal, first and second premolars, 1st molar &amp; greatest density</td>
<td>*most cranial border of palate to that of implant</td>
<td>*most cranial border of palate to that of implant</td>
<td>6.6 ± 3.2 versus 9.0 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>&amp; 5-10mm behind if 0.4, 0.8, 1.2mm</td>
<td>&amp; difference between age groups 18–25 versus 26–63 years &amp; 5mm behind if</td>
<td>+ 2 mm lateral from median no difference f versus m</td>
<td>+by probing versus cephalogram</td>
<td>+by probing versus cephalogram</td>
<td># of caudal nasal floor and oral hard palate</td>
</tr>
</tbody>
</table>

limitations of routine lateral cephalography, it seemed sensible to focus on CT-based methods. Because these were not applied to orthodontics until after 1995, we started our screening window on 1 January 1995. Our screening criteria were intended to be over-inclusive, and this is reflected in the large number of titles and abstracts screened in relation to the number of publications that met inclusion criteria.

Safe palatal anchorage using mini-implants

The two most important considerations for palatal anchorage with OMI s are the quantity (measured as VBH) and the quality of cortical bone at the site of anchorage. Besides secondary stability from bone remodeling around the screw, both characteristics contribute to the stability needed to resist the rotational forces and dynamic loads of between 0.5 and 3 N during the period of orthodontic treatment. Our experience suggests that OMIs with a shaft diameter of 2 mm and length of 10, 12 or 14 mm require at least 5 mm of bony support for anchorage. The needle used to inject the local anaesthetic is helpful for measuring the vertical height of the gingiva at the insertion site (Figure 2). Marquezan and coworkers (2012) have evaluated the mucosal thickness at various sites of the palate and found a decrease from lateral to median and from anterior to posterior regions with highest values at 4 and 8 mm AP / 6 mm ML of 5.26 and 4.39 mm, respectively (respective values at 3 mm ML were 3.37 and 2.71 mm). The covering of keratinized gingival mucosa makes the insertion site less susceptible to infection and inflammation.

Our compilation of average VBHs indicates that the easily accessible paramedian area AP3/ML3–9 should generally provide an adequate quantity of supporting bone to anchor molar distalizers. Because the incisive foramen is sufficiently far away, there is little danger of damaging important anatomical structures. Although Marquezan and coworkers (2012) concluded from their study that the most suitable areas for OMI placement in the palate were located 4 mm posterior to the incisive foramen, in the median or paramedian adjacent to the suture, their table indicates that the total bone thickness was higher at AP 4 mm/ML 6 mm (average 7.28 mm) than at ML 3 mm (average 6.81 mm), as was the site with the highest mucosal thickness of 5 mm (see above). The group had comprised growing patients and adults in order to evaluate the influence of age on palatal tissue, although these data were not presented.
In routine clinical practice, molar distalizers have been anchored empirically, for example, half way from the midpalatal suture to the corresponding first premolar, along the transverse line through the palatal cusp of that first premolar (M4 site, Winsauer et al., 2011, 2012). This site is about 3 mm in the antero-posterior direction from the incisive foramen (AP 3) and 6 mm in a medio-lateral direction from the midpalatal suture (ML6) and within the area of maximal palatal VBH (Figure 3). The footprint-like area (Figure 4) based on our compilation is certainly a more reliable indicator for safe anchorage of molar distalizers than the area suggested in the recently published ‘Anatomical Guidelines for Palatal Miniscrew Insertion’ (Ludwig et al., 2011) in which the authors have averaged the VBH data from four studies (Bernhart et al. 2000; Gracco et al., 2006, Kang et al., 2007, King et al., 2007), taking no account of heterogeneities between studies.

Because of the great individual variability between patients requiring OMIs, there would be an appreciable risk of penetration into the nasal cavity if the procedures were to be carried out ‘blind’ (Table 4). The cephalograms that are a routine part of planning for each procedure are vital for indicating the possibility of insufficient bone height or in cases with impacted teeth or mesiodentes. They offer acceptable screening for those cases that need a more reliable imaging technique to verify the actual palatal bone height. Currently, the imaging technique of choice is cone beam CT technology. It enables the orthodontist to gain the maximal amount of reliable diagnostic information for the individual treatment plan, using a low dose of radiation.

When considering quality of bone, the involvement of cortical bone is important. Although miniscrews anchored in a single layer of cortical bone together with the underlying trabecular bone seem to resist orthodontic forces in the normal range without generating stresses that might result in bone fracture, anchorage that includes both layers of cortical bone reduces the stress on the trabecular bone and appreciably improves the stability of the implant (Kim et al., 2006).

### Table 3

Average vertical bone heights (AVBH) at different AP distances from the incisive foramen and ML distances and from the midpalatal suture. (AVBH > 5mm are highlighted); § references: K Kang et al., 2007, B Baumgaertel, 2009; G Gracco et al., 2008; L Lai et al., 2010; T Taghizadeh, 2010

<table>
<thead>
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<tbody>
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Figure 1 Combined plot of average vertical bone height at various sites of the palate from 5 studies (Baumgaertel, 2009; Gracco et al., 2008; Kang et al., 2007; Lai et al., 2010; Taghizadeh, 2010). The inserted plane reveals the sites, where the average bone height exceeds 5 mm.

Figure 2 The thickness of the gingiva can be estimated with the injection needle of the local anesthetic and a slidable rubber disc.

Figure 3 The M4 site is located halfway from the midpalatal suture to the corresponding first premolar, along the transverse line through the palatal cusps of the first premolars.
With OMIs inserted to the optimal length, failure because of insufficient anchorage (Lombardo et al., 2010) occurs very rarely, if at all (Winsauer and Vlachoianis, 2010). The palatal area AP3/ML3–AP3/ML9 allows molar distalizers to be placed in the optimum position to enable the teeth to be moved ‘bodily’ (Bernhart et al., 2001; Papadopoulos, 2008; Schlegel et al., 2002). Absolute bony anchorage in this area will avoid unwanted effects seen with dual anchorage of molar distalizers (Antonarakis et al., 2008; Kinzinger et al., 2008). This area can also be used for OMI-supported maxillary expanders (Wilmes et al., 2010). In this area, the arteria palatina is rarely encountered and, if so, it is very thin. If miniscrews are placed in a vertical direction in this area, there is hardly any risk of damaging roots of teeth.

**Limitations of this study**

Our pragmatic exclusion of the paper whose full text was available only in Korean may conceivably have altered the

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**Table 4** Average vertical bone height (VBH) values in the adult patients of the 5 studies; standard deviations (SDs) of the means of the palatal VBH in the area 3 mm AP and 3 to 9 mm ML (male/female) related to Figure 3; difference between average and proposed “safe” VBH (5 mm), expressed as corresponding SD; percentage likelihood that the VBH in individuals would be less than the proposed safe 5 mm (marked, if more than 10%); minimum VBH values in individual patients of the studies.

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<td>a. Average VBH values (mm)</td>
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<td>b. SDs (mm) around the average VBH values</td>
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<td>c. Average VBH minus safe VBH (5 mm), in terms of the corresponding SD (mm)</td>
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<td>d. Likelihood (%) that the VBH in individuals would be less than the safe VBH</td>
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<td>e. Minimum value for VBH in individuals (mm)</td>
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spread of the results, but in the absence of a translation we have no way of knowing. In addition, incomplete retrieval of published material may have introduced some inaccuracy into the estimates for mean values and measures of variability on which we based our estimates of risk of palatal perforation with OMIs inserted to the depth (5mm) that seems to be agreed as a minimum requirement for stability. However, it is extremely unlikely that the risk at any site would be zero. Thus the recommendation remains valid that CT-based methods should be used when routine lateral cephalometry suggests that the thickness of palatal bone may be inadequate.

The results did indicate the expected variation in average VBH over the area of the palate, and some suggestion (of unknown statistical significance) of inter-study variation in the relatively few average VBH measurements that were made at exactly the same site in more than one study. We are in no position to say whether this heterogeneity is attributable to study-related differences in selection of patients (their ethnicity, age, and gender) or differences in CT-based technique and the associated software. If we had been able to obtain individual data sets for every patient in all of the studies and if there had been a pre-agreed grid of measurement sites across the palate and pre-agreed age bands for describing children, adolescents and adults, then we might have been able to attempt a synthesizing analysis of the variance, to apportion it to the ethnicity, gender and age of the patients, and the type of CT-based imaging. In the absence of a pre-agreed grid, it might still have been possible, with individual patient data, to attempt a regression-based description of a curvilinear plane of the sort suggested in Figure 1 and analyse the residual variance about the plane of best fit in terms of the explanators listed above. We did write to the authors of all of the studies to enquire about the availability of individual patient data but, except for author AB, they were unwilling or unable to provide them.

A consequence of the inter-individual variability in palatal VBH (even at the sites where it is greatest) is an inter-individual variability of the palatal bone height, cone beam placement of OMIs. However, because of the great inter-individual variability of the palatal bone height, cone beam CT imaging should be used in patients for whom routine cephalometry indicates the possibility of inadequate bone or other complicating factors.

**Conclusions**

Lack of inter-study uniformity over the ethnicity, age and gender of study patients, and the different measurement sites and CT-based methods prevented any meta-analytical synthesis of the data from the individual studies. They could simply be compiled. The compilation indicates that the anterior paramedian palate in the area 3 mm behind the incisive foramen and from 3 to 9 mm lateral to the midpalatal suture generally provides sufficient VBH and in the area up to 12 mm behind the incisive foramen and 9 to 12 mm lateral to the midpalatal suture adequate VBH for secure and safe placement of OMIs. However, because of the great inter-individual variability of the palatal bone height, cone beam CT imaging should be used in patients for whom routine cephalometry indicates the possibility of inadequate bone or other complicating factors.

**References**


