RESEARCH ARTICLE

VALIDITY OF CONE BEAM COMPUTED TOMOGRAPHY VOXEL DENSITY VALUES: A REVIEW.

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Manuscript Info	*Abstract*
	Introduction: voxel density value in CBCT is used regularly in many clinical aspects such as virtual implant planning. Many researchers studied factors affecting it and their significance. Most of the results obtained are contradicting and /or inconclusive. **Objectives**: to compile papers inquiring effect factors affecting voxel grey values and their significance. **Methodology:** internet search was done on two databases using MeSH terms. Resulting studies went through two level screening according to predetermined inclusion and exclusion criteria. **Results**: A total of 27 studies were included. Total number of factors, which were tested in the included papers, were eighteen. **Conclusion**:Significantly affecting factors are (FOV, mA, Objects position inside the FOV, Objects exo-mass, kVp, time between exposure, number of basis, adjacent air to the ROI).Insignificantly affecting factors are (exposure parameters, software, exposure dose, presence of teeth, presence of metallic post in or out the FOV). Inconclusive factors are (Machines model, voxel size, objects mass, receptor type, exposure time). Grey levels in CBCT which is known by Hounsfield Unit of CBCT is not reliable nor repeatable.

Introduction: -

Bone density measurement **(BDM)** is a valuable tool in several dental applications as preoperative dental implant planning, follow up of periodontal surgeries, surgical reconstruction, [1-4]. As well as in diagnosing many systemic conditions as hyperparathyroidism[5-7], osteomalacia[5, 8, 9], osteoporosis[8, 10], osteopetrosis[5, 11], and blood diseases.[5, 12, 13] There are several imaging modalities reported in the literature for BDM with variable degrees of accuracy and reliability; as Dual-energy x-ray absorptiometry (**DEXA**) [14], Multi detector computed tomography (**MDCT**) [15], Quantitative Computed tomography (**QCT**) [16] and cone beam computed tomography (**CBCT**) [17]. While MDCT uses the Hounsfield unites (**HU**) for BDM [18] with accepted accuracy and reliability [19], CBCT uses the term Voxel density value (**VDV**) for BDM, which can be measured at certain point, line, or area on all CBCT reconstructed images [20-22]. Some researchers concluded that CBCT VDVs are accepted as a precise tool for bone density measurements [23, 24]. On the other, other authors stated that CBCT VDV are unreliable.[25-28]

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CBCT is recommended for preoperative implant planning rather than MDCT because of decreased patient absorbed dose [29, 30], integration of different software programmes [31, 32], easy image acquisition [32, 33], availability [34] and improved patient cooperation [22, 35].

As Olivia Nackaerts[36] stated that VDVs are not comparable to predetermined standard values because they are subjected to variations due to several factors such as exposure parameters, field of view (**FOV**), collimation, scattering. [20, 27, 36-38]These factors will interfere with the accuracy and reliability of BDM by CBCT, and in turn this might affect the treatment plan or the evaluation process of the treatment outcome.[28, 36, 37]

Thus, the aim of this present review is to answer a clinically important question which is: "Does CBCT provide accurate and reliable BDM?"

Research methodology

In order to identify published articles studying the accuracy and/or reliability of CBCT regarding BDM, our search strategy was based on performing two searches, the first used separate keywords, while the second used combined keywords. We searched using the following MeSH terms: "cone beam computed tomography", "bone density" as separate searches then a combined search was performed using "cone beam computed tomography (AND) bone density". We performed our search on Medline and Cochrane libraries. Search was done on April the 21st 2016 at10:21 pm CLT. There were not a date nor language restrictions on any of the searches.

Our search resulted in a total of 92264 studies, 84135 from PubMed and 8129 from Cochrane. Summary of search results are in table 1.

In order to analyze the search results, we included all articles studying the accuracy and/or reliability of BDM using CBCT. Only researches in which information regarding (1) machine type, (2) exposure parameters and (3) presence of gold standard were included. For studies using quantitative data, agreement between measurements or accuracy of measurements should be present. We excluded (1) studies using CBCT but evaluating the accuracy of another imaging modality (2) non-quantitative studies, (3) studies using CBCT machines not available in the market.

Table 1: -Results for PubMed and Cochrane search engines

Search engine	Search word	Number of search results
Medline PubMed	Cone-beam computed tomography	7621
	Bone density	76226
	Cone-beam computed tomography And Bone density	288
Cochrane library	cone-beam computed tomography	total 220
		Cochrane Reviews 3
		Other Reviews 3
		Trials 208
		Technology Assessments 6
	Bone density	total 7895
		Cochrane Reviews 444
		Other Reviews 348
		Trials 6857
		Methods Studies 10
		Technology Assessments 91
		Economic Evaluations 142
		Cochrane Groups 3
	Cone-beam computed tomography And Bone density	total 14
		Cochrane Reviews 1
		trials 13

Results:-

All articles were screened by one reviewer on two levels according to the inclusion and exclusion criteria; the initial screening of the articles was conducted using the titles and abstracts, but when these were unclear, the full text was used; this yielded a total of 155 studies. Then the second level was performed by thorough reading and data extraction from the full text; this yielded a total number of 27 article.

The included 27 studies are summarized in Table 2. Studies were gathered according to the searched factor in Table 3

Table 2: -summery of included studies

	Title	1st author	year	journal	N°. & type of machine(s)	Authors conclusion
1	**Effects of image artifacts on gray-value density in limited-volume cone-beam computerized tomography.**	Akitoshi Katsumata	2007	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics	3 machines MSCT: High Speed NX 1st CBCT: 3DX Accuitomo II 2nd CBCT: 3DX FPD	The intensity of the discontinuity artifacts increased when more objects were presented outside the FOV.
2	**Effect of object location on the density measurement and Hounsfield conversion in a NewTom 3G cone beam computed tomography unit**	MO Lagrave`re	2008	Dentomaxillofacial Radiology	1 machine, NewTom 3G Scanner	the location of an object within a CBCT scanner has a minimal effect on the apparent density.
3	**Study of the scan uniformity from an i-CAT cone beam computed**	JA Bryant	2008	Dentomaxillofacial Radiology	1 machine, i-CAT	the effects of the mass and exo-mass is significant.
4	**The reliability of computed tomography (CT) values and dimensional measurements of the oropharyngeal region using cone beam CT: comparison with multidetector CT**	A Yamashina	2008	Dentomaxillofacial Radiology	2 machines, MDCT: Aquilin CBCT: CB Mercuray	The values of CBCT differed markedly from the HU values given by a typical MDCT system and became unstable due to the effects of adjacent tissues and had relatively high SDs.
5	**Relationship**	Akitoshi Katsumata	2009	Oral surgery, oral	One machine	the data

				medicine, oral pathology, oral radiology, and endodontics	CBCT: Alphard Vega 3030	discontinuity–related effect was distinct in limited-volume CBCT scanning.
6	**Reliability of voxel values from cone-beam computed tomography for dental use in evaluating bone mineral density**	Yoshikazu Nomura	2010	clinical oral implants research	2..MDCT : A Somatom Sensation 64 CBCT :3D Accuitomo	This study confirmed that there could be a correlation between CBCT voxel values and BMD, but this relationship is not be a linear one.
7	**Deriving Hounsfield units using grey levels in cone beam computed tomography**	P Mah	2010	Dentomaxillofacial Radiology	13… 1st CT: Toshiba Aquilion CT 2nd CT: Philips Briliance 64 CT 1st CBCT: Asahi Alphard 3030 2nd CBCT: Hitachi CB MercuRay 3nd CBCT: i-Cat 4th CBCT: i-Cat Next Generation 5th CBCT: Imtec Iluma 6th CBCT: Morita Accuitomo FPD 7th CBCT: Morita Veraview Epochs 8th CBCT: NewTom VG 9th CBCT: Planmeca ProMax 3D 10th CBCT: Sirona Galileos 11th CBCT : Soredex Scanora 3D	the results were as accurate as those with medical CT HU. Further, this study has validated the process of converting grey levels to HU with several CBCT scanners as well as conventional CT. Conversion factors can be determined for any given CBCT machine to derive an attenuation coefficient by using reference materials with known chemical compositions and density (specific gravity).
8	**Analysis of intensity variability in multislice and**	Olivia Nackaerts	2011	clinical oral implants research	6…MDCT scanner Somatom Sensation 16 1st CBCT: 3D	The use of intensity values in CBCT images is not reliable,

	cone beam computed tomography				Accuitomo XYZ 2nd CBCT: Galileos Comforts 3rd CBCT: Kodak 9000 3Ds 4th CBCT: Picasso Duos 5th CBCT: Scanora 3Ds	because the values are influenced by device, imaging parameters and positioning.
9	**Qualitative and Quantitative Evaluation of Bony Structures Based on DICOM Dataset**	Bettina Hohlweg-Majert	2011	journal of oral maxillofacial surgery	2 machines, 1st CBCT: ProMax 3D 2nd CBCT: ILUMA CT	only the CT finite element analysis gives information on mineral density and microarchitecture of the spongiosa not CBCT.
10	**Correlation Between Pixel Values in a Cone-Beam Computed Tomographic Scanner and the Computed Tomographic Values in a Multidetector Row Computed Tomographic Scanner**	Jira Chindasombatjaroen	2011	Journal of computer assisted tomography	2 machines, MDCT LightSpeed QX/I CBCT, Alphard Vega 3030	a high correlation and linear relationship between the CT values in an MDCT scanner and pixel values in a CBCT scanner at the centre of the FOV were found for each parameter.
11	**The effect of surrounding conditions on pixel value of cone beam computed tomography**	Kazuyuki Araki	2011	clinical oral implants research	2 machines, MDCT GE Hi-Speed CBCT 3D Accuitomo FPD 8	a high correlation and linear relationship between the CT values in an MDCT scanner and pixel values in a CBCT scanner at the centre of the FOV were found for each parameter. Therefore, linear functions can be used to convert a pixel value from the CBCT machine used in this study to the CT values.
12	**Deriving Hounsfield**	TE Reeves	2012	Dentomaxillofacial Radiology	2 machines, 1st CBCT: Asahi	grey levels taken from CBCT

	units using grey levels in cone beam CT: a clinical application				Alphard 3030 2nd CBCT: Planmeca ProMax 3D	scans can be used to derive Hounsfield units in a clinical environment. This capability should solidify CBCT as the imaging modality of choice in dental implant placement.
13	**Stability of voxel values from cone-beam computed tomography for dental use in evaluating bone mineral content**	Yoshikazu Nomura	2012	clinical oral implants research	2 machines, CBCT, FineCube MSCT, Somatom Sensation 64	Pixel value in CBCT may be affected by various conditions such as beam hardening and surrounding materials, and is therefore not reliable as an index of bone density. Caution is essential when pixel values in CBCT are used to estimate bone density at potential implant sites.
14	**Effect of object location on the density measurement in cone-beam computed tomography versus multislice computed tomography**	Amir Eskandarloo	2012	Dental research journal	4 machines, 1st CBCT: Galileos 3D 2nd CBCT: NewTom 3G 3rd CBCT: Promax 3D. A Multislice CT	the change in position affects the density value. CBCT can show the clinician the points with higher density and the values that are exclusive to each unit, and are comparable to Multislice CT, in cases like the NewTom 3G type of CBCT.
15	**The accuracy of CBCT in measuring jaws bone density**	M. CASSETTA	2012	European Review for Medical and Pharmacological Sciences	1 machine, CBCT Soredex SCANORA 3D	the use of a CBCT to evaluate the bone density of jaws is not useful when the values are taken as absolute values. It does

						not allow an accurate assessment of bone density.
16	**Influence of cone beam CT scanning parameters on grey value measurements at an implant site**	A Parsa	2013	Dentomaxillofacial Radiology	3 machines, MDCT: Philips, Best 1st CBCT: Accuitomo 170, Morita 2nd CBCT: (NewTom 5G, Verona	no statistical differences in both CBCT scanners. Overall, in the Accuitomo scans the FOV, number of projections and spatial resolution had statistically significant influence on voxel grey value. FOV and spatial resolution had a statistically significant influence on voxel grey value measurements in the NewTom scans, whereas the effect for exposure time and dose was statistically insignificant. Both CBCT scanners showed higher grey values than the actual Hounsfield units derived from MSCT (mean 62 HU, standard deviation 243 HU).
17	**Prospects and challenges of rendering tissue density in Hounsfield units for cone beam computed tomography**	Roberto Molteni	2013	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics	2 machine, 1st CBCT NewTomVGi 2nd CBCT Hyperion X9, MyRay	CBCT systems operating at high kVp and high filtration are less prone to beam hardening. Beam hardening causing an overall reduction in the accuracy of CT numbers for density measurements.

						Large FOV CBCT systems are less prone to exomass-related artifacts. smaller irradiated and reconstructed volumes are less prone to inaccurate CT numbers/HUs, caused by scattered radiation and by non-ideal geometry
18	**Computed gray levels in multislice and cone-beam computed tomography**	FabianeAzeredo	2013	American journal of orthodontics and dentofacial orthopaedics	4 machines, MDCT: Siemens Dual Slice Helical CT 1st CBCT: I-CAT Imaging Sciences 2nd CBCT: Sirona Galileos 3rd CBCT: Kodak 9000 3D	1. Software programs were considered similar for gray level assessments in both CT and CBCT images. 2. CBCT images that were not considered reliable for density analysis.
19	**Variability of dental cone beam CT grey values for density estimations**	R PAUWELS	2013	The British journal of radiology	14 machines, 1st CBCT: 3D Accuitomo 170 2nd CBCT: 3D Accuitomo XYZ 3rd CBCT: GALILEOS Comfort 4th CBCT: i-CAT Next Generation 5th CBCT: Kodak 9000 3D 6th CBCT: Kodak 9500 7th CBCT: NewTomVGi 8th CBCT: PaX-Uni3D 9th CBCT: Picasso Trio 10th CBCT: ProMax 3D 11th CBCT: SCANORA 3D 12th CBCT: SkyView 13th CBCT: Veraviewepocs 3D	most CBCT devices showed a good overall correlation with CT numbers. The relatively large amount of noise in CBCT may lead to inaccurate grey values in the medium-density range, and exo mass can affect the grey values inside the FOV in a non-uniform way. it could be possible to obtain pseudo-HU from certain CBCTs.

					MSCT Somatom Sensation 64	
20	**Assessment of CT numbers in limited and medium field-of-view scans taken using Accuitomo 170 and Veraviewepocs 3De cone-beam computed tomography scanners**	Matheus L. Oliveira	2014	Imaging Science in Dentistry	2 machines, 1st CBCT: Veraviewepocs 2nd CBCT: 3De Accuitomo 170	a strong linear relationship between X-ray attenuation and CT number. However, for limited and medium FOV scans, the specific CBCT unit, exposure settings, and anatomic location of the object markedly influence the CT number. The extent of these influences diminishes the practical application of CT numbers to reliably infer tissue density.
21	**Influence of an object's z-axis location and location on the axial plane on the voxel value representation and uniformity in cone beam computed tomography**	Kanako Nishino	2014	Dentomaxillofacial Radiology	1 machine, Alphard-3030	The voxel values in the Alphard-3030 changed based on the z-axis location of the radiation field, even for the same objects. In addition, the voxel values on the same axial plane in the Alphard-3030 were not uniform between the centre and the off-centre locations or among the off-centre locations.
22	**MSCT versus CBCT: evaluation of high-resolution acquisition modes for dento-maxillary and**	Jean-Philippe Dillenseger	2014	European Society of Radiology	3 machines, 1st MDCT Somatom Flash CT (Siemens) 2nd MDCT Aquilion One 320 (Toshiba) A CBCT Newtom 5G (QR s.r.l, Verona)	CBCT is more sensitive to scattered radiation, which has an impact on image homogeneity. CBCT currently it does not

	skull-base imaging					surpass MSCT.
23	**Influence of exposure factors on the variability of CBCT voxel values: a phantom study**	M L Oliveira	2014	Dentomaxillofacial Radiology	1 machine, Picasso-Trio vatech	exposure factors, such as milliamperage and kVp did not influence the variability in CBCT voxel values when the object exceeded the FOV size. However, kVp reduced this variability in scans in which the FOV encompassed the entire object.
24	**Variation in voxel value distribution and effect of time between exposures in six CBCT units**	R Spin-Neto	2014	Dentomaxillofacial Radiology	6 machines, 1st CBCT: Cranex 3D Soredex 2nd CBCT: Scanora 3rd CBCT: 3D NewTom 5G QR Srl 4th CBCT: Promax Dimax 3 Digital Planmeca 5th CBCT: i-CAT Imaging Sciences 3D 6th CBCT: Accuitomo FPD80 Morita	large variation in grey shade distribution is seen in CBCT data sets. The pattern of the variation differs for some units depending on the time interval between exposures.
25	**Standardized method to quantify the variation in voxel value distribution in patient-simulated CBCT data sets**	R Spin-Neto	2015	Dentomaxillofacial Radiology	6 machines, 1st CBCT: Cranex 3D Soredex 2nd CBCT: Scanora 3D Soredex 3rd CBCT: NewTom 5G, QR srl 4th CBCT: i-CAT "first generation" 5th CBCT: 3D Accuitomo FPD80 Morita 6th CBCT: NewTom VG, QR srl	discrepancies in CBCT voxel value distribution are seen when comparing the initial examination of the day with subsequent examinations. Excluding the initial examination of the day, TBE has no predictable effect on the variation of CBCT-derived voxel values.
26	**Use of Gray Values in**	AndreiaFialho Rodrigues	2015	implant dentistry	2 machines, CBCT i-CAT	the grey values obtained in the

					MDCT; Somatom Spirit device	CBCT examinations are significantly influenced by the FOV size. Although the grey values obtained with different FOV sizes in MSCT have shown small differences, these differences were statistically significant.
	CBCT and MSCT Images for Determination of Density: Influence of Variation of FOV Size					
27	**Reduction of scatter-induced image noise in cone beam computed tomography: effect of field of view size and position**	Ruben Pauwels	2016	Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics	1 machine, 3D Accuitomo 170	The use of smaller FOVs and/or peripheral FOV position reduces scatter and increases image quality.

Table 3:-Results of the effect of FOV, kVp and mA on the CBCT voxel density values

	Factor	Number of tested papers	significant	insignificant
1	Machine	13	11	2
2	FOV	9	9	0
3	Objects position inside FOV	6	5	1
4	Objects exo-mass	6	6	0
5	mA	4	2	2
6	Exposure parameters	3	2	1
7	Voxel size	4	3	1
8	Object mass	4	3	1
9	kVp	2	2	0
10	Time between exposure	2	2	0
11	Software	2	0	2
12	Number of basis	2	1	1
13	Receptor type	1	1	0
14	Adjacent air	1	1	0
15	Exposure time	2	1	1
16	Exposure dose	1	0	1
17	Presence of teeth	1	0	1
18	Presence of post inside or outside FOV	1	0	1

Discussion:-

The present review was performed to evaluate validity of voxel density values (**VDV**) of CBCT. As several authors evaluate pre and post-operative outcome of implant by means of VDV on CBCT.[31, 39, 40] while others use VDV in periodontal surgeries and surgical follow up.[41-44]

CBCT provide images comparable to CT but with lower dose. [20, 45] Several factors affect VDV as kilovoltage, milliamperage, FOV, machines model, exo-mass, and others.[36-38, 46, 47] Regarding patient absolute dose the most important factor is FOV. [37, 48]

Search was done on PubMed search engine as it has more than 27.3 million records going back to 1966, selectively to the year 1865, and very selectively to 1809; about 500,000 new records are added each year. As of the same date, 13.1 million of PubMed's records are listed with their abstracts, and 14.2 million articles have links to full-text. Also it uses MeSH terms and provides a tool to facilitate reaching it "MeSH on demand" [49]

 Search was done on Cochrane library as it formed to organize medical research findings so as to facilitate evidence-based choices about health interventions faced by health professionals, patients, and policy makers. Cochrane includes 53 review groups that are based at research institutions worldwide. Cochrane has approximately 30,000 volunteer experts from around the world. [50]

Regarding the **machines model**, total of thirteen papers searched this factor and eleven of them found it significant.[24, 26-28, 36, 38, 51-57]

Researches performed by Katsumata et al 2007 [38] , Nackaerts et al 2011 [36] , Hohlweg-Majert et al 2011 [52], Eskandarloo et al 2012 [55], Parsa et al 2013 [53] , Azeredo et al 2013 [56], Pauwels et al 2013 [28], Molteni et al 2013 [57], Oliveira et al 2014 [54], Spin-Neto et al 2014 [27]and 2015 [26]; compared the resultant voxel density values of different CBCT machine models. In all those studies, the exposure parameters were not the same for all the machines used. All of their results showed significant differences in voxel density values between different CBCT machines. However, that difference could not be exclusively because of the machines model, but different exposure parameters as well.

On the other hand, Mah et al 2010 [51] and Reeves et al 2012 [24] compared between eleven different CBCT machines. All their results showed change between voxel values more than hundred and twenty-five shades. However, they concluded that machines model was an insignificant factor affecting voxel density values.

All of the studies reviewed regarding machines model used improper scientific methodology. The only research which approached the right methodology was spin-Neto 2015 [26] as they had identical parameters in two different machines except for the exposure time that differed by 0.5 sec. That factor was also reviewed and revealed inconclusive outcome.

From our point of view, this factor mostly cannot be tested as a single factor as the studies usually did not fix all the parameters between the tested machines as it is mostly impossible to do so.
Machines model can be considered as an inconclusive factor as it was not tested using properly scientific methodology by any study.

Concerning the **FOV**, total of nine papers discussed the effect of FOV size on voxel grey values. All of them reached the same conclusion that it was a significant factor affecting the voxel density values.[28, 37, 38, 53, 54, 57-60]

Studies done by Katsumata et al 2007 [38] and Oliveira et al 2014 [54] tested the FOV as a single factor by fixing all other parameters on the tested machines. Both concluded that it was a significant factor on voxel density values.

Studies of Katsumata et al 2009 [37], Parsa et al 2013 [53], Molteni et al 2013 [57], Pauwels et al 2013 [28], Dillenseger et al 2014 [60], Rodrigues et al 2015 [59] and Pauwels et al 2016 [58] searched this factor combined with other factors such as voxel size or machines model; this was because of the unavailability of specific voxel sizes at different FOVs which made the FOV not always a separate factor. Their results were also statistically significant.

Testing the effect of FOV should be done on the same machine so all the exposure parameters can be fixed. From the previous studies, this factor is undoubtedly a significant factor on voxel density values.

As regards the **Objects position inside the FOV,** total of six researches searched its effect. There was only one research concluded that it has insignificant effect.[61] All remaining papers found it has significant effect.[36, 47, 54, 55, 58]
Studies done by Nackaerts et al 2011 [36], Eskandarloo et al 2012 [55], Oliveira et al 2014 [54], Nishino et al 2014 [47], Pauwels et al 2016 [58] changed the object position in the FOV of the same machine. All of them, for at least part of their experiments, had all variables fixed except for the tested one. They all concluded that this factor was significant in changing voxel density values.

The results of those studies showed that the effect of object position inside the FOV might be machines and/or exposure parameter dependent as the variations found in densities were not the same.

They did not agree upon the position of least effect on voxel values inside the FOV. One study concluded that it is the peripheral position like the dental arch [58]. Other study concluded exactly the opposite [36], as the later concluded that the peripheral position effect is the greatest not the least.

On the other hand Lagrave`re et al 2008 [61] used single machine and fixed all the variables. Although, difference in voxel values obtained from this study reached hundred and forty-five shades, authors concluded that changes in object locations effect is minimal and insignificant.

In our opinion this factor can easily be tested with proper methodology as all other variables in the machine can be fixed.

Objects exo-mass means the mass of the radiographed object which lies outside the FOV. In vitro this part can affect the voxel value by its presence or absence, by its direction, or by the increase or decrease of the mass. However, clinically its presence or absence, and its increase or decrease are based upon the FOV size. And its direction is based upon the ROI position.
This means that small and medium sized FOV CBCT machines will always have exo-mass.

Total six studies searched this factor [37, 38, 57, 62-64]. All of them concluded it is significant.

Studies by Katsumata et al 2007 [38], Bryant et al 2008 [62], Katsumata et al 2009 [37], Araki et al 2011 [63], Molteni et al 2013 [57], Oliveira et al 2014 [64] used different combinations of radiographed objects and fixed all exposure parameters in each machine used. All their studies concluded that objects exo-mass affect grey value significantly. And They also specified that the effect is directly proportion to the mass itself.

The study done by Bryant et al 2008 [62] concluded that the effect is dependent on its direction and unequal along the FOV. Voxel values was noticed to be high near the exo-mass and decrease gradually to reach the middle which is the most accurate number then continue its decrease till the other side of the FOV with a comb like artifact.

This study also came out with a solution to this issue using algorithms to compensate for the exo-mass effect but only on the machine used there.

The study of Oliviera et al 2014 [64] proved that the exo-mass effect on voxel values is directly proportion to exposure parameters. That confirms that the compensation equation found by Bryant et al 2008 [62] cannot be generalized to all machines nor every exposure protocol.

Total four studies searched the effect of **mA** change on voxel values. Two of them found it is significant, and the other two concluded otherwise.[53, 64-66]

From our viewpoint it is considered a tricky factor to test as it can be changed independently in some machines, or in relation to other factors as exposure time or kVp. However, it is in some machines fixed.

Studies done by Chindasombatjaroen et al 2011 [46] and Cassetta et al 2012 [66] fixed all exposure parameters other than mA to monitor its change effect. They found its effect is significant on the voxel values.

The study done by Oliveira et al 2014 [64] concluded that mA is insignificantly affected the variation of voxel values. However, their results showed large change in variation of voxel values.

Parsa et al 2013 [53] did not separate mA as a single factor as it was changed along the exposure time. Although exposure time was on the factors affecting voxel values, it was found to be inconclusive.

This study concluded that mA had insignificant effect on voxel values. However, the changes done here was subtle as it was changed from 0.83mA to 0.95mA, and from 0.59mA to 0.60. those minimal changes should produce minimal if any effect on voxel grey values.

mA could be seen as debatable conclusion as the final results are tie. But one paper [53] of the insignificant side tested mA as a combined factor not a single one. So, it was eliminated. Now, mA as a factor affecting voxel value can be deduced to be a significant factor.

Regarding the **exposure parameters:** it is inherently multiple factors and testing it as a single entity might not help to detect which of them actually affecting the voxel values.

mA, kVp, FOV, number of basis all are exposure parameters and all were found to be significant. Only one study tested exposure parameters as a single entity[67].

Nomura et al 2010 [67] used four different exposure protocols on one CBCT machine. They interchanged two kVp and two mA settings. Although they concluded that voxel values of CBCT is not reliable nor repeatable, they also concluded that this factor affected voxel values insignificantly.

Voxel size has limitations in most machines to be changed alone. It is usually attached to FOV, and with lesser extent the rest of the exposure parameters.

Total four researches tested this factor. three of them found it is significant, and one found it otherwise.[37, 53, 57, 60] Katsumata et al 2009 [37], Parsa et al 2013 [53] and Dillenseger et al 2015 [60] tested voxel size as a combined factor. And their results showed significant changes on voxel values.

Molteni et al 2013 [57] used two voxel sizes; 0.3mm, and 0.15mm to test the effect of this change on voxel values. However, number of basis was not fixed. Here voxel size is a combined factor as well, and it did not show any significant changes on voxel values.

Although three out of four researches results showed it was a significant factor, a final deduction of this factors influence was inconclusive. As, it was not tested as a single factor by any of the studies.

Objects mass is not machine dependent, so it can be easily tested as a single factor. Total four researches tested this factor. three of them found it was significant.[51, 62-64]

Bryant et al 2008 [62] searched in this factor as a combined factor with objects position. Which was deduced to be a significant factor. They concluded that it was a significant factor.

P mah et al 2010 [51] also tested objects mass. The results showed significantly affected voxel values. but FOV of the used CBCT machines were not mentioned. The effect of exo-mass might be present in one or more of the phantoms radiographing set ups. This effect also might have been in some of the machines and not in others.
Araki et al 2011 [63] used one CBCT machine and fixed all the parameters except the objects mass. They concluded its effect on voxel values was significant.

Oliveira et al 2014 [64] used one CBCT machine in their study. They fixed all exposure parameters and only changed the objects mass by insertion of an implant simulating metallic rod. Their results showed that this factor had an insignificant effect on voxel values.

Two researches which found this factor significant were excluded as they tested it in combination with another factor.

This resulted in a tie. as it only has one paper for each conclusion.

Both studies did not accurately represent clinical situation. Each paper only used one machine, and nothing of the exposure parameters of each machine is remotely related to one another. This factor might be affected by machines model and/or exposure parameter. It needs further researches with proper methodology and on multiple machines to reach a definite conclusion. As its outcome is inconclusive.

kVp is mostly not attached to other parameters. In few machine models it is fixed, others are attached to mA. It can be considered in our opinion an easy factor to test for. Total of two papers searched this factor. One of those studies also investigated the relation between kVp and exo-mass. Both concluded that it is a significant factor.[46, 64]
Chindasombatjaroen et al 2011 [46] compared between two kVp 80 and 100 in single CBCT machine and fixed all other parameters. Significant variation occurred to voxel values in response.

Oliveira et al 2014 [64] used one CBCT machine and fixed all other parameters. They found that kVp was a significant factor to voxel values in the presence of exo-mass. Its significance decreases by the absence of exo-mass. Since, most of CBCT machines and most of the protocols used have exo-mass, mostly kVp is a significant factor in clinical situations to voxel values change.

Regarding **Time between exposures** there were two papers searched this factor. Both researches were conducted with the same team on two successive years and reached that it was significant.[26, 27]
Testing for this factor is easy. As it requires absolute fixation of every variable.

Spin-Neto et al 2014 and 2015 [26, 27] used six CBCT machines in their studies. They fixed all parameters for each machine. They tested the machines successively with; zero intervals, 15min intervals, and 30min intervals. Repetition of those protocols were done on another day

The results were different voxel values between every exposure at the first session and its corresponding one at the second, and between every exposure and its previous one in every group and in every session.

Each of the tested machine showed different pattern of variation in response to each time intervals.

Time between exposure was found to be a significant factor and its effect was massive, differed from one machine to the other, and was unpredictable even in the same machine.

Concerning the **Software** used to measure voxel values. This factor is the only one that can be tested for retrospectively on any DICOM file and compare between different programmes on the same file.

Two researches tested that factor. Both concluded its insignificance.[56, 61]

Lagrave`re et al 2008 [61] and Azeredo et al 2013 both tested this using two and five programmes respectively. Results showed insignificant difference on voxel values in both studies.

Number of basis is mostly a combined factor as it is mostly attached to voxel size and/or exposure time and/or rotation angle.

Two papers searched this factor. However, each one concluded exactly the opposite of the other.[53, 57]

Parsa et al 2013 [53] used multiple exposure sets which made sure that every variable was tested in complete fixation of the others. Number of basis was found to be significant as single factor.

On the other hand Molteni et al 2013 [57] tested number of bases effect on voxel value but not as a single factor. Voxel size was not fixed. these results are not conclusive as voxel size itself does not have a conclusion on its significance.

So, number of basis can be considered a significant factor to voxel values.

Only one paper tested **receptor type**[38]. This factor is very hard to be tested as it is always in different machine and mostly different machines possess different sets of exposure parameters.

Katsumata et al 2007 [38] used two CBCT machines with different receptors. One was FPD the other was IIT/CCD. Here it is a combined factor as it is in two different machines with two different exposure parameter sets. A significant effect on voxel values was noticed. But it is an inconclusive factor.

Presence of adjacent air to the ROI is an area specific in the radiographed object. Only one research tested this factor.[68]

Yamashina et al 2008 [68] tested this factor by using phantom with drilled holes to read the density on the periphery of the holes and away from them.

They found its effect is significant on voxel value.

Exposure time factor is usually a combined factor with voxel size and/or number of basis. Two papers searched this factor one is opposing the other. [26, 53]

Parsa et al 2013 [53] used two CBCT machines with multiple combinations of exposure parameters sets. Those multiple sets did not totally clarify whether this factor is combined or not.

They concluded that it bestowed an insignificant effect on voxel values.

Spin-Neto[26] unintentionally tested exposure time between two different machine and results showed significant changes in voxel values. They here tested it surely as combined factor.

It is an inconclusive factor as it was tested as combined factor by both of the testing studies.

Exposure dose is a factor which is based upon other factors. It is affected by the exposure parameters which in turn have some affect voxel value significantly and others do not. Two studies tested this factor.[53, 67]

parsa et al 2013 [53] and Nomura et al 2010 [67] both tested this factor as a single factor and concluded that its effect is insignificant.

Most of the machines in the market does not provide a direct dose manipulation protocol.

Presence of teeth had one study searched it. It is considered a clinical form of objects mass and/or objects exo-mass according to its position. The only study of it was done by Nomura et al 2013 [69] concluded it is an insignificant factor.[69]

Presence of metallic post in or out of FOV is considered the clinical form of objects mass and/or objects exo-mass. Also, one research tested it and found it is not significant at both stages. The study was done by Nomura et al 2013. [69]

Conclusion: -
Factors affecting voxel values are 18 factors. they can be divided into three groups; Significantly affecting factors, insignificantly affecting factors, Inconclusive factors.

Significantly affecting factors
FOV, mA, Objects position inside the FOV, Objects exo-mass, kVp, time between exposure, number of basis, adjacent air to the ROI.
All of the significantly affecting factors bestow an unpredictable effect on voxel values except for the exo-mass. A correcting equation was introduced to reduce the effect of exo-mass on the I Cat machine by JA Bryant [62].

Insignificantly affecting factors
exposure parameters, software, exposure dose, presence of teeth, presence of metallic post in or out the FOV.
All insignificantly affecting factors were tested by single research paper except for software which was tested by two papers. This necessitates further investigations on those factors.

Inconclusive factors
Machines model, voxel size, objects mass, receptor type, exposure time.
All of the inconclusive factors need further investigations to reach a proper conclusion.
Finally, voxel values of CBCT are not reliable nor repeatable.

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