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REVIEW ARTICLE

3D printing from microfocus computed tomography (micro-CT) in human specimens: education and future implications

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ABSTRACT

Microfocus CT (micro-CT) is an imaging method that provides three-dimensional digital data sets with comparable resolution to light microscopy. Although it has traditionally been used for non-destructive testing in engineering, aerospace industries and in preclinical animal studies, new applications are rapidly becoming available in the clinical setting including post-mortem fetal imaging and pathological specimen analysis. Printing three-dimensional models from imaging data sets for educational purposes is well established in the medical literature, but typically using low resolution (0.7 mm voxel size) data acquired from CT or MR examinations. With higher resolution imaging (voxel sizes below 1 micron, <0.001 mm) at micro-CT, smaller structures can be better characterised, and data sets post-processed to create accurate anatomical models for review and handling. In this review, we provide examples of how three-dimensional printing of micro-CT imaged specimens can provide insight into craniofacial surgical applications, developmental cardiac anatomy, placental imaging, archaeological remains and high-resolution bone imaging. We conclude with other potential future usages of this emerging technique.

INTRODUCTION

Over the last two decades, three-dimensional (3D) printing (also known as additive manufacturing) has captured the collective imagination of the medical field and is booming in popularity. Once a tool predominantly confined to prototype manufacturing in the industrial and engineering arenas, the reduction in size of printing machinery, flexibility of usage and reduction of cost of many modern printers has made this method of construction more widely available.

Data from which medical 3D printed models have originated frequently included CT or less frequently MRI and ultrasound.[1] The 3D data sets from the imaging are then segmented, processed and converted to a 3D mesh format (*i.e.* standard tessellation language file) for printing. The 3D printer then interprets the data into a model by successive deposition of synthetic material in two-dimensional layers (an example of 3D printing in action can be seen at: http://www.gosh.nhs.uk/news/press-releases/2015-press-release-archive/3d-printing-makes-difficult-procedure-easier-carry-out-children)

Whilst printed models created from CT and MR examinations have been widely utilised for orthopaedic and

craniofacial surgical planning,[2,3] dentistry[4] and anatomical education,[5] there are limitations to printing delicate body structures and small specimens. A novel imaging modality, termed microfocus CT (micro-CT) imaging, provides high-resolution 3D digital data sets comparable to levels of resolution as light microscopy without the need for anatomical dissection. Where data from CT or MR examinations typically have voxel sizes around 0.7 mm, with micro-CT the voxel sizes can reach below 1 micron (<0.001 mm). As a result, internal organ architecture (*e.g.* bone trabeculations, vascular channels, cell-type specific relationships) can be better characterised,[6–8] and where necessary the data sets can be post-processed and magnified to create accurate anatomical models for morphological review, education, procedure planning and specimen handling.

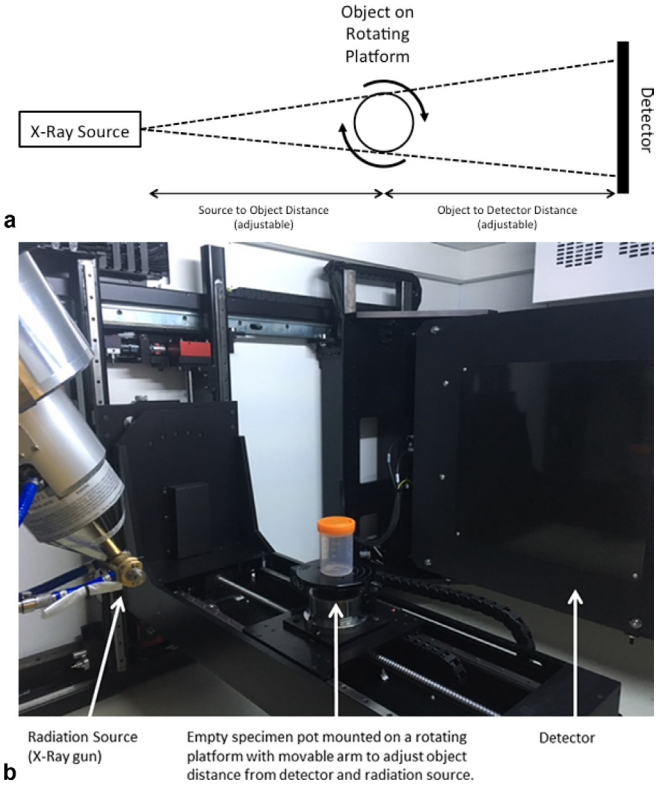
In this review, we briefly describe how micro-CT imaging works and provide examples where 3D printing from micro-CT imaged specimens can provide insight into craniofacial surgical applications, placental imaging, developmental cardiac anatomy, high resolution bone imaging and archaeological remains. We conclude with other potential future clinical usages of this technique.

How does a micro-CT scanner work?

Like medical CT scanning technology, a micro-CT scanner relies on an X-ray beam to irradiate the object of interest and photo-sensitive detectors to record the unabsorbed photon signals. After software post-processing techniques are applied to the data (*e.g.* filtered back projection), a 3D imaging volume is produced. Whilst micro-CT scanners have been designed similar to medical CT in which a fixed object is imaged with a rotating gantry radiation source, industrial-specification micro-CT scanners can be designed in the opposite way: with a fixed radiation source being used to image an object on an adjustable, rotating platform (Figure 1). The adjustable platform distance from the radiation source and detector allows for a large range of magnifications and thus image resolution.[9] When combined with flexible image parameter selection [whereby features such as the voltage, current, exposure time per projection, number of projections and target material as well as selection of filters (if required)], micro-CT has a wide range of applications that can be investigated.

Key limitations to this technique however, include the trade-off between field of view and geometric magnification of the specimen (*i.e.* high resolutions require a small field of view) and being mostly able to image *ex vivo* objects due to the high radiation doses and long scanning times (10 min to several hours, depending on resolution, contrast and quality desired). In addition, to achieve the best quality images, tissue preparation is a key consideration. Where inherent stark tissue contrast already exists (*e.g.* trabeculated calcified bone or lung parenchyma) no preparation may be required. Where differentiation of tissue substructures of similar densities are present, the immersion or intravascular administration of a contrast agent may be needed. This can involve a variety of different agents such as iodinated fluid, metal or silicone-based compounds.[10,11] Further details of clinical applications in micro-CT imaging including its uses in small animal studies and early clinical applications have been reviewed previously.[9]

Figure 1. An example of one micro-CT construct design, widely used for *ex vivo* and industrial specimen imaging. (a) Diagram demonstrating the basic concept of machinery design with (b) matching photograph of the inside of a micro-CT machine. The object being imaged is rotated on a platform, in the path of the radiation source (*i.e.* X-ray gun). The "source to object" and "object to detector" distances are adjustable, and allow for different levels of magnification and, therefore, resolution of the resultant image. The entire construct is housed within a lead lined cabinet, shielding the operator from harmful ionizing radiation. Reproduced with permission from Hutchinson JC et al. [9] micro-CT, microfocus CT.



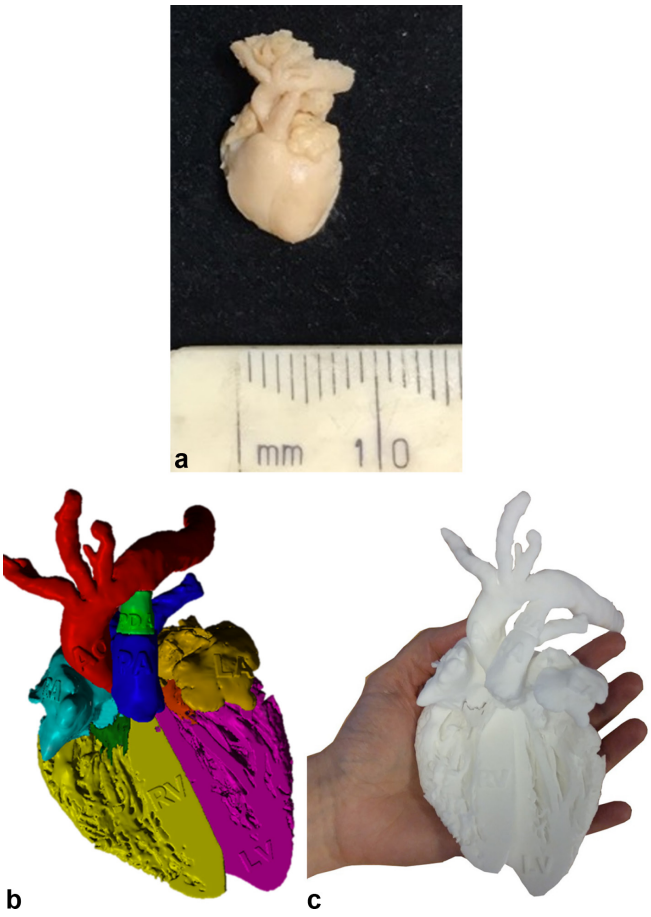
3D PRINTING FROM MICRO-CT IMAGING

In this section, we wish to highlight individual situations whereby micro-CT derived 3D printing and modelling may be useful. We start with potential uses in early life, disease and complex disorders through to death and archaeological remains. We begin with discussion of congenital cardiac anatomical defects and placental vascularity followed by surgical planning techniques for craniofacial surgery and end with those relating to archaeological remains of human bone and post-mortem foetal imaging.

CARDIAC IMAGING

In utero, the human heart is the first organ to develop and starts to beat rhythmically by the fourth week of gestation. Visualisation of 3D cardiac anatomy at different gestational ages are crucial for understanding how normal and abnormal hearts develop. Many congenital cardiac abnormalities are complex and require expertise to characterise with the limited resolution of

Figure 2. 3D printing from micro-CT of an archival 16 week gestation foetal heart for educational purposes. (a) External appearances of the foetal heart, measuring under 1 cm in length, (b) virtual 3D volume rendered micro-CT imaged model with cardiac segments colour-coded and (c) final 3D printed model, resized to 10 × 10 × 10 original dimensions for use as an educational tool. 3D, three-dimensional; micro-CT, microfocus CT.



standard imaging (*e.g.* antenatal and post-mortem ultrasound or MRI). Micro-CT examination of *ex vivo* human foetal cardiac specimens are, therefore, ideal for providing high-resolution imaging and deriving realistic 3D printed models for correlation with pre-natal imaging and education.

The specimens (Figure 2a) can be scanned with micro-CT technology and then post-processed using segmentation software (ScanIP, Synopsis, London, UK) to delineate the regions of interest required. 3D computer models of foetal hearts can be colour coded to highlight the three cardiac segments, the atria, ventricles and great arteries, as an aid to training. Furthermore, small components of these segments such as the four cardiac valves, branching pattern of the pulmonary trunk and aorta, papillary muscles and even ventricular trabeculations can be identified in hearts as small as 10 mm in length (from foetuses of approximately 16 weeks gestation) (Figure 2b). The detail from micro-CT imaging also allows comparisons of complex structures such as the oval fossa to be made at different stages of foetal development.

Physical 3D printed models of foetal hearts can then be created from the imaging data sets. Life-size models, although not very informative, allow the appreciation of heart size at differing gestations and can be used to demonstrate the challenges in diagnosis at earlier gestations. Rescaling the cardiac models (1000 times larger than life for a 16 week gestation foetal heart; Figure 2c) allows better appreciation of the anatomical features to the naked eye and these are routinely used to teach on cardiac morphology courses.

PLACENTAL VASCULATURE

There is limited published literature on the three-dimensional structure of the foetoplacental vascular tree, due to the small size of vessels and complexity of the branching structures. When the placenta fails to develop, the foetus becomes hypoxic and growth restricted and placental insufficiency is reportedly responsible for up to one third of antenatal stillbirths in high-income countries.[12]

Micro-CT can capture data regarding placental vascularity and may open a new window into our understanding of normal pregnancy and the role of the placenta in major obstetric disorders, including foetal growth restriction, pre-eclampsia and complicated twin pregnancies.

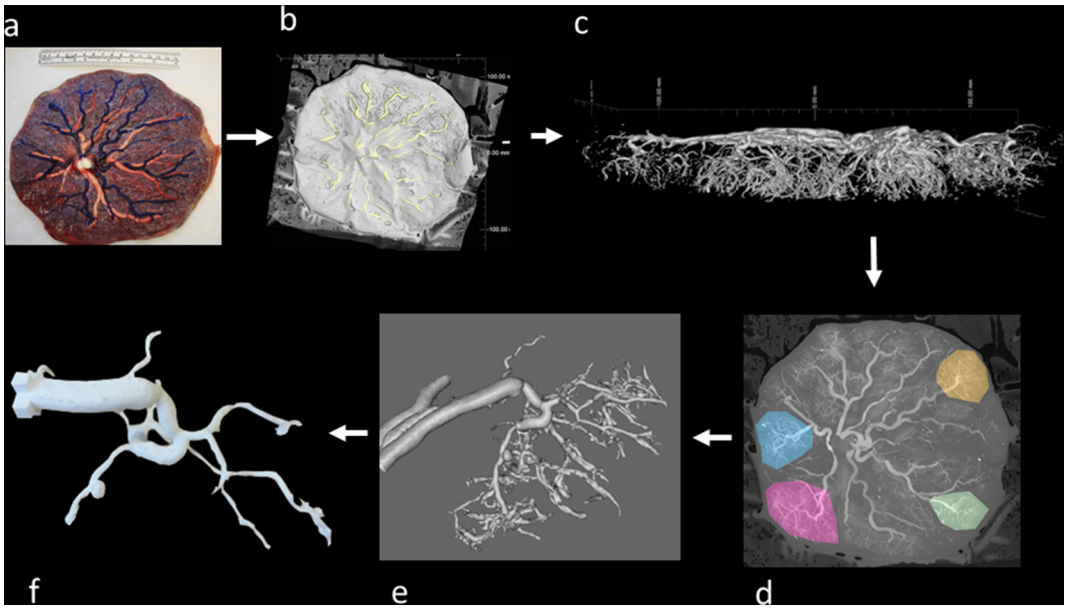
Prior to imaging, due to lack of inherent tissue contrast, the placental preparation requires umbilical artery cannulation and manual perfusion with a lead-based contrast agent [Microfil prior to formalin fixation, Figure 3 (Pratt et al[13])]. Micro-CT of the placenta (at voxel size of approximately 120 μm) allows the 3D chorionic and deep branching vessel structure to be captured and quantified.[14,15] Vascular regions of interest can be thresholded to extract the vascular structure, and converted to a 3D mesh file (MeshMixer), and imported to Cura software for 3D printing (Ultimaker, Chorley, England, (FDM) printer).[16]

3D printing from micro-CT imaging data allow the complexity of placental vasculature to be appreciated. There is the potential for specific models to help counsel patients, providing an easily accessible way to explain placental function and the cause of pathologies such as foetal growth restriction or complications from twin pregnancies. There is also the possibility for models to serve as an educational tool for allied healthcare professionals dealing with maternal health from primary to tertiary care settings and public engagement activities.

Craniofacial surgical planning

In addition to the aforementioned educational purposes, 3D models (whether physical or computational) are greatly beneficial to surgeons who are able to practice a range of complex manoeuvres prior to a planned operation.[17] They can also benefit patient or parental understanding prior to consent, where the surgical approach and potential areas of risk can be

Figure 3. Imaging to 3D printing of placental vasculature. (a) The placental arterial system is injected with a radio-dense contrast agent (Microfil, red colouring). (b) After micro-CT imaging, the raw data are converted into a volume rendered 3D image, with the vascular tree highlighted in yellow. (c) The vascular tree was then extracted from the data set and (d) regions of interest were highlighted to identify distal capillary beds for further analysis. (e) Using a software called MeshMixer, the areas of interest were further selected and used for 3D printing. (f) The final 3D printed model of a section of the placental vasculature is shown. 3D, three-dimensional; micro-CT, microfocus CT.



better explained and understood using precise individualised patient data.[18]

Whilst micro-CT imaging does not currently allow for *in vivo* imaging of patient anatomy (which still relies on medical CT and MRI techniques), they can help in the imaging of tools to aid complex virtual reconstructions (Figure 4). Some of the simplest items to image with micro-CT and, potentially print, are those with inherent high contrast to noise, *i.e.* metallic tools such as screws, plates, springs. At present, these are only printed for educational demonstration rather than for use in surgery.

The micro-CT 3D generated virtual models of the surgical tools in craniofacial techniques are primarily used to allow accurate pre-operative planning on computer generated anatomical models, selection of correct size of tools and virtual reconstruction of post-surgical appearances. This ability to evaluate surgical outcomes may enable development of future tailor made micro-CT image generated 3D printed tools and plates focused on the unique individual requirements.[19]

In addition to the virtual modelling of surgical tools, micro-CT scanning also has the potential to test for defects as well as tensile strength of prostheses,[20] and may inform the design of more robust implants. Micro-CT imaging has already long been utilised in industry to assess for material deficiencies in electronic assemblies and aircraft engine turbine blade inspection.[21] Future research could focus on better predicting the longevity and likely "wear and tear" of devices prior to insertion, especially if known to be placed under significant strain (*e.g.* joint replacements).

Postmortem foetal autopsy

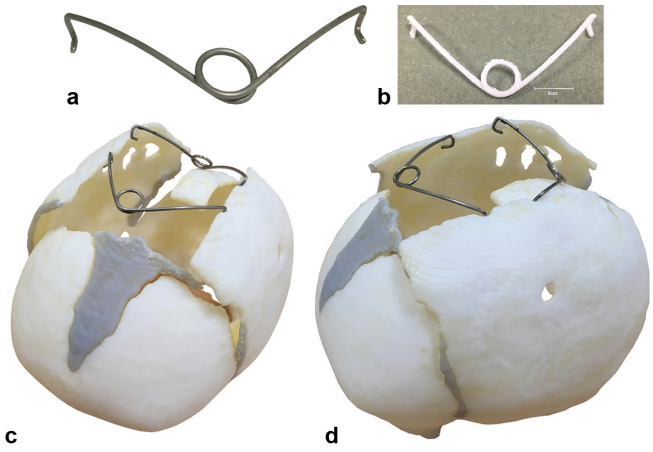
Whilst death is never an easy subject to discuss, post-mortem imaging is an important area of research and has the potential to alter future clinical management, particularly where a perinatal death has occurred and where parents are planning a future pregnancy. Post-mortem perinatal micro-CT imaging has been shown to be a highly accurate and less invasive alternative to conventional autopsy, especially for foetuses in whom conventional imaging provides insufficient resolution.[22,23]

Helping parents understand reasons for the foetal loss may be enhanced with a printed model of the pathology, such as in cases of congenital heart disease or lethal skeletal dysplasias. Micro-CT imaging of anatomical detail such as a femur with multiple fractures from a foetus with osteogenesis imperfecta Type 2a can help to explain to parents what abnormalities were present, and 3D printing at a magnified scale can allow practical handling (Figure 5). Further work may include assessment of parental acceptability and the situations in which 3D models will be of most benefit.

ARCHAEOLOGICAL HUMAN SPECIMENS AND BONE ARCHITECTURE

Aside from parental counselling described above, post-mortem imaging can also provide useful feedback on physician's understanding of diseases. Recently, a collaboration of University College London researchers have successfully performed 3D printing of a complete set of children's bones dating from the late 19th century. The collection, known as "Parrot's bones", comprises of over 50 fragments of foetal and neonatal bones,

Figure 4. Use of 3D modelling in craniofacial surgery. (a) Metallic cranial spring used for holding apart resected skull bones in the treatment of craniosynostosis in children, (b) resultant 3D printed model of the spring to life scale as a demonstration model. The micro-CT imaged spring can be virtually manipulated and uploaded to a computer graphics programme along with patient anatomical information to enable surgeons to plan complex procedures, understand whether the degree of sutural separation from the procedure would be sufficient and potentially review the likely cosmetic outcome of surgery. (c, d) 3D printed model of infant skull photographed from oblique anteroposterior and left parietal views respectively. The model demonstrates post-surgical appearances of an infant's skull following parasagittal osteotomies and cranial spring insertion for sutural craniosynostosis. The skull and grey rubber material (representing fibrous sutures) interposed between the surgical incision sites were reconstructed using the patient's medical CT imaging data. The metallic springs here are examples of the real devices used in the procedure. 3D, three-dimensional; micro-CT, microfocus CT.

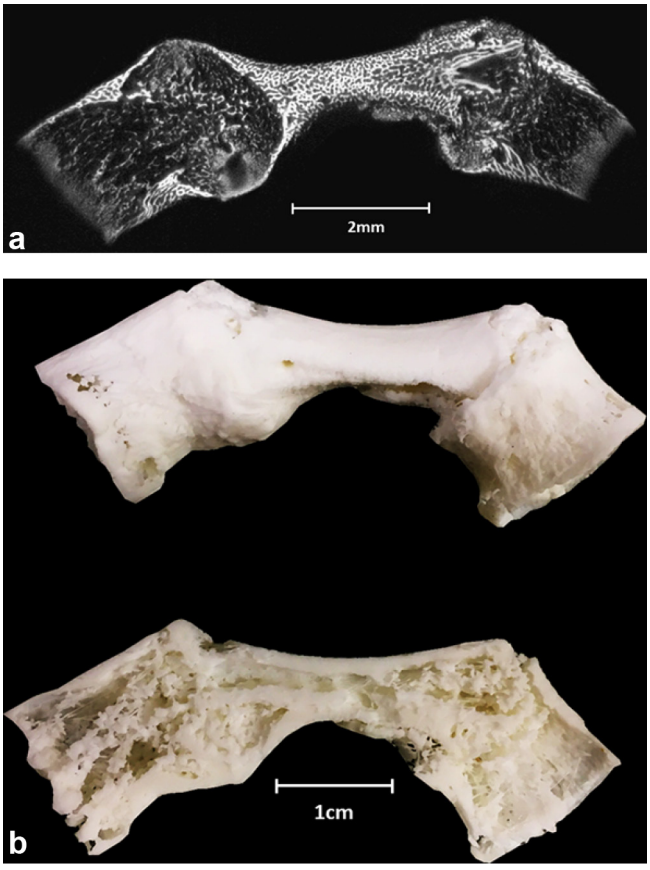


believed by an eminent French physician (Dr Joseph Marie Jules Parrot) to show signs of rickets. He postulated that neonatal rickets occurred as a manifestation of pre-existing congenital syphilis.[24] These are of great historical interest as it had been uncertain for years whether the pathology described was really undiagnosed rickets or syphilis.

Manual handling of fragile specimens such as these must be minimised, whereas 3D printed models can be handled and examined in detail without fear of breaking or destroying valuable original data. Moreso, where several bones had been sectioned in non-conventional oblique planes by the original examiners, so matching bones was challenging and impossible with gross inspection in around half of the cases.

Conventional radiography and CT techniques did not provide sufficient detail for 3D analysis of bony microstructure and thus micro-CT imaging was utilised. By subsequently 3D printing the bone sections to twice their actual size, the models were robust enough to handle. This meant that physically matching the cut sections with each other was possible in almost all cases based on plane of dissection, matching trabecular markings and areas

Figure 5. 3D printing from an extract femur in a 19 week gestation foetus with osteogenesis imperfecta femur Type 2a. (a) Micro-CT imaging of the femur with voxel size of 18 μm. (b) 3D printed model of the whole femur (top) and longitudinally sectioned femur (bottom), four times life size. The internal bony trabeculation is disordered and there is gross new bone formation at both metaphyseal ends of the bone in keeping with healing in utero fractures. 3D, three-dimensional; micro-CT, microfocus CT.



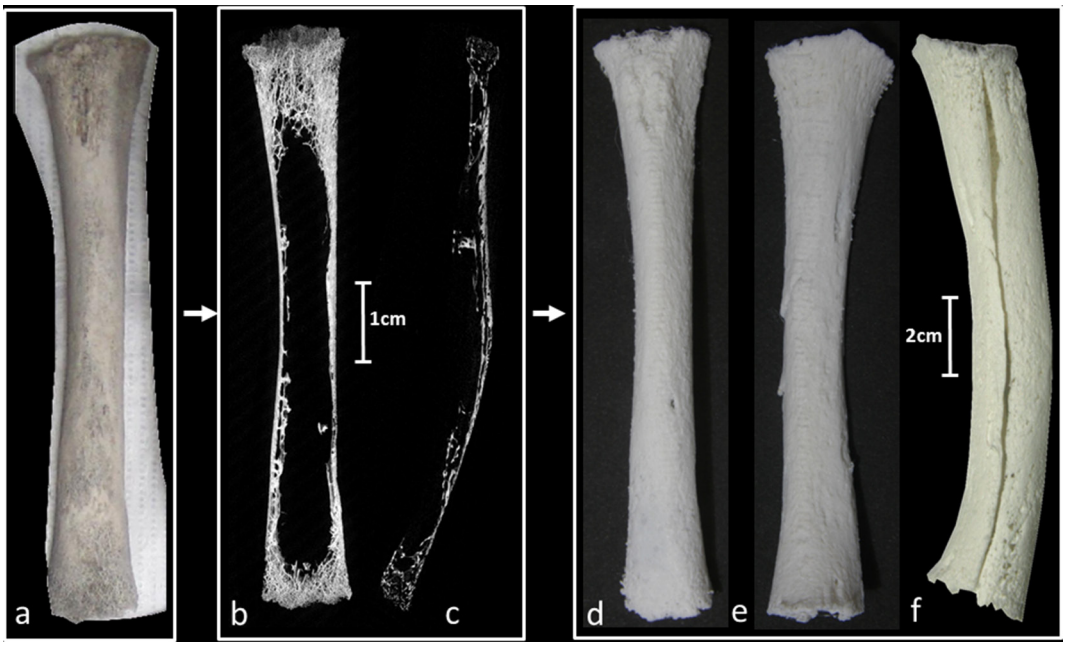
of pathological disease, as previously documented by Parrot[25] (Figure 6). Radiological review of the micro-CT findings failed to identify typical features of rickets, and these pathological changes may better be explained as the result of syphilis.

FUTURE DIRECTIONS

Other emerging applications for high-resolution 3D printing include those for forensic science, where micro-CT of bony injuries can aid in correctly matching a suspected murder weapon to impressions within the bone, and the use of subsequent 3D printing findings for jury presentation in criminal trials.[26–28] In otolaryngology, successfully created inner ear anatomical models have also been printed with the prospect of aiding evaluation and development of new prosthetic devices.[29]

It is likely that further developments for high-resolution 3D printing will be combined with advances in computational analysis and more versatile types of printing material. Those that can accurately mimic the elasticity and flexibility of tissue can provide more realistic models of disease,[30] aid in anatomical

Figure 6. Imaging to 3D printing of a neonatal right tibia from "Parrot's bone" collection. (a) One-half of an original bone specimen, cut by the 19th century French doctor in a longitudinal section and subsequently mounted onto polystyrene, with cut surface facing the mounted material. (b) Micro-CT image of the same specimen in both longitudinal 2.5 mm thick slab view and (c) non-manipulated micro-CT sagittal plane. The bone was extremely porous and also bowed in the sagittal section making handling particularly challenging. (d) A 3D printed version of the bone specimen twice life size and (e) the subsequently matched longitudinal "half section" within the collection. This was only possible by 3D printing the entire collection and physically matching the components together by trabecular pattern, size and pathology as shown in (f). 3D, three-dimensional; micro-CT, microfocus CT.



models for interventional and surgical simulation[31] and more adaptable prostheses.[32] It is also possible that 3D printing from micro-CT may be surpassed by other forms of high-resolution imaging, such as synchrotron or lab-based radiation phase contrast imaging, which may offer higher contrast to noise ratio and improved soft tissue microstructure detail.[33–35] So far, it has been used to create 3D anatomical models of small insects[36] but may have human applications. Nevertheless, these alternative high-resolution imaging modalities are currently far costlier than current micro-CT machines (which cost approximately £250,000) and are currently being developed by several manufacturers to provide a more "user-friendly" interface for clinical usages, which is likely to lead to their increased uptake and application in the near future.

As with all methods of 3D printing, any future increase in popularity will be met with issues surrounding accuracy, quality and clinical validation of the models along with cost–benefit analyses and the related logistics of running a service. Where quality and accuracy are involved, it is important to remember that the multistep process of imaging, segmentation, application of smoothing factors before even the 3D printing occurs, can all lead to inherent stepwise losses in detail and resolution, even when the initial micro-CT imaging is of <0.001 mm resolution. This may not be clinically relevant where the differences are minimal, but is still to be evaluated.

Centralised 3D printing within certain specialist hospital trusts where such techniques have been optimised may, therefore, be more appropriate,[37] and newer computing technologies that can automatically generate standard tessellation language files from imaging data may also minimise production time[38] and simplify the workflow.

CONCLUSIONS

A variety of applications have been described for high-resolution 3D printing from micro-CT data. We can now model smaller and more complex anatomical structures that were previously beyond the limits of conventional medical scanning parameters. The applications of micro-CT and 3D printing for research, education, training, surgical planning and novel prostheses are fast expanding. The increased availability of 3D printers and the variety of printing materials will aid future developments and will lead to more rapid and simplified software segmentation and more advanced computational analyses. This, in turn, will expand our ability to understand structures that were once beyond the limits of our imaging technology.

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