Non-invasive Imaging Technology

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Non-invasive imaging technology is a commonly used diagnostic tool in modern medicine. Commonly used are computed tomography (CT), positron emission tomography (PET), ultrasound (US), PAI (photoacoustic imaging) and MRI (magnetic resonance imaging) . This review explores the use of these modalities for imaging biodegradable implants.

Keywords: implant imaging ; multimodal imaging ; computed tomography (CT) ; positron emission tomography (PET) ; ultrasound (US) ; photoacoustic imaging (PAI) ; magnetic resonance imaging (MRI)

1. Introduction

Because of the invasive nature of implantation practice and associated organism reactions to the presence of foreign materials, imaging has been used as a tool to monitor the patient's condition ever since the discovery of X-rays in 1895. With the development of technologies and the increase in variety, the possible aspects and options for imaging have increased, allowing the visualization not only of structural condition, but also biological reactions and interactions.

Currently, implants used in orthopaedics, dentistry, reconstructive and cosmetic surgery use a large variety of materials, including permanent implants made of polymers (polyurethane, polyethylene, polypropylene, polymethylmethacrylate etc.) [1], ceramics (aluminium oxide, zirconium oxide, carbon-silicon etc.) and metals (titanium, stainless steel, gold, cobalt-chromium etc.) [2] However, it is unavoidable that most, if not all of the used materials have side effects, requiring additional treatment or even removal surgeries [3]. In some cases, complications such as patient discomfort, osteopenia due to stress shielding and chronic inflammatory reaction could be reduced or avoided if the implants would disappear after their effect is no longer required. For this reason, the development and application of biodegradable implants has become an attractive topic in implantology. This requires high quality testing and trials to confirm the safety and quality of these implants. One of these requirements is to have adequate imaging capabilities to follow up tissue healing and implant degradation in vivo.

Because of the ongoing diversification and narrow specialization in the field of science, the available information has become increasingly diverse and complicatedly interlinked. Concerns have been raised about the insufficient mutual understanding of the needs and capabilities among the specialists in the related fields such as medicine, biotechnology and imaging.

2. Features of the Imaging Techniques

2.1. Computed Tomography

Computed tomography, being the three-dimensional version of the conventional planar X-ray scan, relies on the same principles of using electromagnetic radiation (photons) and the difference in its attenuation rate by different matter. As photons interact with the surrounding matter, they can be absorbed by a photoelectric effect, or undergo scattering through incoherent (Compton) or coherent (Rayleigh) scattering.

In the photoelectric effect, the incident photon is absorbed by the atom while displacing the electron from its shell, which creates the contrast in the rays absorbed by the matter, creating the image. This effect is dependent on electron binding energies, as the lower binding energy allows lower energy photons to interact, and the probability is generally proportional according to formula Z^3/E^3 (Z = atomic number; E = photon energy). Except for the absorption edge points in the absorption spectrum of the substance, where there is a sharp rise in absorption coefficient as the energy increases, and the energy of the photon becomes equal to the energy of the electron shell. The combination of the scattering and absorption coefficients is represented as mass absorption coefficient (in cm^2/g). In radiology, the mass absorption coefficient has little practical use, instead these values are multiplied by density to obtain linear absorption coefficient (in cm^{-1}). While the clinical CT photon energies are between 5 (mammography) and 150 (abdominal) keV [4], the actual

usable energies are further limited by the volume (and density) of the imaging target and technical limitations of the available equipment.

2.2. Positron Emission Tomography

Positron emission tomography uses positrons that are emitted during beta plus (β^+) decay of radionuclides that are the signalling components of the radiotracers. The emitted positron interacts with a surrounding electron and the mutual annihilation reaction produces two photons of gamma energy spectrum (511 keV) that move in opposite directions at a 180° angle from each other. The photons are detected, and the annihilation event location is reconstructed using corresponding algorithms.

While a metabolically inactive implant would have little to no interaction with the radiotracer, PET allows us to specifically image the metabolic activity of chosen pathways, which is indispensable for the evaluation of the tissues affected by the implantation. For this reason, the targets of the imaging are metabolites and pathways that are relevant for the study focus. In the case of biodegradable implants, this involves their interaction with the surrounding tissues during the inflammatory stage and the following processes of tissue regeneration, implant integration, degradation and replacement. Osseointegration of bone implants and the substitution of degraded material with new bone can be monitored through the increase of calcium, for example through the use of ^{18}F that binds to hydroxyapatite, thus creating fluorapatite [5]. Inflammation associated with trauma healing and the presence of foreign material in the body is routinely imaged by quantifying the increase in glucose metabolism by using fluorodeoxyglucose (FDG) [6]. Wound healing and regeneration of the surrounding tissues can be associated with the growth of blood vessels and the activity of associated integrins such as $\alpha_V\beta_3$ [7][8] and $\alpha_V\beta_5$ [9], which are targeted by tracers based on RGD-peptides (e.g., ^{68}Ga-NODAGA-RGD [9]). There are also groups of biomarkers, such as matrix metalloproteinases (MMPs, a family of endopeptidases), that have a varied role in biochemical activity, for example MMP-9 has been shown to be associated with early extracellular matrix (ECM) re-organization [10], and MMP-12 is linked to macrophage activity and vascular pathologies [11].

2.3. Ultrasound Imaging

As one of the most safe, comfortable and simple imaging modalities, ultrasound is widely used to study structures and physical processes happening under the cover of the soft tissues. Ultrasound imaging uses the principle of sound waves echoing from the borders of mechanically different tissues [12], due to the variation of acoustic impedance. At the same time, the higher the sound frequency, the higher is the resolution but lower the penetration depth. Increased energy increases the imaging depth, however that can lead to side effects such as heating, acoustic cavitation and acoustic streaming [13]. The heating is one of the primal concerns associated with implant imaging, as the healing process can be by thermal damage [14].

Acoustic impedance is defined as material density and sound velocity in that material. The larger the difference between two tissues, the higher is the number of sound waves that are reflected, and the clearer is the image border. Considering that a significant number of orthopaedic implants is inside the bone, there are at least two acoustic impedance borders in between—from muscle to bone and from bone to implant. As a result, only a very limited amount of echo signal from implant within the bone can reach the receiver. Taking into account the attenuation, scatter, reflection and all the noise, ultrasound is of limited use for imaging such implants. Furthermore, it is important that both density and sound velocity are heavily dependent on the structure and composition of the materials, which can significantly differ even in similar alloys, composites and polymers.

2.4. Photoacoustic Imaging

Photoacoustic imaging (PAI) relies on the optical absorbance qualities of the tissues and included optical contrast agents down to molecular level. The target chromophores absorb the specific wavelength laser pulses, and the optical energy is converted into detectable sound pressure waves. These chromophores can be endogenous (free and bound water, oxyhaemoglobin, deoxyhaemoglobin, melanin, lipids) and exogenous (mostly small molecule dyes—indocyanine green, Methylene Blue Dye, nanoparticles, designed reporter gene agents etc.) [15].

The use of PAI for implant monitoring has been previously explored in studies such as by Lee et al. [16] , who achieved reasonable ability to distinguish titanium implant covered by bone or meat, at depths relevant for dentistry applications. However, the depth penetration limit and noticeable optical attenuation makes it increasingly difficult to image the targets that are located deeper than 10–20 mm, limiting the clinical application of PAI to targets near the surface [17]. At the same time, PAI resolution is dependent on the depth based on “factor of 200 rule of thumb”, with resolution being 1/200th of the depth [18][19]. For preclinical applications, where small animal studies are prevalent, PAI is less limited by depth, and can be used to gather molecular data from the whole target area [20].

2.5. Magnetic Resonance Imaging

MRI is one of the most advanced, non-invasive and low-discomfort imaging modalities, which is only limited by high costs, personnel qualification level and incompatibility with ferromagnetic materials. MRI is based on nuclear magnetic polarization created through static magnetic field (B_0), which is disturbed with a pulse of radiofrequency (RF) field at Larmor frequency (f_o), which in turn is calculated based on the strength of magnetic field and gyromagnetic ratio (γ) of the targeted nucleus or particle (with formula being $f_o = \gamma \times B_0$) [12]. The resulting disturbance in equilibrium is measured as alternating voltage in surrounding detection coils. The speed at which the disturbed magnetic polarization goes through the process of normalization can be used to differentiate the condition of the tissues and reconstruct this as a visual image.

MRI is best at imaging soft tissues and liquids, because of the high content of H^+ protons [21]. This makes it suitable for imaging inflammation through gadolinium contrast [22] or by detecting liquid accumulations such as oedema and synovitis. Similarly, MRI is actively used to study vascularization through blood flow quantification analysis using perfusion MRI techniques such as arterial spin labelling (ASL), dynamic susceptibility contrast (DSC), dynamic contrast enhanced (DCE), and intravoxel incoherent monition (IVIM) tools [23].

Due to the operating principle of MRI, hard objects without free H^+ protons, like bones and implants, are not optimal imaging targets. However, with bone still being living tissue, it remains possible to image osteolysis at the damage sites [24], giving a clear view of the borders. It is also possible to detect non-ferromagnetic implants such as poly(lactic-co-glycolic acid) (PLGA), tricalcium phosphate (TCP) and polylactic acid (PLA) based on their negative contrast [25][26] and that should carry over to other biodegradable ceramic and polymer implants. Some materials such as glass and plastics are known to be diamagnetic—magnetized in the direction opposite to the magnetic field. However, there is no data available about diamagnetic biodegradable implant materials such as bioglass and polymers [27]. While magnesium and zinc are also non-ferromagnetic, their difference in magnetic susceptibility from surrounding tissues still produces a low level of imaging artefacts and geometric distortions [28][29]. Iron, as a strongly magnetic material, makes implants unsuitable for MRI imaging.

3. Conclusions

When making use of multimodal imaging, the imaging techniques need to be chosen based on how suitable they are for the intended combination of the target(s) and the aim(s). As an example, angiogenesis is a common and reliable imaging biomarker for evaluating tissue healing, because new blood vessels are required to support the growth and functioning of the new tissues. It can be imaged using all imaging modalities mentioned in this paper (CT, PET, US, PAI and MRI). By way of example, using PET, the angiogenetic process (i.e. new blood vessel formation associated to vascular endothelium proliferation) can be studied non-invasively by assessing the regulation of the integrin expression (among the integrin superfamily the $\alpha_V\beta_3$ isoform is the most used). The $\alpha_V\beta_3$ expression is quantified using a tracer such as ^{68}Ga-NODAGA-RGD [30][31] and is one of the few ways to produce images of in vivo metabolism. The drawback of using PET is limited resolution (1–2 mm), which, while rarely crucial in clinical studies, can be a limiting factor for small animal studies due to the scaling. However, PET is commonly combined with CT and also with MRI, which have well established angiography techniques, allowing us to image vasculature in high detail. At the same time, the different modalities allow us to better visualise the borders between the implant and the tissues, which is also usable for artefact correction. Alternatively, because PET has necessary intervals between imaging, using different tracers to image the same target is problematic. In such cases, PAI can be utilised to image $\alpha_V\beta_3$ expression, and PET to follow bone mineralization with the help of ^{18}F-NaF.

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