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REVIEW

Diagnostic and prognostic utility of non-invasive imaging in diabetes management

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Abstract

Medical imaging technologies are acquiring an increasing relevance to assist clinicians in diagnosis and to guide management and therapeutic treatment of patients, thanks to their non invasive and high resolution properties. Computed tomography, magnetic resonance imaging, and ultrasonography are the most used imaging modalities to provide detailed morphological reconstructions of tissues and organs. In addition, the use of contrast dyes or radionuclide-labeled tracers permits to get functional and quantitative information about tissue physiology and metabolism in normal and disease state. In recent years, the development of multimodal and hydrid imaging techniques is coming to be the new frontier of medical imaging for the possibility to overcome limitations of single modalities and to obtain physiological and pathophysiological measurements within an accurate anatomical framework. Moreover, the employment of molecular probes, such as ligands or antibodies, allows a selective *in vivo* targeting of biomolecules involved in specific cellular processes, so expanding the potentialities of imaging techniques for clinical and research applications. This review is aimed to give a survey of characteristics of main diagnostic non-invasive imaging techniques. Current clinical appliances and future perspectives of imaging in the diagnostic and prognostic assessment of diabetic complications affecting different organ systems will be particularly addressed.

Key words: Medical non-invasive imaging; Diabetes; Diabetic complications; Molecular imaging; Multimodal imaging; Hybrid scanners

Core tip: Non-invasive imaging techniques are increasingly employed in every medical field, both for diagnostic purposes and for monitoring of pathological progression and/or efficacy of treatments. Several imaging modalities are currently available to provide structural and functional information about tissue and organ physiology, and thanks to technical improvements and development of hybrid devices, multimodal imaging combining advantages of different techniques offers now new potentialities for research and clinics. Aim of

this review is to overview the principal features of most used diagnostic imaging modalities and to explore main current and forthcoming applications for the study and management of diabetes and its complications.

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INTRODUCTION

While X-ray diagnostic imaging has been in use for more than 100 years, it is in the last 40-45 years that imaging has made a great impact on healthcare due to the development of several modalities. Medical imaging technologies may be roughly divided into structural and functional imaging categories. The former entails the assessment of anatomical and morphological features of tissues and organs. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) scans are the prototypal and the most used non-invasive technologies for this imaging class. However, structural imaging alone may not provide the clinician or researcher with all the necessary information to fully characterize the pathophysiology of diseases. As such, functional imaging has come into existence and is comprised of a multitude of non-invasive, quantitative imaging techniques that are currently in use to study tissue and organ physiology, to probe molecular processes, and to study pathophysiological molecules and metabolites. The parallel development of specific contrast agents has significantly helped to improve the signal to noise ratio of the acquired images, and to gather both structural and functional information during the same scan sequence or within the same modality. Functional imaging is mainly achieved through the use of CT, MRI, and US, as well as through positron emission tomography (PET), single-photon emission computed tomography (SPECT), and optical imaging. Complementary information from structural and functional imaging can assist to determine the nature, location and extent of disease in patients, to guide interventions and to monitor the effects of treatment. Just for an example, MRI can be used to quantitatively determine the three-dimensional structure of an organ or tumour mass and by using the contrast agent, *e.g.*, gadolinium, it is also possible to monitor the blood flow which is an indicator of its functional state.

An accurate visual representation of the anatomy and sometimes of the functional state of the patient has been a goal of clinicians for several decades in many medical fields, although this aspect is often still neglected in diabetic patients. Nevertheless, the rapid rise in the prevalence of diabetes to 382 million individuals worldwide during the last 20 years and the expected rise to 592 million by 2030[1] has global implications and requires paradigm-shifting approaches to diagnosis, treatment monitoring, and prevention. Over the long term, hyperglycaemic conditions can lead to serious diseases affecting the cardiovascular system, eyes, kidneys, nerves, and teeth[2-6]. In addition, people with diabetes also have a higher risk of developing infections, cognitive impairment and dementia[7,8], and lower limb amputations[9].

The present review aims to overview the current principal diagnostic appliances of imaging in the field of diabetes and its complications. In addition, mention will be also deserved to molecular and multimodal imaging, the two more recent approaches to non-invasive imaging tests that, by progressing in parallel with advancements in molecular pathology and with refinement of techniques, represent the new frontier of medical imaging and management of patients with diabetes.

DIAGNOSTIC IMAGING APPROACHES

A short analysis and comparison of the most employed techniques in diagnostic imaging can be of help in the evaluation of the approaches deserving advanced research with a view to both present application and future clinical translation. Table 1 sums up the main characteristics of the principal imaging modalities.

SPECT and PET

In nuclear medicine images of various body parts are produced by using small amount of radioactive tracers, administered intravenously or orally. Then, external detectors capture and form images from the radiation emitted by the radiopharmaceuticals.

There are two main nuclear imaging modalities: SPECT and PET, characterized by a very high sensitivity range (femto- to picomolar concentration range) but a limited spatial resolution (Table 1). Typical SPECT radionuclides are γ photon emitters (Table 2) and they are usually employed to label tracers of blood flow such as N-isopropyl-^{123}I-iodoamphetamine (^{123}I-IMP) and ^{99m}Tc-hexamethyl-propylene amine oxime (^{99m}Tc-HMPAO). Different SPECT radioisotopes can have one or more energy emission lines, therefore several processes can theoretically be imaged simultaneously by setting SPECT scanners at different energy windows. Among the limits of SPECT imaging there are the low temporal resolution, the limited number of available radiopharmaceuticals, and the difficulty to achieve absolute quantitative information due to lack of attenuation and scatter corrections necessary at the time of image reconstruction[10].

PET differs from SPECT in that it relies on nuclides that are neutron-deficient, positron (β^+) emitters, with shorter half-lives (Table 2). It offers several advantages over SPECT. First of all, the large number of available

Table 1 Relevant features of the most common imaging modalities

Imaging modality	Anatomy	Metabolism/ function	Spatial resolution	Weakness
SPECT	Poor	Yes	0.3-3 mm	Radiation
PET	Poor	Yes	1-4 mm	Radiation
CT	Yes	Yes	0.5-1 mm	Radiation
MRI	Yes	Yes	50-500 μm	Expensive
Ultrasound	Yes	Yes	Approximately 200 μm	Poor depth penetration
Optical	Poor	Yes	0.1-10 mm	Poor depth penetration

SPECT: Single-photon emission computed tomography; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging.

Table 2 Main nuclides used in nuclear medicine to label radiopharmaceuticals

SPECT			PET		
Nuclide	Half-life	γ (KeV%)	Nuclide	Half-life	β^+ (KeV%)
^{99m}Tc	6.02 h	89	^{18}F	109.8 min	96.9
^{111}In	2.83 d	90.2	^{11}C	20.4 min	99.7
^{123}I	13.2 h	83	^{13}N	9.98 min	99.8
^{125}I	60.14 d	6.5	^{15}O	2.03 min	99.9
			^{124}I	4.18 d	25.0
			^{64}Cu	12.7 h	17.9
			^{68}Ga	68 min	90.0
			^{82}Rb	1.2 min	99.9

Radiation types: γ: Isomeric transition (gamma) decay; β^+: Positron decay; KeV%: Percentage of energy per decay. SPECT: Single-photon emission computed tomography; PET: Positron emission tomography.

radiolabeled compounds allows to image a large variety of functional cellular processes such as glucose and amino acid metabolism, neurotransmission, receptor affinity, gene expression, cell and molecular targeting. Moreover, the possibility of corrections at the time of image reconstruction allows quantitative measurements[11]. However, one of the main disadvantages of PET is that all radionuclides decay at the same energy (photon energy of 511 KeV)[11]. Therefore, it is not possible to simultaneously discriminate between different radiotracers at different energy windows. Furthermore, the short half-life of radioisotopes restrains the clinical use of PET mainly at those clinical centers which are equipped with a cyclotron. For this reason, radiopharmaceuticals with longer half-lives, such as ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{18}F-fluoro-6-thia-heptadecanoic acid (^{18}F-FTHA), have been implemented to assess glucose and fatty acid metabolism, respectively[12].

X-ray CT

A CT scan consists of an X-ray beam (generated by an external source) passing through the body where a portion of the X-rays are either absorbed or scattered by the internal structures and organs, while the remaining X-ray pattern is transmitted to a rotating detector along multiple linear paths to create cross-sectional pictures of the body[13]. CT scan involves a higher radiation dose than the conventional radiography. However, the radiation dose for a particular study depends on multiple factors: volume scanned, number and type of scan sequences, the desired resolution and image quality.

On the basis of the high spatial resolution (Table 1), CT scans can provide detailed information to diagnose, plan treatment for, and evaluate many conditions in adults and children. Additionally, the detailed images provided by CT scans may eliminate the need for exploratory surgery. CT scans are very good at imaging bone, soft tissue and blood vessel, even if the use of dyes with high atomic numbers is sometimes useful to improve soft tissue contrast. Iodine-based compounds (classified into non-ionic and ionic) are mainly used as water soluble CT contrast agent to be injected intravascularly or into any sinus or body cavity, and can also give an indication of the renal function (*e.g.,* kidney filtration). Concerns about CT scans include the risks from exposure to ionizing radiation and possible allergic or toxic reactions to the intravenous contrast agents. The overall adverse reactions occur in 1% to 3% of people with non-ionic contrast agents and in 4% to 12% with ionic contrast agents[14]. Skin rashes may appear within a week to 3% of people[15].

Two of the most prevalent clinical and diagnostic applications, especially on the cardiovascular field, are the CT angiogram (CTA) and artery calcium scoring. The former can be used to view arteries and veins and requires contrast dye injected into the bloodstream. CTA images can be 3D reconstructed to overview all the organ vasculature and can be rotated and viewed from all angles.

As the artery calcium score test is concerned, it does not use X-ray contrast, and pictures are taken to look for the presence of calcium depots in the blood vessels, mainly in the coronary arteries. Calcium deposits are a very specific sign of coronary artery disease, as they are associated with cholesterol and scar tissue buildup in the arteries. While the amount of calcium in the arteries increases with age, patients who have significantly elevated amounts of calcium depots are at increased risk to heart attacks or other cardiovascular complications[16].

Magnetic resonance

MRI uses strong magnetic fields and pulses of radio waves to produce cross-sectional images of organs and internal structures in the body at high spatial resolution (Table 1). Because the signal detected varies depending on the water content and local magnetic properties of a particular area of the body, MRI provides an excellent soft tissue contrast. Unfortunately, its sensitivity is low (micro- to millimolar

concentration range) and at present there are a limited number of ligands. The physical basis of magnetic MRI is the quantum interaction between a nuclear spin of certain atoms (^{1}H, ^{13}C, ^{19}F, ^{23}Na, ^{31}P and others) and an external magnetic field. MRI scanner detects the radio frequency signal which is emitted only by excited atoms in the body, when they are perturbed by an applied pulse in the range of the radio waves. Image contrast depends on three parameters: the proton density, the longitudinal relaxation time which corresponds to the energy transfer between excited spins and tissue (T1, spin-lattice relaxation time), and the transverse relaxation time which is related to the decay of magnetization by interaction between nuclei (T2, spin-spin relaxation time)[17]. Variable image contrast can be achieved by using different pulse sequences and by changing the imaging parameters. Signal intensities on T1, T2, and proton density-weighted images relate to specific tissue characteristics. Moreover, it is possible to employ contrast agents that magnetically modify the proton spin environment to provide a positive enhancement (T1-targeted), mostly achieved by gadolinium chelates, or negative enhancement (T2- and T2*-targeted probes), by using paramagnetic ultra-small particles of iron oxide (USPIOs)[18].

In 1990, Ogawa *et al*[19] discovered that deoxyhemoglobin acts as a natural contrast agent to study brain activity on the basis of changes in blood flow, thus providing a functional value to MRI. Functional MRI based on the blood-oxygen-level-dependent (BOLD) contrast is applied both in the research field and, to a lesser extent, in the clinical arena. In this latter case, it is used to anatomically map the brain and detect the effects of tumors, stroke, head and brain injury, or diseases such as Alzheimer's[20-22].

Although MRI does not use ionizing radiation and no harmful side-effects are known to be associated with temporary exposure to the strong magnetic field, there are important safety concerns to consider before performing or undergoing an MRI scan. The magnet, indeed, may cause pacemakers (and any other implanted medical devices that contain metal) to malfunction or heat up during the exam.

While MRI provides information on the spatial location and local chemical environment of protons, proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive technique providing biochemical information about tissues. ^{1}H-MRS is based on the principle that the resonance frequency of protons is also dependent on their chemical environment (*e.g.*, protons have a slightly different resonance frequency in lipids than in water). Therefore, protons can be visualized at a specific chemical shift (peak position along the X-axis) depending on their chemical environment. The panel of metabolites that can be recognized by MRS include some amino acids, neurotransmitters, choline, lactate, lipids, creatinine, and myo-inositol. MRS is currently used to investigate brain and metabolic disease[23-25].

Ultrasound imaging

Diagnostic ultrasound, or US, is an imaging method that uses high-frequency sound waves (1 to 12 MHz) and their echoes to produce relatively precise images of structures within the body (Table 1). The transducer probe is the main part of an ultrasound machine. It generates and receives sound waves using a principle called the piezoelectric effect. The sound waves travel into the body and hit a boundary between tissues (*e.g.*, between fluid and soft tissues or between soft tissues and bone). Some of the sound waves get reflected back to the probe, while some others travel on further until they reach another boundary and get reflected. The machine calculates the distance from the probe to the tissue or organ (boundaries) by using the speed of sound in tissue and the time of each echo's return, and then displays a 2D-image based on the echoes' intensity. Transducer probes come in many shapes, sizes and frequency of emitted sound waves. This latter parameter determines how deep the sound waves penetrate into the body, and so affects the resolution of the image.

Contrast enhanced ultrasound extends ultrasound techniques to the exploitation of gas-filled microspheres [microbubbles (MB)] as an ultrasound contrast medium. MB are commercially available for clinical use in cardiovascular imaging, being confined by their size to the intravascular space. Their proven clinical tolerability, along with the advantages of real-time imaging, high spatial resolution, and the relatively low cost of equipment renders molecular targeting of MB an attractive option for future development from its current preclinical stage to the actual clinical application[26-29]. A variant of US is based upon the Doppler effect (Doppler US). When the object reflecting the ultrasound waves is moving, it changes the frequency of the echoes as a function of its velocity. Doppler US measures the change in frequency of the echoes to calculate how fast the object is moving, and it is mostly used to measure the rate of blood flow.

Optical imaging

Optical imaging is based on the detection of molecular emission in the electromagnetic spectrum (visible and near-infrared) by a high sensitive and high resolution charge-coupled device digital camera. It extends over a wide range on the imaging resolution scale (Table 1) and is often complementary to other imaging modalities.

Optical imaging offers a number of important advantages over the existing radiological imaging techniques. It uses non-ionizing radiation, which significantly reduces patient radiation exposure, provide high sensitivity detection (pico- to nanomolar concentrations) and allows for repeated studies over time. Moreover, optical imaging has the potential to differentiate among soft tissues, and between native tissues and tissue labeled with contrast media (either endogenous or exogenous compounds), using their

different photon absorption or scattering profiles at different wavelengths. Optical imaging encompasses a host of light-based imaging modalities, including diffuse optical tomography (DOT), optical coherence tomography (OCT), and hyper-spectral imaging, that holds great potential for improving disease prevention, diagnosis, and treatment in healthcare facilities.

DOT modality utilizes red and near-infrared light (λ 650-900 nm) to probe the optical properties of tissues. By measuring the spatio-temporal variations of transmitted and back-scattered light intensities, it is possible to image regional variations in the chemical concentration of specific molecules to detect cellular physiological changes (*e.g.*, neuronal activation). The limited spatial resolution (approximately 1 cm) of DOT is balanced by a high temporal resolution (approximately 10 ms), a potential large optical penetration depth (up to several cm) which depends on the characteristics of the light source and by the light-transmittance of the tissue, a high intrinsic contrast associated with hemoglobin (contrast factor of 10-100 in most soft tissues), and the capability of spectral discrimination of multiple chromophores. DOT has been used in multiple thick tissue imaging appliances, including brain functional imaging, breast cancer imaging, and tissue oxygenation analysis. Methods to improve DOT imaging performance by combining multi-modality information such as from X-ray, CT and MRI are also being explored[30-33].

OCT detects light that has been back-scattered from structures at a particular depth by exploiting constructive and destructive interference between the returning light and a reference beam. It is a technique for obtaining sub-surface images (up to 2 mm), now in use in a variety of applications, including art conservation, artery disease, and diagnosis of diabetic retinopathy[34].

HIS imaging, or imaging spectroscopy, represents a hybrid modality for optical imaging which combines the power of conventional digital imaging and spectroscopy. Indeed, it provides a three-dimensional matrix, or image cube, merging information coming from every pixel of the entire 2D-image with the optical spectrum over a large number of wavelengths (typically tens to hundreds)[35]. The high spatial and spectral resolution offered by HIS allows to detect and quantify tissue environment in the early stages of disease progression. In the medical and clinical scenarios, HIS has exhibited a great potential in the early diagnosis of several forms of cancer, peripheral artery disease, burn wounds, diabetic foot, and ischemic tissue pathology[36-39].

Hybrid techniques for multimodal imaging

To overcome single modality limitations (*e.g.*, the strong variation in sensitivity, spatial and/or temporal resolution, and quantitative analysis capabilities), multimodal imaging which combines techniques with complementary strength has grown up fast in clinical practice. Most of the examinations, however, are performed on separate machines, with some drawbacks that can impact on the diagnostic accuracy: an inaccurate anatomic matching due to patient repositioning, side-by-side or co-registration of images, time-consuming and expensive processes. In the last decade, the development of combined PET-CT integrated systems has revolutionized the concept of hybrid imaging[40]. On the success of PET-CT hybrid scanners, more recently also SPECT-CT hybrid devices have been introduced[41]. However, there are also some negative aspects in using CT as complementary anatomical imaging modality, such as the additional radiation to the patient and the poor soft tissue contrast in the absence of contrast agents. These shortcomings do not apply to MRI and, hence, the idea to combine PET and MRI in a unique device. Hybrid PET-MRI scanners are currently available mainly for preclinical studies on small animals, and in a proof-of-principle phase for clinical applications. Hybrid bimodal PET-MRI imaging is attracting great interest because, unlike PET-CT that requires sequential acquisition of PET and CT images, it makes available the simultaneous acquisition of PET and MRI images, and potentially performs dynamic imaging to obtain valuable functional information within an accurate anatomical framework[42-44].

Targeted molecular imaging

The significant advancement provided by molecular targeting of imaging probes with respect to the traditional diagnostic techniques of morphological, functional or metabolic imaging runs parallel to the advancements in the hybrid imaging systems[45,46]. Molecular imaging approach allows the selective *in vivo* targeting of biomolecules that are specifically expressed in cellular processes contributing to the development of a variety of disease states. It requires the availability of appropriate molecular probes, composed by a label system that can be visualized by imaging devices and a ligand that recognizes and binds the molecular target (*e.g.*, antibody, peptide, small synthetic or natural molecules). The application of targeted molecular imaging has already proven valuable in clinical oncological practice for early detection and diagnosis as well as in prognosis[47]. Despite its great capability, however, molecular imaging approach in other medical fields is still mainly confined to the laboratory settings and almost exclusively used in preclinical studies. Many areas of research are very active in this field, especially studies centered on the detection of pre-disease states or molecular states that occur before typical disease symptoms are overt[48,49]. Other important areas of interest are the imaging of gene expression and the development of novel biomarkers[50,51]. Nevertheless, at present there are some barriers to a widespread clinical translation

Table 3 Synopsis of imaging modalities and their applications in diabetes

	SPECT/PET	CT	MR	US	Optical	Application
Pancreas (β-cell function)	[^{18}F]-tracer		MRI		Luminescence	Mainly preclinical[61,62]
Pancreas (transplant/ inflammation)	[^{18}F]-tracer		MRI	High-frequency		Preclinical and clinical[63-68]
Kidney			MRI/BOLD-MRI	B-mode/Doppler		Clinical[70-78]
Brain	[^{123}I]- and [^{99}Tc]-tracer		MRI/MRS	Doppler		Clinical[22,82,83]
Vessels/ atherosclerosis	[^{18}F]-tracer	Angio-CT	MRI	B-mode		Clinical[85-95,100-106]
Ulcerations	[^{99}Tc]-tracer	Hybrid SPECT/CT	MRI	Doppler	HIS	Clinical[113,114,116,117]
Heart	[^{18}F]-, [^{123}I]- [^{11}C]-tracer	Hybrid PET/CT	MRI/MRS	Doppler		Clinical[95,120-126,130,131,134,135]
Visceral fat		CT/dual energy CT	MRI/MRS	B-mode		Clinical[142,145,146]

SPECT: Single-photon emission computed tomography; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; US: Ultrasound; MRS: Magnetic resonance spectroscopy; BOLD: Blood-oxygen-level-dependent; HIS: Hyperspectral imaging.

of molecular imaging: the paucity of approved molecular imaging agents; the difficulty of combining the suitable characteristics of the probe (feasibility of synthesis, pharmacokinetics, high binding efficacy and specificity) with the lack of toxicity in patients; the reduced interest for industrial investment considering that, by its very nature, molecular imaging (as well as personalized medicine) decreases the size of the possible patient set from a commercial point of view[52,53].

MEDICAL AND CLINICAL APPLICATIONS OF IMAGING IN DIABETES

A general view of the different non-invasive imaging approaches and their applications on the medical and clinical settings is offered in this section. Some advantages and drawbacks of alternative or combined approaches are also described. Table 3 sums up the most employed imaging modalities in the diagnosis and monitoring of diabetic complications and end-organ damage.

Pancreatic islet and beta cells imaging

The loss of functional β-cells is decisive in the development of both type 1 (T1D) and type 2 (T2D) diabetes. T1D is characterized by an autoimmune reaction against pancreatic β-cells, while T2D leads to β-cell dysfunction due to insulin resistance[54,55].

The possibility to non invasively imaging the severity and the extent of a critical mass of β-cell destruction could significantly aid in the diagnosis and treatment of diabetes. However, imaging of β-cells is a major challenge due to the small size of pancreatic islets, the low density distribution of islets throughout the pancreas, and the scarce inherent contrast from the surrounding tissues.

A variety of currently available imaging techniques, including MRI[56,57], bioluminescence imaging[58,59], and nuclear imaging (PET and SPECT) have been tested for the study of β-cell diseases[60]. The majority of the cited studies was carried out on animal models, and even though the translational potential of some of the methods is hampered by the depth of the pancreas in the human body, in many cases the possibility of a clinical transfer embodies a real opportunity.

Since zinc plays a critical role in the biosynthesis and secretion of insulin, Lubag *et al*[61] demonstrated the feasibility of utilizing zinc-responsive T1-contrast MRI for monitoring islet β-cells function in animal models. Currently, there are two approaches that have been developed for monitoring β-cell function using MRI: manganese-enhanced and a zinc-responsive contrast agent[62].

Moreover, MRI proved to be useful at diagnosing and monitoring immune cell infiltration of the pancreas[63-66] by using superparamagnetic iron oxide nanoparticles as T2-weighted negative contrast agent.

Very recent preclinical studies proposed the use of PET imaging to evaluate the loss of pancreatic islet cells in a rodent model of T1D, using [^{18}F]-fallypride, a dopamine D2/D3 receptor radiotracer[67].

Finally, PET, MRI and US have been used in several trials to investigate the efficacy of different imaging modalities for visualizing transplanted islets[68]. Since these methodologies have different advantages and disadvantages, their use in combination is recommended for accurate assessment of the condition of transplanted islets[69].

Diabetic nephropathy and kidney imaging

In diabetic patients, renal functional deterioration is the result of heterogeneous renal structural changes and represents 35%-40% of new cases of renal insufficiency requiring dialysis. Renal damage occurs in multiple stages and diagnostic tests that help to identify early stages of kidney alterations will provide significant benefits to get the disease under control. In the early stages of diabetic nephropathy, kidney size may be enlarged from hyperfiltration[70-72]. With progression of kidney disease in diabetes, the kidneys diminish in size due to glomerulo-sclerosis[70]. US

imaging is typically performed to assess kidney size[73]. Moreover, a renal ultrasound examination can reveal hyperechogenicity that is suggestive of chronic kidney disease, and can assist in ruling out any obstruction. In addition, Doppler US can support in both the evaluation of renal parenchymal perfusion and the computation of renal resistance parameters to assess endothelial dysfunction and microvascular impairment in the kidneys of diabetic patients[74].

Also quantitative diffusion-weighted MRI and BOLD-MRI can play a role in the evaluation of renal disease[75-77] and may facilitate the development of more effective follow-up and treatment modalities[78].

Brain imaging in diabetes

The technique of choice to image the brain is MRI that spans from coarse anatomical studies of atrophic areas to the more detailed investigations of both functional and structural alterations in both gray and white matter of specific cerebral areas. It has been suggested that the risk of decreases in cognitive ability, usually associated with aging, is increased in type 2 diabetic patients. Some recent and comprehensive reviews focused on the relationship between diabetes and brain abnormalities[22,79]. A consistent number of studies were aimed to measure volumetric differences in diabetic population by MRI. During aging, a global brain atrophy with an average decline in the brain volume of 0.1%-0.5% per year is physiological[80,81]. However, brain volume in T2D patients is reduced of 0.5%-2.0% relative to controls[22], correspondent to an extra 2-5 years of normal aging. Brain atrophy can be generalized or focal, with the medial temporal lobe mainly involved[22], and can be related to either the white or the gray matter, or both. Ryan *et al*[79] reported that insulin resistance is a predictor of gray matter atrophy and cognitive impairment. Moreover, the analyses of T2-weighted MR brain images of diabetic patients revealed micro- and macrovascular alterations induced by the chronic inflammation associated with hyperglycemia, which could play a role in the hyperintense lesions of the white matter observed[82]. Several MRI studies indicated a significant correlation between T2D and brain infarct, mostly lacunar necrosis[22], and such parameters as insulin resistance, nephropathy, diabetes duration and high systolic blood pressure are suggested as main determinants of the increased occurrence of brain infarcts in the diabetic population[22].

At present, there are few studies on brain metabolism of diabetic patients by MR spectroscopy[23-24,83]. They were mainly addressed to determine the alterations of the resonance peaks of brain metabolites and neurotransmitters under different conditions of cognitive impairment[22].

Brain microvascular function can be investigated by imaging of cerebral blood flow and cerebrovascular reactivity. The former is assessed by SPECT (using ^{123}I- or ^{99}Tc- labeled tracers), MRI (phase-contrast or arterial spin-labeling modalities) and transcranial Doppler US. Cerebrovascular reactivity, assessed by MRI or trancranial Doppler US, is the measure of the microvascular reserve defined as the increase of blood flow under maximal cerebral vasodilation induced by acetazolamide or CO_2. At present, however, studies on cerebral blood flow and cerebrovascular reactivity in patients with T2DM show conflicting results[22].

Imaging of vasculature and vascular changes

Non-invasive techniques provide information on macrovascular anatomy, as well as on functional parameters concerning vessel flows, tissue perfusion, microcirculation, all of which are affected by complications concurring in the high morbidity and mortality on diabetic patients.

Ultrasonography is mainly used to assess the atherosclerotic burden in non coronary arteries. Doppler US has been successfully employed for an early and accurate characterization of the vasculopathy of lower limb arteries (a strong risk factor in the development of diabetic foot ulcers)[84], thus favoring the prevention or delay of foot complications, especially amputation. Moreover, the measurement of the carotid intima-media thickness (IMT) by US has been demonstrated a useful marker of the progression of atherosclerosis throughout the body, and an excellent predictor of cardiovascular events even in diabetic population[85,86]. Furthermore, carotid IMT can be used to evaluate the efficacy of new treatments[87-90].

At present, techniques based on CT technology, such as coronary artery calcium scoring and coronary multi-slice CT angiography, are considered the most robust imaging techniques for non-invasive visualization of coronary atherosclerosis, assessment of plaque composition and level of calcification[91-93]. Also MRI is emerging as an important modality to assess atherosclerotic plaque burden and morphology in non coronary arteries[94,95].

Nevertheless, because altered vessel morphology may be ambiguous, the ability to non invasively evaluate molecular and cellular pathological processes becomes crucial in terms of early detection and preventive treatment. The use of functional and molecular imaging approaches will provide valuable diagnostic tools. Recently, by using MRI in experimental studies on rodent diabetic models, Medarova *et al*[96] evaluated pancreatic vascular volume, microvascular flow, and permeability, that are common disease biomarkers for both T1D and T2D[97-99].

Moreover, PET imaging studies reported a strong relation between peripheral artery atherosclerosis and increased regional ^{18}F-FDG uptake (glycolytic metabolism) in subjects presenting impaired glucose tolerance and T2D[100,101]. In addition, inflammatory condition associated with atheroma or atherosclerosis progression has been investigated by both single and

dual-modal imaging, using ^{18}F-FDG-PET/CT[102], USPIO-MRI[103-105], nanoparticle PET-CT[106]. Finally, it is very promising, but mainly limited to the preclinical field, the use of nanoparticles appropriately functionalized with ligands or antibodies *vs* cell membrane molecules (VCAM-1, PECAM-1, E-selectin, P-selectin) to detect activated endothelial cells in different imaging modalities (OCT, MRI, enhanced US, PET)[107-109], or even in the same acquisition session (hybrid MRI or PET-CT and MRI-PET scanners)[110,111] in order to obtain a molecular contrast.

Imaging of ulcerations and diabetic foot

Lower extremity and particularly foot ulcers are among the most frequent complications of diabetes. It is estimated that 15%-25% of T1D and T2D patients are affected by skin ulcers in their lifetime[112]. Factors as peripheral neuropathy and vascular disease contribute to the development of skin ulcerations. Some valuable information on vasculopathy can be provided by Doppler US examination in patients with diabetic foot[113]. Moreover, in the last few years hyperspectral imaging (HIS) has been launched as a useful diagnostic tool to monitor microvascular changes and tissue perfusion impairment associated with diabetic ulcer formation and healing[114]. By selecting proper wavelengths within the visible and very near infrared region (400-1000 nm) of the electromagnetic spectrum, HIS allows to acquire spatial maps of oxy- and deoxyhemoglobin and, thus, to quantify tissue oxygenation. In the management of diabetic foot ulcers, it represents a valuable tool in the assessment of wound healing potential and in guiding the proper therapy in order to prevent infections and amputations. If left untreated, a relevant cases of foot ulcers lead to infection, limited joint mobility, muscular alterations and deep-tissue necrosis[112]. Bones may also be involved in two different clinical conditions associated with diabetic complications, such as osteomyelitis and Charcot osteoarthropathy[115]. The former is mainly due to direct bone contamination from a soft-tissue ulcer and accounts for approximately one third of diabetic foot infections, whereas the latter is a chronic and progressive inflammatory disease affecting the bone and joints. Both osteomyelitis and Charcot foot are conditions with an increased risk of lower limb amputation from 25% to 50%. It has been suggested that about 50% of those amputations could be avoided by an early diagnosis and a multidisciplinary approach. The major diagnostic difficulty is in distinguishing osteomyelitis from non-infectious bony disorders as Charcot foot[115].

X-ray planar radiographs are relatively inexpensive and readily available, but their sensitivity is quite poor and false negative results are not so rare, especially in the first stages of osteomyelitis. Bone biopsy is considered the technique of choice for detection of osteomyelitis, however conventional imaging (MRI, SPECT and hybrid SPECT/CT) are valuable support in the early diagnosis of infections and their accurate anatomical localization[116]. In addition, due to their non-invasive nature, imaging studies proved particularly useful in monitoring the progression of the disease and the efficiency of specific treatments. Valabhji *et al*[117] show the effective role of MRI also in guiding the time course of the antibiotic therapy in the management of diabetic foot complicated by osteomyelitis. Unfortunately, the major limitation of MRI imaging is its inability to accurately differentiate osteomyelitis from other inflammatory bone disease. Similarly, the use of SPECT imaging modality that combines technetium methyl-diphosphonate (^{99m}Tc-MDP) bone scan with technetium hexamethylpropylene amine oxime (^{99m}Tc-HMPAO)-labeled leukocytes scan is adequate for osteomyelitis diagnosis[118], but is poor in the anatomical localization of the infection, due to the limited spatial resolution of nuclear imaging.

Recently, new hybrid imaging technologies combining SPECT localization of ^{99m}Tc-HMPAO-labeled leukocytes and high resolution X-ray CT have been introduced and provided effective in the differential diagnosing of osteomyelitis in patients with diabetes[116]. The use of ^{18}F-FDG-PET has emerged as a possible alternative nuclear imaging modality combined with CT in the diagnosis of bone infection secondary to diabetic ulcerations. However, at present, the data on the role of PET and PET/CT in the evaluation of diabetic foot infections are limited and the results reported are rather inconsistent, especially in the absence of an appropriate reference standard[119].

Imaging of diabetic cardiomyopathy

Accumulating data from experimental, pathological, epidemiological, and clinical studies have shown that diabetes mellitus results in cardiac functional and structural changes, independent of hypertension, coronary artery disease or any other known cardiac disease, which support the existence of diabetic cardiomyopathy. The pathophysiology of diabetic heart disease is likely multifactorial, involving altered myocardial metabolism, endothelial dysfunction and vascular disease, autonomic neuropathy, and increased myocardial fibrosis. Most of the conventional non-invasive imaging modalities can provide valuable insights into the disease process and can be useful for monitoring disease progression and evaluating the effectiveness of medical interventions.

Ventricular function and perfusion: Conventional diagnostic imaging modalities currently aids in non-invasive assessment of both systolic and diastolic dysfunction in diabetic patients. Pulsed wave Doppler studies measuring transmitral inflow, deceleration time and isovolumic relaxation time are the gold standard to diagnose ventricular diastolic dysfunction[120,121]. Moreover, tissue Doppler imaging and strain rate imaging are considered more sensitive for detection

of LV dysfunction than conventional trans-thoracic echocardiography, especially in the early stages of diabetes in which the sole sub-endocardial dysfunction is overt. Cardiac MRI has recently emerged as a very good imaging tool for the diagnosis of structural and functional disorders of the myocardium. Gadolinium-enhanced cardiac MRI has been found to be useful in the prediction of major adverse cardiac events in diabetic patients without previous history of ischemic heart disease[95,122]. Cardiac MRI is also useful to detect diastolic dysfunction and myocardial steatosis[95]. Among the available imaging modalities, only PET allows quantitative assessment of myocardial blood flow using radiotracers kinetics[95,123,124]. The combined images by MRI and PET provide a high spatial resolution detection of myocardial metabolic abnormalities and currently represent the more valuable imaging analysis in the diagnosis and prognosis of diabetic disease. Unfortunately, many diabetic patients with advanced stages of cardiomyopathy have had mechanical interventions that have inserted metallic devices into the heart (*e.g.*, defibrillators, left ventricular assist devices) that preclude the possibility to use MRI. Under these circumstances, the low anatomical (spatial) resolution of PET can be compensated by the combined PET/CT imaging. This recent hybrid modality is also particularly indicated in the case of diabetic patients with or at risk of coronary artery disease, since CT is currently considered very reliable in evaluating coronary artery calcium plaque burden and, with the aid of contrast agents, it provides an accurate coronary angiogram[125,126].

Cardiac autonomic neuropathy in diabetes: It is one of the diabetic complications that increase the risk of myocardial infarction and sudden death in diabetic patients. The need of an early diagnosis of cardiac autonomic neuropathy (CAN) for clinical decision-making of these patients is evident considering that it was estimated that the 5-year mortality rate is 5 times higher in diabetic patients with CAN compared with patients without evidence of CAN[127]. CAN detection requires several indirect tests to assess the activity of both the parasympathetic and the sympathetic branches of the autonomic system. However, the only direct method to assess cardiac autonomic activity is by using nuclear imaging. Currently, either SPECT and PET clinical imaging is limited to assess sympathetic activity and innervation, with parasympathetic imaging limited mostly to preclinical and translational studies[95]. Cardiac sympathetic imaging is focused on synaptic junction, and in particular on the pre-synaptic endings, where the norepinephrine transporter (NET) protein, also known as uptake 1, is localized[128]. NET is responsible for the most part of the re-uptake of synaptic norepinephrine that is released following sympathetic nerve endings stimulation. Several studies used radiolabeled analogs of norepinephrine to evaluate the cardiac neuronal activity and function. The most commonly used is metaiodobenzylguanidine (MIBG), a molecule that is taken up by NET protein but that is not catabolized by monoamine oxidase or catechol-o-methyltransferase, thus allowing to accumulate into the sympathetic synaptic endings[129]. MIBG can be easily labeled with the radionuclide ^{123}I, a γ photon emitter and, thus, imaged by SPECT scanner. Besides, some PET tracers have also been developed based on molecules sharing similarities with norepinephrine, including ^{11}C-meta hydroxyephedrine (^{11}C-HED), ^{11}C-epinephrine (^{11}C-EPI) and ^{11}C-guanyl-meta-octopamine (^{11}C-GMO). Both clinical and experimental studies with these tracers have provided significant information on cardiac sympathetic dysfunction in many diseases, diabetes included[130-132].

More recently, experimental and pre-clinical studies tested a new ^{18}F-labeled NET substrate (namely, ^{18}F-LMI1195) designed to allow PET cardiac neuronal imaging with high sensitivity and resolution[133].

Altered myocardial metabolism: It is commonly accepted that one of the mechanism leading to diabetic cardiomyopathy is the accumulation of fatty acids in myocardial tissue (myocardial steatosis). When the fatty acid uptake oversteps the oxidative capability of myocyte, the exceeding fatty acids are stored in the cell cytoplasm as triglycerides. Intracellular triglycerides are inert *per se*. However, a proportional part of them are transformed in toxic intermediates through non-oxidative pathways. At present, myocardial triglycerides can be quantified (thus having an estimate of their toxic metabolites) by means of ^{1}H-MRS scanners with field strength $\geqslant$ 1.5 Tesla. Several experimental and clinical studies have used ^{1}H-MRS to correlate the increased myocardial triglyceride content and ventricular dysfunction in diabetes[95]. Magnetic resonance spectroscopy is also suitable to monitor the effect of pharmacological treatment of diabetes on intra-myocardial triglyceride accumulation[134,135].

Measuring of visceral and liver fat

Excessive body fat is a major risk factor for several diseases, including insulin resistance, T2D, and cardiovascular disease. In addition, fat accumulation in specific body tissues and/or organs (named, ectopic fat) such as visceral, intrahepatic and intramuscular lipid stores, pericardial, perivascular and perirenal fat depots, is considered an important predictor of cardiometabolic and vascular risk[136,137]. Therefore, regional fat distribution might be a more predictive factor for specific risks than obesity itself and an accurate measurement of fat accumulation might represent an additional prognostic value in the risk assessment of patients. Dual energy X-ray absorptiometry (DEXA) is considered the reference choice to evaluate body composition[138]. It measures three different compartments: fat mass,

non-bone lean mass and bone mineral content. DEXA is accurate, time and cost effective, widely available, and has low radiation exposure but is, on the whole, unable to discriminate among fat depots, except for a software that has been recently proposed to quantify the visceral fat compartment[139]. For this reason, MRI and CT are currently considered the gold standard methods to measure adiposity and accurately distinguish between subcutaneous and ectopic visceral fat. However, the use of CT for fat distribution analysis is discouraged, especially in children, due to the high levels of radiation exposure. More recently, several studies have reported grey-scale and/or contrast-enhanced US as a promising technique to measure subcutaneous adipose tissue thickness and abdominal visceral fat[140,141]. Moreover, a strong correlation between US and CT assessment of fat depots was found[140]. If adequately validated, US might represent the clinical standard methodology for longitudinal studies on fat content and distribution in response to treatment[142]. In addition, contrast-enhanced US showed a good sensitivity (> 95%) and specificity (> 90%) even in revealing fatty liver[143,144]. However, as hepatic fat quantification is concerned, also CT, dual-energy CT (80 and 140 kVp), MRI and ^{1}H-MRS perform very well, with high specificity, and are considered the front runners in the non invasive diagnosis and quantification of moderate to severe liver steatosis[145-147].

CONCLUSION

Considering the current trends in medicine, it can be expected that diagnostic non-invasive imaging techniques, particularly multimodal hybrid devices, will become increasingly available in the clinical arena and assume an always more important role in supplementing the clinical evaluation of the diabetic patient.

The challenge is to combine the diagnostic utility of imaging tools with therapeutic entities ("theranostics") in order to improve risk stratification and personalized therapy for diabetes management. It poses both scientific and technical problems: molecular and cellular biology and pathology on one side, and physical and chemical methodologies on the other. As for the contribution of medicinal chemistry, it is required the use of nanometer-scale materials to provide molecular imaging with simultaneous treatment. The nanomaterial platforms have to integrate molecular targeting ligands, therapeutic moieties and complementary imaging (multi)-modalities. Recently, Arifin *et al*[148] have introduced a biohybrid theranostic agent composed by human pancreatic islets encapsulated in a porous matrix together with functionalized Gd-gold nanoparticles which could serve as a contrast agent for three complementary imaging modalities (MRI, CT and US). They found that microcapsules containing islet cells were able to restore normoglycemia in a mouse diabetic model and could be tracked by trimodal non-invasive imaging. Analogously, Barnett *et al*[149] reported the theranostic capabilities of functionalized magneto-capsules containing human pancreatic islet β-cells in mouse and swine pre-clinical models. Moreover, dextran-coated iron oxide nanoprobes, suitable for MRI, have been functionalized with small interfering RNA[150,151] to silencing specific genes of choice. Although important in proving new principles, at present these contributions are still in an exploratory, preclinical stage. Future studies should be performed in models endowed with increased power of predicting human efficacy and safety, thus warranting clinical translation and development in a demanding regulatory environment.

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