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Molecular imaging of diabetes and diabetic complications: Beyond pancreatic β-cell targeting

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ABSTRACT

Diabetes is a chronic non-communicable disease affecting over 400 million people worldwide. Diabetic patients are at a high risk of various complications, such as cardiovascular, renal, and other diseases. The pathogenesis of diabetes (both type 1 and type 2 diabetes) is associated with a functional impairment of pancreatic β-cells. Consequently, most efforts to manage and prevent diabetes have focused on preserving β-cells and their function. Advances in imaging techniques, such as magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, and single-photon-emission computed tomography, have enabled noninvasive and quantitative detection and characterization of the population and function of β-cells *in vivo*. These advantages aid in defining and monitoring the progress of diabetes and determining the efficacy of anti-diabetic therapies. Beyond β-cell targeting, molecular imaging of biomarkers associated with the development of diabetes, e.g., lymphocyte infiltration, insulitis, and metabolic changes, may also be a promising strategy for early detection of diabetes, monitoring its progression, and occurrence of complications, as well as facilitating exploration of new therapeutic interventions. Moreover, molecular imaging of glucose uptake, production and excretion in specified tissues is critical for understanding the pathogenesis of diabetes. In the current review, we summarize and discuss recent advances in noninvasive imaging technologies for imaging of biomarkers beyond β-cells for early diagnosis of diabetes, investigation of glucose metabolism, and precise diagnosis and monitoring of diabetic complications for better management of diabetic patients.

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1. Introduction

Diabetes mellitus is mainly characterized by chronic hyperglycemia caused by insulin insufficiency, or as a consequence of peripheral insulin resistance and insufficient insulin production [1–3]. Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by immune-mediated destruction of pancreatic β-cells, accounting for 5–10% of all diabetes cases [2]. By contrast, type 2 diabetes mellitus (T2DM) is mainly characterized by insulin resistance and progressive β-cell failure, accounting for over 90% of all diabetes cases [3–5].

According to the International Diabetes Federation Diabetes Atlas released in 2017, the global prevalence of diabetes among adults was 9.1% and approximately 5 million people died of diabetic complications in 2015 [6]. By 2015, 415 million adults worldwide suffered from diabetes, and the number was estimated to reach 642 million by 2040. Furthermore, additional 318 million people had prediabetes (impaired fasting glucose and/or impaired glucose tolerance) [6]. Extensive studies have revealed that both genetic susceptibility and environmental factors play vital roles in the pathogenesis of both T1DM and T2DM [5,7–13]. In particular, environmental factors, such as high-calorie diet, reduced physiological activity, and sedentary lifestyle, are highly associated with T2DM [14].

Diabetic patients are at higher risk of developing cardiovascular, renal, retinal, neurological, foot, and other diseases (referred to as diabetic complications) than healthy subjects [15]. Based on the epidemiological data of the International Diabetes Federation Diabetes Atlas collected in 2015 and the WHO general health expenditure figures, diabetes has become a heavy economic and medical burden worldwide [16]. The global cost of diabetes and diabetic complication treatments is about $ 1.31 trillion, accounting for 1.8% of the global gross domestic product in 2015 [17].

Diabetes and diabetic complications greatly impact the medical system, and place a heavy burden on the individual, family, and society. Therefore, effective technologies are needed to facilitate the study of the mechanisms responsible for the development of diabetes, and assist early diagnosis and precise management. Advances in imaging techniques have produced numerous opportunities for the characterization and quantification of *in vivo* biological behaviors in the living subjects in a noninvasive manner, by providing valuable information at the structural, functional, and molecular levels [18,19]. Compared with conventional diagnostic imaging techniques, such as computed tomography (CT), magnetic resonance (MR) imaging (MRI), and ultrasound imaging, which typically provides anatomical information, molecular imaging techniques, such as optical imaging, targeted ultrasound imaging, MR spectroscopy (MRS), positron emission tomography (PET), and single-photon-emission computed tomography (SPECT), take advantage of specific molecular probes or tracers that enable detection of disease-specific molecules. All these imaging techniques have been extensively investigated, and used in the preclinical and clinical studies for the diagnosis and treatment monitoring of diabetes.

The pathogenesis of diabetes (both T1DM and T2DM) is associated with a functional impairment of pancreatic β-cells and/or decrease in β-cell mass (BCM) [20]. Consequently, most efforts to manage and prevent diabetes have been focused on preserving BCM and its function. Therefore, the ability to noninvasively image the population and function of BCM would definitely help define and monitor the progress of diabetes, evaluate the efficacy of anti-diabetic therapies, and stratify patients for selected therapies. Molecular imaging of BCM is the most intensively investigated area of current diabetes imaging. Advances in this field have been comprehensively reviewed recently [21–24].

Despite of the above, molecular imaging of BCM is very challenging and difficult because of the very small proportion of β-cells constituting the pancreatic tissue (the islets constitute only 1–2% of the overall pancreatic volume, and β-cells comprise 60–80% of this islet mass [25]), as well as the sparse distribution of the β-cell population within the pancreas [26,27]. Thus far, molecular imaging of β-cells *in vivo* by either manganese-based MRI, or a series of PET/SPECT and optical imaging approaches targeting the biomarkers of β-cells have not yield satisfactory results. That was either because of the possible toxicity of MRI contrast agents, making longitudinal imaging of BCM impossible, or insufficient sensitivity to accurately image the very small population of β-cells *in vivo*. As an example, the volume of BCM to be imaged is far beyond the capabilities of current PET imaging techniques [23].

Beside β-cells, glucose uptake and glucose production regulated by insulin also play critical roles in the pathogenesis of hyperglycemia and diabetes. Moreover, biomarkers associated with the development of diabetes, e.g., lymphocyte infiltration, inflammation, and metabolic changes, may act as alternative markers for diabetes and better management of diabetes to improve prognosis. In the current review, we summarize the most recent advances in the molecular imaging of biomarkers other than β-cells for the study of glucose metabolism in various tissues, and for timely and more precise diagnosis and management of diabetes and its complications.

2. Molecular imaging of insulitis

T1DM is an autoimmune disease characterized by the destruction of pancreatic β-cells in the pancreatic islets of Langerhans by infiltrating lymphocytes [28]. Microvasculature alterations, immune and inflammatory infiltration (inflammation of the islets, also known as insulitis), and autoimmune destruction of β-cells are the three major characteristics of T1DM development [29]. Microvasculature alterations and lymphocyte infiltration within and around the pancreatic islets are considered to signify the occult phase of T1DM, whereas the destruction of β-cell bulk by T cells is considered to signify the overt phase [30]. Because of their occurrence in the early phases of T1DM, molecular imaging of insulitis and microvascular changes accompanying insulitis might provide early information for the identification of individuals at risk before complete destruction of β-cells, and constitute an early biomarker of responses to interventions. Although pancreas biopsy or a

serum test for circulating autoantibodies can be used for insulitis detection, these approaches are either invasive and cannot be frequently repeated, or provide only a limited insight into the events in the pancreas as a whole. Noninvasive imaging techniques would overcome these limitations. Currently, the major modalities used for molecular imaging of insulitis and microvascular changes are MRI, PET, and SPECT imaging (Table 1).

2.1. MRI tracking of infiltrating lymphocytes

During the initiation phase of T1DM, autoimmunity is associated with the infiltration of lymphocytes, which subsequently destroy β-cells, into the islets. Therefore, noninvasive *in vivo* visualization of the infiltrating lymphocytes would identify pre-diabetic patients, possibly enabling early intervention and halting of disease development.

MRI is one of the leading modalities for *in vivo* tracking of lymphocytes. The lymphocytes can be labeled by either antigen-unspecific labeling strategies or antigen-specific labeling strategies. In 2002, Moore, et al. [31] labeled lymphocytes isolated from nonobese diabetic (NOD) mouse using cross-linked iron oxide nanoparticles derivatized with a membrane translocation signal (CLIO-Tat). Labeled cells were successfully located using MRI in the pancreatic islets after intravenous injection [31]. Although the MR signal cannot be quantified, which limits its clinical application, and this labeling strategy is not antigen-specific and does not allow specific tracking of the recruitment of autoreactive lymphocytes, this study was nonetheless pioneering, demonstrating successful *in vivo* tracking of lymphocytes in the diabetic mouse model. The same group later improved the method by using antigen-specific magnetic labeling [32]. In the improved method, superparamagnetic nanoparticles were coated with a NOD-relevant V7 peptide and an appropriate major histocompatibility complex class I (MHC I), which allowed antigen-specific labeling of $CD8^+$ T cells isolated from transgenic NOD mice but not T cells from healthy mice. By using labeled T cells, MRI enabled successful and noninvasive detection of the inflammation of pancreatic islets by autoreactive T cells [32]. In another study, Billotey el al. [33] used anionic magnetic nanoparticles (MNPs), which have a negative surface charge, for effective cellular internalization for T cell labeling. By using MRI to monitor T cell population *in situ* for up to 20 d after transplantation in NOD mice, the authors demonstrated that the labeled T cells can home-in on the pancreatic lymph nodes, enabling noninvasive imaging of the autoimmune reaction in T1DM [33].

2.2. PET/SPECT tracking of infiltrating lymphocytes

Although lymphocytes labeled with MRI contrast agents have been tested for *in vivo* MRI tracking, *in vivo* and whole body imaging attempts are somewhat disappointing. That is mainly because it is not possible to label the lymphocytes with sufficient amount of contrast agents for analysis, either because of a limited coupling efficiency or toxicity of high concentrations of the contrast agents. Consequently, it is difficult to generate a high enough signal for MRI detection outside the body.

In contrast to MRI, the sensitivity of radiolabeled lymphocytes is sufficient for *in vivo* PET and SPECT imaging. Traditional *ex vivo* cell radiolabeling approaches utilize ^{111}In-oxine, ^{111}In-tropolonate, and ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO) for SPECT; and ^{18}F-FDG and ^{64}Cu/^{89}Zr-labeled antibodies for PET. *In vivo* tracking of radiolabeled lymphocytes for diabetic management has only been

Table 1
Representative examples of noninvasive imaging approaches for detecting insulitis.

Strategy	Imaging probe	Imaging modality	Disease model/patient type	Preclinical/clinical	Ref.
Tracking of labeled lymphocytes	Mouse lymphocytes labeled with cross-linked iron oxide nanoparticles derivatized with membrane translocation signal	MRI	NOD mice	Preclinical	[31]
	Mouse $CD8^+$ T cells endocytosed with superparamagnetic nanoparticles coated with NRP-V7 peptide and an appropriate MHC I	MRI	NOD mice	Preclinical	[32]
	Mouse T cells labeled with anionic magnetic nanoparticles	MRI	NOD mice	Preclinical	[33]
	Human peripheral blood lymphocytes labeled with ^{111}In-oxine	SPECT	Patients with acute-onset T1DM	Clinical	[34]
	Rat lymphocytes labeled with ^{111}In-oxine	SPECT	BB/W rats and W-line BB/W rats	Preclinical	[35]
Imaging probe migration from leaky vessels and/or phagocytosis by macrophages	Long-circulating magnetofluorescent nanoparticles	MRI	Transgenic T1DM mice	Preclinical	[30]
	Monocrystalline iron oxide nanoparticles	MRI	Transgenic T1DM mice	Preclinical	[36]
	PGC covalently linked to GdDTPAs labeled with fluorescein isothiocyanate	MRI	STZ-induced T1DM mice	Preclinical	[37]
	Magnetic nanoparticles ferumoxtran-10	MRI	T1DM patients	Clinical	[38]
	Magnetic nanoparticles ferumoxytol	MRI	Patients with recent-onset T1DM	Clinical	[40]
	Monocrystalline iron oxide nanoparticles	MRI	NOD mice	Preclinical	[41]
IL-2 receptor targeting	^{123}I-IL-2	SPECT	BB/W rats	Preclinical	[43]
	^{123}I-IL-2	SPECT	NOD mice	Preclinical	[44,45]
	^{123}I-IL-2	SPECT	T1DM patients, pre-diabetic patients, Hashimoto's thyroiditis patients, and coeliac disease patients	Clinical	[46]
	^{99m}Tc-IL-2	SPECT	T1DM patients	Clinical	[47]
	^{99m}Tc-IL-2	SPECT	Patients with T1DM, LADA, T2DM, and pancreatic cancer	Clinical	[48]
	^{18}F-IL-2	PET	Rats inoculated with activated hPBMC	Preclinical	[49]
	^{18}F-IL-2	PET	SCID mice inoculated with activated T lymphocytes	Preclinical	[50]
Visualization of the islet blood-flow changes	None	Ultrasound imaging	Virus-inducible BBDR T1DM rats	Preclinical	[51]
	Size-isolated microbubble contrast agent	Ultrasound imaging	STZ-induced mice, NOD mice, and adoptive-transfer mice	Preclinical	[52]

NOD, nonobese diabetic; NRP-V7, NOD-relevant peptide V7; MCH I, major histocompatibility complex class I; T1DM, type 1 diabetes mellitus; BB/W, biobreeding/Worcester; PGC, protected graft copolymer; GdDTPA, gadolinium-diethylenetriaminepentaacetic acid residue; STZ, streptozotocin; LADA, latent autoimmune diabetes in adults; hPBMC, human peripheral blood mononuclear cells; SCID, severe combined immunodeficiency; BBDR, biobreeding diabetes resistant.

reported in a few studies. In a study reported in 1982 [34], peripheral blood lymphocytes were labeled with ^{111}In-oxine and then re-injected intravenously into patients with acute-onset T1DM. At 24 h post-injection, the labeled cells were clearly visualized in the spleen and the pancreas; however, lymphocytic pancreatic infiltration was only observed in a few patients, and the imaging quality was very poor [34]. In another preclinical study [35], lymphocytes were labeled with ^{111}In-oxine and were then injected into spontaneously diabetic biobreeding/Worcester (BB/W) rats, diabetes-resistant W-line BB/W rats, and control rats. Unfortunately, no correlation was observed between the numbers of ^{111}In-oxine-labeled lymphocytes and the presence or intensity of insulitis. Therefore, it has been concluded that autologous transfusion of radiolabeled lymphocytes cannot be used to visualize the pancreas in the rat models [35]. The reasons for failure of the approach involving the use of radiolabeled lymphocytes for *in vivo* detection of diabetic insulitis more than 30 years ago included lymphocyte sensitivity to radiation and the very low resolution of SPECT used in these studies.

2.3. MRI of microvascular changes accompanying insulitis

Microvascular dysfunction usually occurs during the inflammation of a pancreatic islet, resulting in alterations in the blood flow, vasculature volume, and vascular permeability. Therefore, microvascular abnormalities in the vicinity of pancreatic islets are an early biomarker for the early diagnosis and monitoring of T1DM [29].

Denis et al. [30] demonstrated that MRI using long-circulating magnetofluorescent nanoparticles could be used to detect microvascular changes associated with insulitis in transgenic T1DM mouse models. Accumulation of extravasated nanoparticles was caused by increased vasculature permeability and the invading phagocytic macrophages. The onset and evolution of insulitis could then be evaluated *in vivo* and in real time, enabling the investigation of the natural history of T1DM in individual animals [30]. A similar MRI imaging strategy was used to noninvasively monitor autoimmune inflammation in the pancreas of a live mouse [36]. This enabled a sensitive detection of the reversal of diabetes after anti-CD3 monoclonal antibody therapy in NOD mice [36]. Noninvasive MRI visualization of microvascular changes in a streptozotocin-induced mouse model of T1DM was also performed using a long-circulating contrast agent, namely, protected graft copolymer covalently linked to gadolinium-diethylenetriaminepentaacetic acid residues labeled with fluorescein isothiocyanate (PGC-GdDTPA-F) [37]. T1-weighted MRI revealed a substantially higher accumulation of the contrast agent in the pancreas of diabetic animals than in healthy animals [37].

Based on the findings in T1DM animal models [30,36], a clinical study was successfully performed to visualize insulitis in patients with recent-onset diabetes by MRI with ferumoxtran-10. The molecule used is an MNP with a dextran coating. Its size is similar to that of particles used in animal experiments [38], and ferumoxtran-10 has been used for non-invasive detection of metastatic to clinically occult lymph nodes in prostate cancer [39]. The clinical MRI study involved 10 patients with T1DM and 12 non-diabetic controls. It was anticipated that MRI would detect ferumoxtran-10 upon migration from leaky vessels and phagocytosis by inflammatory cells, particularly macrophages. Indeed, MRI with ferumoxtran-10 detected T2 signal decay of the pancreatic parenchyma, which permitted effective visualization of the pancreas and distinguishing of recent-onset diabetes patients from non-diabetic controls [38]. In a later study [40], which introduced crucial technological advances for MR signal quantification and sensitivity, the same group demonstrated that ferumoxytol, an FDA-approved MNP, is engulfed by macrophages, marking an early and integral part of the local pancreatic inflammation. Thereafter, MRI was used to detect pancreatic inflammation with high sensitivity in a pilot study involving human subjects (Fig. 1A, B) [40].

In addition to showing great potential for direct clinical translation for the diagnosis and treatment guidance of diabetes, the MRI-MNP strategy described above can also be used to advance basic research. For example, MRI-MNP can serve as a sensitive prediction tool for diabetes in the NOD mouse models, before the eventual progression of insulitis to overt diabetes, thus enabling the identification of a previously unknown pathway that regulates diabetes progression [41].

2.4. PET/SPECT imaging of biomarkers associated with insulitis

Because of the very small number of infiltrating lymphocytes in insulitis, and the low number of biomarkers expressed on these lymphocytes, direct *in vivo* imaging of lymphocyte infiltration in insulitis relies on highly sensitive imaging techniques, such as PET and SPECT.

Currently, the number of investigated specific biomarkers for molecular imaging of insulitis is limited. The most studied biomarker to date is interleukin-2 (IL-2). IL-2 is a small single-chain glycoprotein of 133 amino acids that is mainly produced by activated T lymphocytes [42]. Radiolabeled IL-2 can be used for *in vivo* specific detection of IL-2 receptors, which are highly expressed on T lymphocyte surface in chronic autoimmune diseases. The most frequently used IL-2 imaging agents for the diagnosis of chronic autoimmune diseases, such as insulitis in T1DM, are ^{123}I-IL-2 and ^{99m}Tc-IL-2.

Signore et al. [43] labeled IL-2 with ^{123}I to generate ^{123}I-IL-2, and then injected it into BB/W diabetes-prone and normal rats. An excellent linear correlation ($R^2 = 0.923$) was observed between the infiltration index of lymphocytes and the radioactivity accumulated in the pancreas of BB/W rats. This pioneering work demonstrated the potential of using radiolabeled IL-2 for *in vivo* imaging of infiltrating lymphocytes during autoimmune diseases, including T1DM. In later studies, ^{123}I-IL-2 was tested in both diabetic animal models [44,45] and T1DM patients [46]. In both cases, high pancreatic uptake of the contrast agent was observed, demonstrating the potential of ^{123}I-IL-2 for SPECT imaging of infiltrating lymphocytes associated with insulitis.

IL-2 was also labeled with ^{99m}Tc, and the resulting radiotracer ^{99m}Tc-IL-2 was tested in 42 newly diagnosed T1DM patients before and after 1 year of treatment [47]. Significant pancreatic accumulation of ^{99m}Tc-IL-2 was observed in 31% of patients. In ^{99m}Tc-IL-2-positive patients, the insulin requirement and pancreatic inflammation were significantly reduced after 1-year treatment with nicotinamide. The study demonstrated that ^{99m}Tc-IL-2 scintigraphy may potentially be used to assess autoimmune phenomena in the endocrine pancreas [47]. In a recent study [48], ^{99m}Tc-IL-2 SPECT imaging was tested in patients with T1DM, latent autoimmune diabetes in adults (LADA), T2DM, and pancreatic cancer. The study demonstrated that ^{99m}Tc-IL-2 SPECT imaging could identify CD25$^+$ lymphocytic infiltration in the pancreas of patients with pancreatic cancer, as well as patients with T1DM and LADA, allowing noninvasive monitoring of interventions in patients with autoimmune diabetes. However, large-scale clinical studies are needed to confirm these findings [48]. To address the limited resolution of SPECT, IL-2 was also labeled with ^{18}F for PET imaging of activated T lymphocytes in mouse models [49,50]. Unfortunately, no patient studies with such agents have been performed.

IL-2-based radiotracers have been validated for *in vivo* PET or SPECT detection of T lymphocytes in the pancreas. However, because of the non-specificity of IL-2 receptor in diabetes-based inflammation, and since IL-2-based radiotracers do not distinguish between insulitis and pancreatic cancer, the diagnostic detection value for T1DM with radiolabeled IL-2 is generally limited. Instead, its application for monitoring intervention effects of well-diagnosed T1DM and longitudinal therapy-associated monitoring of insulitis show great clinical promise.

2.5. Other approaches for imaging of insulitis

In contrast with MRI and nuclear imaging, ultrasound is cheap and does not involve radiation exposure. A recent preclinical study demonstrated the ability of ultrasound imaging to noninvasively visualize changes in blood vessels and blood flow in pancreatic inflammation,

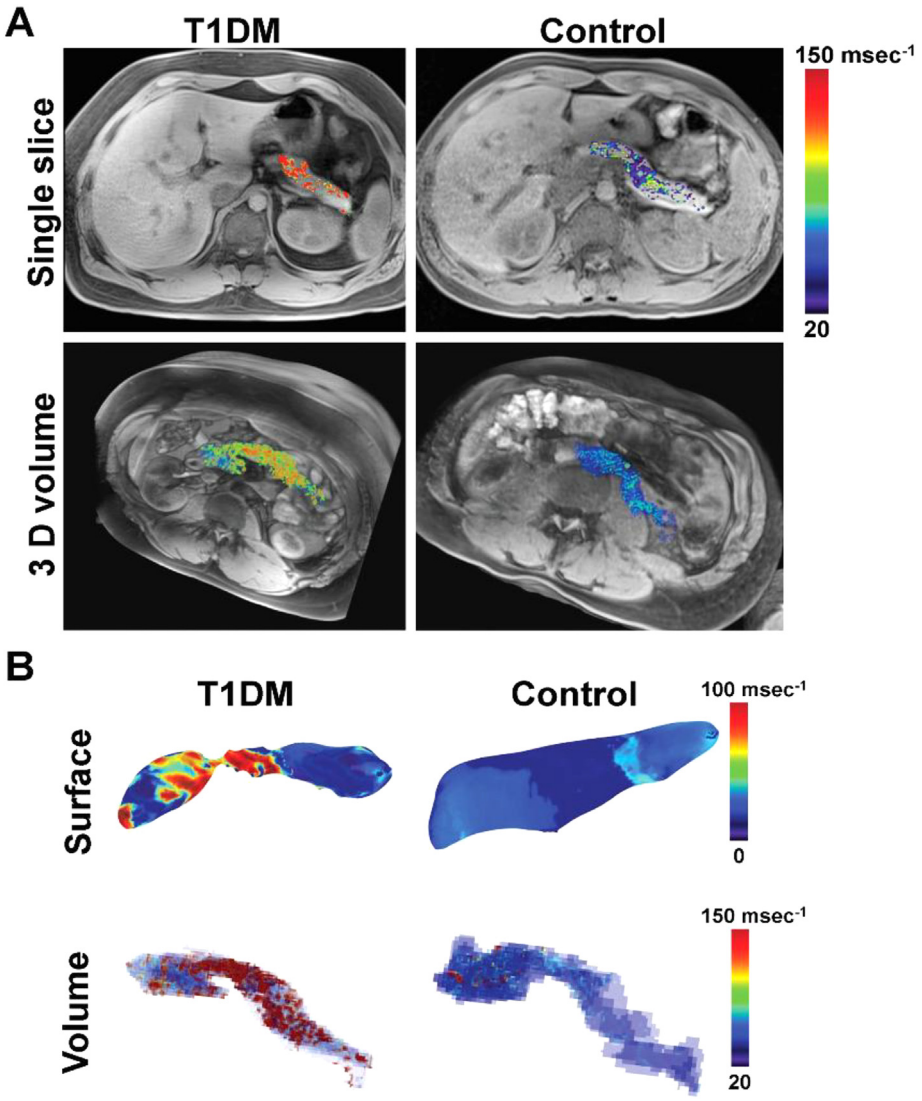

Fig. 1. MRI of microvascular changes accompanying insulitis. (A) Increased pancreatic nanoparticle (ferumoxytol) accumulation in patients with recently diagnosed T1DM compared with a normal control subject as determined by single-slice and 3D volume MRI. (B) Two different visualization models (surface mapping and see-through models of pancreata without surface weighting) revealed the intrapancreatic heterogeneity of ferumoxytol accumulation in patients with T1DM. By contrast, minimal nanoparticle accumulation was observed in control individuals, and their pancreata appeared essentially homogenous. Adapted with permission from [40].

prior to T1DM onset, in a virus-inducible BioBreeding diabetes-resistant T1DM rat model [51]. In another preclinical study, noninvasive and longitudinal imaging using contrast-enhanced ultrasound enabled visualization of the islet blood-flow changes associated with diabetes progression in models of T1DM [52]. Hence, the ultrasound imaging method could be used to predict the early onset of diabetes and to monitor the efficacy of therapy for T1DM.

As T1DM is an autoimmune disease, autoantibodies against islet antigens are commonly present during the preclinical period of this condition; these autoantibodies could serve as biomarkers for either early T1DM diagnosis or assessment of the efficacy of therapies against T1DM [53]. Currently, autoantibody measurements mainly focus on blood sample examinations. Future studies regarding molecular imaging using imaging probes specific for autoimmune antibodies would benefit the noninvasive detection of autoantibodies associated with T1DM development.

3. Imaging glucose metabolism in diabetes

Under physiological conditions, increased insulin secretion by β-cells after a meal stimulates glucose uptake by peripheral tissues, including the liver, skeletal muscle, and adipose tissue, and suppresses hepatic glucose production (HGP), leading to a rapid decrease in blood glucose levels [54]. During fasting, increase in serum glucagon levels stimulates HGP, including glycogenolysis and gluconeogenesis, which is essential for avoiding hypoglycemia [55,56]. Failure of insulin to stimulate glucose uptake by various tissues and to suppress HGP are the key events in the development of hyperglycemia upon the occurrence of insulin resistance [55–57]. Furthermore, the brain, in particular the hypothalamus, also plays an important role in the maintenance of glucose homeostasis [58,59].

In the past two decades, noninvasive imaging technologies, such as PET, CT, and MRI, have been widely used to study glucose metabolism in key glucose-metabolizing tissues, including the liver, skeletal muscle, and adipose tissue, as well as the hypothalamus in humans (Fig. 2) [60–64]. Application of imaging technologies to the study of glucose metabolism in diabetes greatly extended the knowledge of the dynamics of glucose metabolism, the pathogenesis of diabetes, and diabetic complications. In the current section, recent applications of imaging technologies in the investigation of glucose metabolism in several key glucose-metabolizing tissues are briefly discussed.

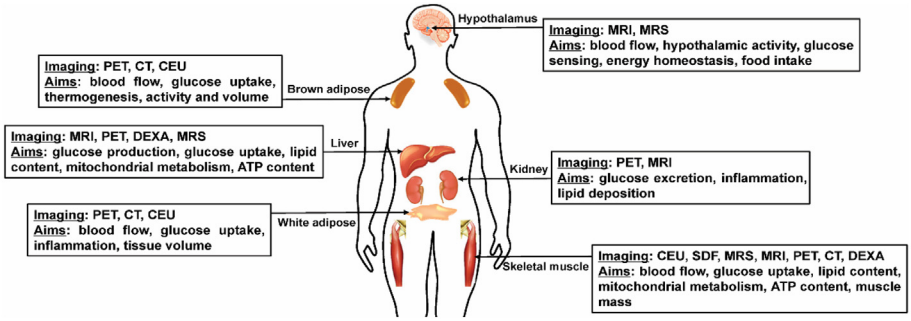

Fig. 2. Noninvasive imaging of glucose metabolism in various tissues. Various imaging approaches have been used to visualize blood flow, glucose transport and uptake, glucose production, and glucose excretion. Imaging technologies provide real-time and dynamic images of glucose transporter and metabolism in various tissues. PET, positron emission tomography; CT, computed tomography; CEU, contrast-enhanced ultrasound; MRI, magnetic resonance imaging; DEXA, dual energy X-ray absorptiometry; MRS, magnetic resonance spectroscopy; SDF, sidestream dark-field imaging.

3.1. Imaging glucose uptake by various tissues

The skeletal muscle accounts for the majority of insulin-simulated glucose uptake among insulin-sensitive tissues after a meal or glucose load. However, the dynamics of glucose uptake in various tissues remain largely unknown. Recently, several imaging technologies have been used to study the roles of blood flow and perfusion in glucose uptake in response to glucose load in various tissues, including the skeletal muscle and adipose tissue. Contrast-enhanced ultrasound imaging revealed that insulin rapidly opens the skeletal muscle capillaries to uptake glucose [65,66]. Various imaging technologies, including sidestream dark-field imaging, ultrasound, and PET with ^{15}O-H_2O or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) as tracers, showed that the skeletal muscle capillary density and microvascular perfusion were reduced in human under diabetic conditions [67–71]. Furthermore, these imaging technologies also revealed that insulin increased the brachial artery diameter and blood flow in the skeletal muscle of lean healthy subjects but not in that of obese diabetic patients [68,69]. These imaging findings indicated that certain cardiovascular diseases (CVDs), such as hypertension and cardiac insufficiency, with reduced blood perfusion in tissues, might cause glucose dysregulation and even diabetes. Clearly, a reciprocal causal relationship exists between diabetes and certain CVDs.

Glucose transporter 4 (GLUT4) is the key glucose transporter isoform in skeletal muscle cells. GLUT4-green fluorescent protein (GFP) imaging revealed that the t-tubules could play a major role in insulin signaling and GLUT4 translocation in the skeletal muscle [72]. GLUT4-GFP imaging also demonstrated that GLUT4 translocation was impaired in the skeletal muscle of insulin-resistant mice [73]. GLUT2 is the main glucose transporter isoform in the liver [74], and deletion of GLUT2 from the liver represses hepatic glucose uptake (HGU) but not HGP in mice [75]. Several studies further indicated that insulin and glucose could play important roles in regulating GLUT2 expression and translocation in hepatocytes [76–79]. PET imaging using ^{18}F-FDG revealed that the glucose uptake rate in subjects with loss-of-function mutation in *AKT2*, encoding a key upstream molecule of GLUT translocation, was significantly reduced in the skeletal muscle (36.4%), liver (16.1%), and brown adipose tissue (BAT) (29.7%) [80].

PET imaging using ^{18}F-FDG, ^{15}O-H_2O, or ^{11}C-3-*O*-methylglucose as tracers revealed that insulin-stimulated glucose uptake in the skeletal muscle was impaired in obese diabetic patients compared with lean normal subjects [81–85]. In newly diagnosed T2DM patients, PET imaging with ^{18}F-FDG showed that rosiglitazone, a thiazolidinedione (TZD), but not metformin, enhanced insulin- and exercise-stimulated glucose uptake in the skeletal muscle [86]. MRI, dual energy X-ray absorptiometry (DEXA), and other imaging systems further showed that the force and mass of the skeletal muscle were reduced in insulin-resistant subjects or diabetic patients compared with healthy subjects [87–89]. Furthermore, DEXA scans indicated that the skeletal muscle loss in diabetic patients can be attenuated by insulin sensitizers, such as metformin and TZDs [90]. PET imaging using ^{18}F-FDG or ^{15}O-H_2O as probes showed that the body mass index is negatively correlated with glucose uptake in the skeletal muscle and adipose tissue [54], and that weight loss increases insulin sensitivity and glucose uptake in the skeletal muscle of obese patients with or without diabetes [83,84]. Furthermore, resistance training increased insulin sensitivity in the skeletal muscle of offspring of overweight and obese mothers [91], whereas in T2DM patients, supervised resistance exercise increased muscle mass and insulin sensitivity as evidenced by DEXA scans [92]. These imaging findings strongly support the notion that moderate physical exercise exerts a beneficial effect on hyperglycemia by maintaining or increasing muscle mass in diabetic patients.

BAT is the main site of adaptive thermogenesis, and reduced BAT activity is highly associated with obesity and T2DM [93]. Generally, cold exposure can activate BAT activity. PET/CT imaging using ^{18}F-FDG revealed a rapid increase in BAT activity soon after cold stimulation and a more gradual decline after rewarming [94]. Cold exposure improves glucose metabolism in healthy human by stimulating BAT activity, as demonstrated by PET/CT imaging with ^{18}F-FDG in various studies [95,96]. By using ^{18}F-FDG-PET/CT imaging, Hanssen et al. [97] observed that cold-stimulated glucose uptake in BAT was reduced under fasting-induced insulin resistance in human. In support of these findings, PET imaging also revealed that ephedrine activated BAT to uptake glucose in lean but not obese young human subjects [98]. These data suggest that glucose uptake in BAT is reduced during insulin-resistance. Moreover, PET/CT scans indicated that the BAT volume and resting energy expenditure rate in healthy lean south Asian adults are lower than those in Caucasians, which might determine their higher susceptibility to obesity and T2DM [99].

PPARγ agonists (also known as TZDs), such as rosiglitazone and pioglitazone, have significant hypoglycemic effects [100]. One of the side effects of PPARγ agonists is weight gain [101,102]. PET imaging using ^{18}F-FDG indicated that glucose in the expanding subcutaneous adipose tissue was stored in the form of triglycerides, ameliorating hyperglycemia in human [103]. Furthermore, PET imaging using ^{18}F-FDG or ^{15}O-H_2O as probes revealed that treatment with rosiglitazone, but not metformin, increased adipose glucose uptake in T2DM patients [104,105]. These imaging findings explain to a large extent the paradox of obesity and T2DM upon PPARγ agonist treatment. These findings also support the notion that PPARγ agonists mainly target the adipose tissue to decrease blood glucose levels, whereas metformin mainly targets the liver to exert a hypoglycemic effect in diabetic patients.

Collectively, imaging-based findings shed light on the dynamics of glucose uptake by the liver, skeletal muscle, and adipose tissue, and demonstrate that a reduction in glucose uptake by these tissues precedes fasting hyperglycemia upon insulin resistance. Noninvasive imaging of glucose uptake by various tissues, in combination with fasting blood glucose and insulin levels, may comprise an effective strategy for evaluating the risk of T2DM in certain susceptible populations.

3.2. Imaging hepatic glucose production

During fasting, an increase in HGP *via* glycogenolysis and gluconeogenesis after glucagon stimulation, is essential for maintaining euglycemia [55,56]. In the past decades, various imaging systems were used to determine the HGP rate, the contribution of glycogenolysis and gluconeogenesis to HGP, and their changes during diabetes in human. By using ^{13}C-MRS, Fried et al. [106] found that HGP rate in healthy human increased 3-fold in the first 15 min after galactose administration and then returned to the baseline. By using ^{2}H- and ^{13}C-MRI, Jones et al. [107] found that the average HGP rate in fasting healthy human was 10.7 ± 0.9 μmol $kg^{-1}\cdot min^{-1}$. Furthermore, by using ^{13}C-MRI, Shulman's group [108,109] determined the contributions of hepatic glycogenolysis and gluconeogenesis to the overall glucose production in healthy subjects. During the first 12 h of fasting, net hepatic glycogenolysis accounted for approximately 40%, and gluconeogenesis accounted for approximately 60%, of overall glucose production in healthy human [108,109]. The authors further showed that gluconeogenesis accounted for approximately 64% of the overall glucose production during the first 22 h of fasting in human. The contribution of gluconeogenesis to the overall glucose production increased to 82% and 96% in the subsequent 14-h and 18-h periods of the fast, respectively [110]. By using ^{2}H-MRI, glycogenolysis was demonstrated to be accounted for approximately 60% of glucose production after an overnight fasting in healthy women [111]. Overall, these imaging-based findings indicate that gluconeogenesis accounts for the majority of glucose produced during long-term fasting in human.

By performing MR analysis using multiple tracers ([3,4-$^{13}C_2$]glucose, $^{2}H_2O$, and [U-$^{13}C_3$]propionate), Eunsook et al. [112] reported that 3-d feeding of a high-fat diet increased hepatic gluconeogenesis but decreased glycogenolysis without affecting the overall glucose production in healthy humans. This finding provides direct evidence that an increase in gluconeogenesis precedes increased HGP and hyperglycemia during over-nutrition. Notably, it also provides the rationale for the clinical observation that metformin, which is believed to exert hypoglycemic effects mainly by suppressing HGP [113], can delay or even prevent the onset of T2DM in patients with prediabetes [114].

^{1}H-MRS has also revealed that HGP in T2DM patients is higher than that in healthy subjects [115]. By using dynamic PET imaging with ^{18}F-FDG, Gastaldelli et al. [116] demonstrated that acute administration of exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, improved hepatic insulin resistance, suppressed HGP, and enhanced HGU in male subjects. In obese patients who underwent bariatric surgery, PET imaging using ^{18}F-FDG revealed a significant reduction in HGP 6 months after the surgery [117]. These findings indicate that increased HGP is the central event in the development of fasting hyperglycemia in humans.

Collectively, application of imaging technologies for the study of hepatic glucose metabolism expands the general understanding of the regulation of gluconeogenesis and glycogenolysis in humans. In particular, quantitative evaluation of the contributions of gluconeogenesis and glycogenolysis to the overall HGP, and the switch between these processes during obesity or insulin resistance shed light on the dynamics of hyperglycemia and T2DM. Imaging of the HGP rate may also be useful for evaluating the risk of T2DM in healthy or pre-diabetic individuals, thereby indicating whether these subjects should take metformin or other drugs to delay or prevent the onset of diabetes.

3.3. Imaging lipid deposition and mitochondrial dysfunction in the liver and skeletal muscle

Imaging technologies, such as ^{1}H-MRS, revealed that elevated hepatic lipid deposition was associated with hepatic insulin resistance, increased HGP, and decreased HGU [56,118]. In healthy men, MRS showed that the liver lipid content was positively correlated with HGP, independent of obesity [119]. In obese subjects without diabetes, MRS revealed that the increased hepatic lipid content was associated with insulin resistance in the liver, skeletal muscle, and adipose tissues [120]. In patients with diabetes or nonalcoholic fatty liver disease, PET and ^{1}H-MRS showed that the liver fat content was inversely associated with HGU and positively associated with HGP [115,121–123]. DEXA and ^{1}H-MRS revealed that HGP in obese white women was higher than that in black women, and the liver fat content in obese white females was higher than that in obese black females [124]. ^{1}H-MRS demonstrated that both pioglitazone and rosiglitazone suppressed HGP, and reduced the hepatic lipid content in obese diabetic patients [125,126].

Beyond the liver, increased lipid deposition has also been proposed to play a crucial role in the development of insulin resistance in the skeletal muscle [127–129]. ^{2}H-DEXA scans revealed that a 21-d bed rest increased fat deposition and reduced insulin sensitivity in the skeletal muscle of healthy subjects [130], suggesting that an increase in lipid content precedes insulin resistance in the skeletal muscle. Further, ^{1}H-MRS and CT imaging in patients with diabetes or metabolic syndrome showed that lipid content in the skeletal muscle of these patients was higher than that in healthy subjects of various races [131–133]. Moreover, CT, PET, and MRS using [6,6-$^{2}H_2$]glucose, [2,2-$^{2}H_2$]palmitate, or ^{18}F-FDG as tracers further indicated that visceral adiposity could play a critical role in triggering fat deposition in the skeletal muscle and subsequent insulin resistance [120,134,135].

Real-time assessment of postprandial fat storage in the liver and skeletal muscle using ^{13}C-MRS revealed that fatty acid uptake by these organs was elevated in T2DM patients, which resulted in excessive lipid stores and, consequently, exaggerated insulin resistance therein [136]. Weight loss significantly reduced skeletal muscle fat content and insulin resistance in obese patients, as indicated by single voxel ^{11}H-MRS [137]. MRI and ^{18}F-FDG PET imaging showed that bariatric surgery resulted in sustained weight loss, reduced lipid deposition, and enhanced insulin sensitivity in various tissues, including the skeletal muscle in morbidly obese patients [138]. These imaging-based findings suggest that increased lipid deposition is the key factor triggering insulin resistance in the liver and skeletal muscle.

Mitochondrion is the organelle in which tricarboxylic acid (TCA) cycle and oxidative phosphorylation take place. Mitochondrial dysfunction, including increased generation of reactive oxygen species and impaired ATP production, plays a critical role in the development of insulin resistance in peripheral tissues [139–144]. Jones et al. [107] used ^{2}H- and ^{13}C-MRS to show that the TCA cycle flux rate in the human liver was 5.4 ± 1.4 μmol·$kg^{-1}\cdot min^{-1}$. By using ^{13}C-MRS, Befroy et al. [145] determined the mean rates of hepatic TCA cycle flux (V_{TCA}) and anaplerotic flux (V_{ANA}) to be 0.43 μmol $(g\text{-liver}\cdot min)^{-1}$ and 0.60 μmol $(g\text{-liver}\cdot min)^{-1}$, respectively, in healthy and lean human liver. The difference in hepatic TCA flux rate reported in these studies should be validated further.

By using ^{31}P-MRS, Sharma et al. [146] reported that ATP levels in the liver of obese patients with non-alcoholic fatty liver disease and insulin resistance were lower than those in non-obese healthy subjects. Similar analysis using ^{31}P-MRS showed that hepatic ATP synthesis rate in diabetic patients was lower than that in healthy subjects. Moreover, hepatic ATP synthesis rate was positively correlated with the peripheral and hepatic insulin sensitivity, but negatively correlated with the body mass index and fasting plasma glucose [147]. Likewise, ^{31}P-MRS showed that in the skeletal muscle of T2DM patients, phosphocreatine and ATP levels were lower than those in healthy subjects [148]. ^{31}P-MRS also revealed that insulin-stimulated ATP synthesis rate was reduced in insulin-resistant offspring of parents with T2DM [149]. Furthermore, phosphocreatine level in the skeletal muscle was negatively correlated with glycated hemoglobin A1c (HbA1c), fasting blood glucose, and insulin sensitivity [148].

Clearly, these imaging-based observations demonstrate that increased lipid deposition plays an important role in triggering mitochondrial dysfunction, which is one of the key mechanisms of insulin resistance in the liver and skeletal muscle. Imaging lipid content in the

liver and skeletal muscle is important for evaluating insulin sensitivity in these organs, and for predicting the risk of diabetes. Lifestyle change, such as endurance exercise, should be considered as an effective strategy to reduce lipid content in the liver and skeletal muscle when certain thresholds are reached in subjects with or without T2DM.

3.4. Imaging glucose excretion from the kidney

Generally, when the blood flows through the kidney, most of the glucose is reabsorbed by a sodium glucose co-transporter 2 (SGLT2) in the renal cortex. Recently, SGLT2 inhibitors have been used to treat T2DM patients by inducing glucose excretion from the kidney [74,150]

Microscopic autoradiography revealed that dapagliflozin, an inhibitor of SGLT2, could specifically bind to SGLT2 in the proximal renal tubules in rat and mouse kidney, explaining the direct mode of action of SGLT2 inhibitors [151]. By using PET imaging with the SGLT-specific tracer ^{11}C-methyl-d-glucoside, glucose reabsorption in the renal cortex and its inhibition by SGLT2 inhibitor ipragliflozin was visualized in rats [152], further confirming the action mode of SGLT2 inhibitors. In human and in animal models, treatment with SGLT2 inhibitors markedly increases glucose excretion in urine [153,154]. Further, ^{1}H-MRS revealed that a 24-week treatment with ipragliflozin improved hyperglycemia by ameliorating visceral adiposity in T2DM patients [155,156]. In T2DM patients, ^{23}Na-MRI indicated that a 6-week treatment with the SGLT2 inhibitor dapagliflozin reduced sodium content in the skin and skeletal muscle [157], which exerts additional beneficial effects for renal and cardiovascular diseases. In support, SGLT2 inhibitors have been shown to exert beneficial effects on heart failure and non-diabetic kidney diseases independent of their hypoglycemic effects [158,159]. Dapagliflozin also stimulates glucose uptake, represses pro-inflammatory chemokine secretion, and improves the differentiation of human epicardial adipose tissue cells [160]. In Japanese T2DM patients, DEXA scans revealed that a 12-week treatment with the SGLT2 inhibitor, luseogliflozin, reduced skeletal muscle mass and body fat [161]. The observed reduction in skeletal muscle mass suggests the need for further studies to evaluate the potential effects of SGLT2 inhibitors on the muscle mass of diabetic patients [161].

Overall, these imaging findings indicate that inhibiting glucose reabsorption by the kidney to induce glucose excretion in urine is the main mechanism underpinning the hypoglycemic effect of SGLT2 inhibitors. In addition to targeting glucose uptake and glucose production, increasing glucose excretion (in urine or *via* other potential pathways) holds great promise for the treatment of diabetes. In particular, targeting SGLT2 to induce glucose excretion from the kidney is insulin-independent. Thus, SGLT2 inhibitors can be recommended to diabetic patients with severe insulin resistance and/or pancreatic β-cell failure as mono-therapy or combination therapy with other anti-diabetic drugs.

3.5. Imaging glucose metabolism in the hypothalamus and other tissues

Hypothalamus is the key tissue that controls the energy balance of the entire body, and also plays important roles in regulating glucose homeostasis by sensing glucose and lipid levels [58,59]. MRS and other MRI strategies revealed that hypothalamic dysfunctions, such as inflammation and gliosis, were associated with insulin resistance and obesity in humans [162,163].

The cerebral blood flow in the hypothalamus is linked to global insulin sensitivity in humans [164,165]. Arterial spin labeling MR perfusion imaging showed that high-fat diet pronouncedly reduced the cerebral blood flow in the hypothalamus to inhibit its activity in healthy humans [166]. Furthermore, MRI revealed increased brain perfusion and no change in hypothalamic perfusion in lean adolescents in response to oral glucose ingestion, while increased hypothalamic blood flow was observed in obese adolescents [167]. This finding suggests that, in obesity, failure of glucose to repress hypothalamic activity results in excessive energy consumption, thereby promoting further weight gain.

GLUT4 is the main glucose transporter isoform in the hypothalamic neurons. GLUT4 senses hypothalamic glucose levels (approximately 1.5 mmol/L under euglycemia, increasing to 4.5 mmol/L after glucose infusion, as revealed by MRS imaging) to control the blood flow and whole-body glucose metabolism [168]. MRI analysis indicated that glucose load resulted in a decrease in the hypothalamic regional cerebral blood flow compared to fructose load, with an increase in the systemic glucose, insulin, and GLP-1 levels in healthy humans [169,170]. Furthermore, in addition to different responses to various nutrients, PET imaging using ^{18}F-FDG revealed that glucose metabolism in the hypothalamus in females was faster than that in males [171].

MRI revealed that in patients with high visceral adipose tissues, the brain reaction to insulin was selectively impaired in the hypothalamus, possibly altering the homeostatic balance and reducing the inhibitory control over feeding, culminating in overeating [164]. Further, MRI indicated that glucose failed to inhibit the hypothalamic activity in obese patients without diabetes, in contrast to lean healthy subjects [172]. MRI and magnetoencephalography revealed that insulin acted on the hypothalamus to suppress HGP in healthy but not obese human subjects [164,173–175]. MRI analysis also showed that the impaired hypothalamic responsiveness to glucose ingestion in obese diabetic patients was normalized by a short-term calorie restriction [176,177]. Several other imaging studies confirmed the notion that enhanced hypothalamic insulin sensitivity can greatly contribute to the beneficial effects of calorie restriction or weight loss on hyperglycemia in human [176,178]. In support of these clinical imaging observations, knockdown of an insulin receptor in the hypothalamus increased food intake, subcutaneous fat, and HGP in mice [179]. Collectively, these observations indicate that the failure of insulin or glucose to repress hypothalamic activity results in overeating and increased HGP.

Interestingly, MRI revealed that ingesting glucose at 0°C and 22°C, and water at 0°C, reduced the hypothalamic activity, which was associated with increased satiation in healthy man, whereas ingestion of water at room temperature increased the hypothalamic activity [180]. Importantly, ingestion of glucose at 0°C resulted in a significantly greater repression of the hypothalamic activity than ingestion of glucose at 22°C [180]. However, further studies are needed to verify whether ingestion of food at low temperature could be recommended to obese or diabetic patients.

Hypoglycemia is one of the major risks of diabetic patients who receive insulin therapy. PET imaging using ^{18}F-FDG showed that in mice, upon insulin stimulation, glucose transport from the plasma to the brain increased with decreasing plasma glucose levels, particularly those below 2.5 mmol/L [181]. ^{11}C-O-methylreboxetine analysis has confirmed the notion that noradrenergic activation is important for modulating brain responses to insulin-induced hypoglycemia in human [182]. Recently, expression of GLP-1 receptors in various regions of the human brain, including the hypothalamus, has been reported [183]. One study using MRI indicated that GLP-1 affected the central regulation of appetite in lean males [184]. Another MRI study further revealed that the hypothalamic response was a crucial factor impacting the effect of exenatide, a GLP receptor agonist, on the repression of food intake in obese adults [185].

An imaging system involving optical measurement of skin autofluorescence, which likely emanates from accumulated advanced glycation end products, has been developed [186,187]. This imaging system has been used to noninvasively screen subjects of various races with abnormal glucose metabolism [188–190]. The approach has some advantages over traditional methods, such as measurements of the blood glucose and HbA1c levels.

In summary, imaging analyses have demonstrated that hypothalamus is an important target tissue of insulin in human, and plays important roles in glucose sensing and maintaining global energy homeostasis. Insulin resistance in hypothalamus triggers obesity, systemic

insulin resistance, and HGP. Furthermore, noninvasive measurements of skin auto-fluorescence might constitute a novel method for screening abnormal glucose metabolism in a large population. In addition, imaging technologies have demonstrated that targeting various steps of glucose metabolism, including glucose uptake, production, and excretion, could constitute an effective strategy for treating T2DM in human. Imaging changes in the function of various organs might inform the choice of hypoglycemic drugs for different individuals.

4. Molecular imaging of diabetic complications

Diabetes is usually associated with, or coexists with, several chronic vascular and nonvascular complications, which affect multiple organs and are thus responsible for the morbidity and mortality associated with this condition. Vascular complications include microvascular (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular complications (e.g., coronary artery disease, cerebrovascular disease, and peripheral vascular disease). Nonvascular complications encompass gastroparesis, sexual dysfunction, and loss of skin integrity. [2].

The complications of diabetes severely affect the quality of life. Therefore, early prediction and diagnosis of diabetic complications, and early identification of individuals at risk of developing such complications would greatly improve the care of diabetic patients. Currently, many molecular imaging techniques have been used in the preclinical studies and clinical practice for the diagnosis of diabetic complications, the monitoring of their progresses and the evaluation of disease prognosis (Fig. 3, Table 2). The following sections briefly summarize representative examples of using imaging approaches for the detection of diabetic complications in specific organs or tissues.

4.1. Imaging diabetes-related coronary artery disease

Cardiovascular diseases are the most common cause of death in patients with diabetes, and are responsible for 70% of diabetes-related deaths: of these, approximately 40% are from ischemic heart disease, 15% from other forms of heart disease, principally congestive heart failure, and approximately 10% from stroke [191,192].

Compared to invasive procedures, such as catheter angiography, several noninvasive imaging methods, such as carotid artery ultrasound

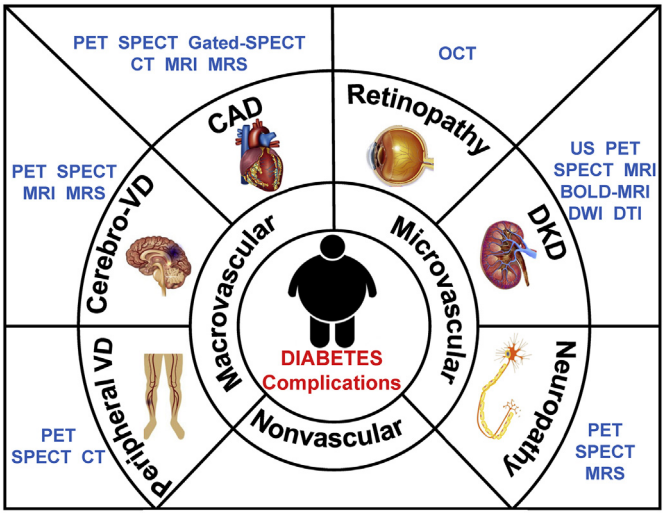

Fig. 3. Schematic overview of the major diabetic complications and representative imaging approaches that have been used for the noninvasive imaging of diabetic complications. VD, vascular disease; CAD, coronary artery disease; DKD, diabetic kidney disease; PET, positron emission tomography; SPECT, single-photon-emission computed tomography; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; BOLD-MRI, blood oxygenation level-dependent MRI; DWI, diffusion weighted imaging; DTI, diffusion tensor imaging; OCT, optical coherence tomography.

[193–195], cardiac CT [196–198], and MRI [199], have been used to detect atherosclerotic lesions in diabetic patients. In general, cardiac CT with high temporal and spatial resolution is widely available. However, the technique is compromised by the occurrence of severe image artifacts from certain prosthetic heart valves, the fact that the heart rate has to be regulated by β-blockers prior to imaging for the patient with very high heart rate, or scanners with relatively low temporal resolution [200].

In addition to structural imaging, such as CT, molecular imaging techniques involving PET and SPECT of atherosclerosis have also been extensively investigated. Molecular imaging of biomarkers related to atherosclerosis, such as coronary artery calcification (CAC) and inflammation, have been widely used.

CAC is a well-established biomarker of atherosclerosis, and the presence of CAC has been shown to have prognostic utility as a screening tool in asymptomatic populations [201]. ^{18}F-NaF has been initially used as a PET radiotracer for detecting tumor bone metastasis because of its high affinity to calcium apatite crystals. In addition to bone scanning, ^{18}F-NaF is also used for CAC screening. ^{18}F-NaF may be used for the imaging of molecular calcium deposits in the early stages of plaque formation, and has the potential for identifying micro-calcifications within nascent atherosclerotic foci that are invisible to CT imaging (Fig. 4A–C) [202,203]. Moreover, the accumulation of ^{18}F-NaF correlated with the calcium score, although 40% of patients with scores >1000 displayed no radiofluoride uptake in one study [204]. Coronary arterial ^{18}F-NaF uptake was also found to be related to the total plaque burden, coronary event history, and specific features of coronary atherosclerosis determined by CT analysis. Therefore, ^{18}F-NaF PET imaging in combination with cardiac CT may constitute a new molecular imaging approach to identify high-risk patients and coronary atherosclerotic lesions [205].

^{18}F-FDG, which is the most commonly used PET radiotracer in the clinic, has been extensively used for identifying inflammation associated with atherosclerotic plaques [201,206]. ^{18}F-FDG PET signal during imaging indicates increased metabolic activity of the macrophages within atherosclerotic lesions, and may also reflect contributions from local hypoxia and the efficiency of tracer delivery by the microcirculation [206]. ^{18}F-FDG PET analysis of 90 age- and sex-matched subjects with different glucose tolerance revealed that the maximum target-to-background ratio in patients with impaired glucose tolerance and T2DM was higher than that in the control group [207]. These findings indicate that ^{18}F-FDG PET imaging has a potential for early detection of vulnerable plaques and for determining the risk stratification of patients with abnormal glucose metabolism.

Serial ^{18}F-FDG PET scans in 56 patients with impaired glucose tolerance or diabetic patients with carotid atherosclerosis were performed to compare the effect of an insulin sensitizer (pioglitazone) with that of an insulin secretagogue (glimepiride) on atherosclerotic plaque [208]. Although both treatments reduced fasting plasma glucose and HbA1c levels to a comparable extent, pioglitazone rather than glimepiride reduced atherosclerotic plaque inflammation, as evidenced by ^{18}F-FDG PET imaging (Fig. 4D) [208]. This finding suggested that pioglitazone might constitute a promising strategy for the treatment of atherosclerotic plaque inflammation in patients with impaired glucose tolerance or diabetic patients. Taken together, these studies confirmed the importance of ^{18}F-FDG PET in the early diagnostic imaging of atherosclerotic plaques, and in monitoring the therapeutic effect of drugs for the treatment of atherosclerotic plaques in diabetic patients.

However, the use of ^{18}F-FDG PET for the detection of inflammation in atherosclerosis has some limitations. For example, ^{18}F-FDG reflects the metabolism of glucose, and as such, it is not specific to inflammation, and high uptake of ^{18}F-FDG by cells of the myocardial muscle may hamper the interpretation of coronary signals [209]. To overcome the potential limitations of ^{18}F-FDG, noninvasive detection of atherosclerotic plaques by using several other PET and SPECT radiotracers has been extensively investigated in both preclinical and clinical studies. These include macrophage-specific PET radiotracers, such as translocator protein-

Table 2
Summary of representative radiotracers for PET or SPECT imaging of diabetic complications as illustrated in the present review.

Diabetic complications	Radiotracer	Target or mechanism of action	Imaging modality	Preclinical/clinical	Ref.
Coronary artery disease	^{18}F-NaF	Calcium deposition	PET	Clinical	[202–205]
	^{18}F-FDG	Hexokinase	PET	Clinical	[207,208]
	^{11}C-PK11195	Peripheral benzodiazepine receptor	PET	Clinical	[210]
	^{68}Ga-DOTATATE	Somatostatin receptors	PET	Clinical	[211]
	^{18}F-FLT	Thymidine kinase	PET	Preclinical/clinical	[212]
Cardiomyopathy	^{99m}Tc-sestamibi	Myocardial perfusion	SPECT	Clinical	[219]
	^{201}Ti-chloride	Myocardial perfusion	SPECT	Clinical	[219,220]
	^{18}F-FDG	Hexokinase	PET	Clinical	[220]
	^{82}Rb-chloride	Myocardial perfusion	PET	Clinical	[222]
Cardiac autonomic neuropathy	^{123}I-MIBG	Adrenergic receptor	SPECT	Clinical	[226,227]
	^{11}C-HED	Adrenergic receptor	PET	Clinical	[228]
	^{18}F-LMI1195	Adrenergic receptor	PET	Preclinical/clinical	[229–232]
Kidney disease	^{15}O-H_2O	Renal blood flow	PET	Clinical	[239]
	^{82}Rb-chloride	Renal blood flow	PET	Clinical	[240]
	^{99m}Tc-DTPA	Renal blood flow	SPECT	Clinical	[241]
	^{99m}Tc-MAG3	Renal blood flow	SPECT	Clinical	[242]
Brain abnormalities	^{99m}Tc-HMPAO	Blood flow	SPECT	Clinical	[252,253]
Foot complications	^{18}F-FDG	Hexokinase	PET	Clinical	[259,260]
	^{99m}Tc-HMPAO-WBCs	Inflammation	SPECT	Clinical	[261–263]

^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FLT, ^{18}F-fluorothymidine; ^{123}I-MIBG, ^{123}I-metaiodobenzylguanidine; ^{11}C-HED, ^{11}C-hydroxyephedrine; ^{99m}Tc-DTPA, ^{99m}Tc-diethylenetriaminepentaacetic acid; ^{99m}Tc-mercaptoacetyl-triglycine, ^{99m}Tc-MAG3; ^{99m}Tc-HMPAO, ^{99m}Tc-hexamethylpropylene amine oxime; WBC, white blood cell.

targeting radiotracers (e.g., ^{11}C-PK11195 [210]), somatostatin receptor-binding tracers (e.g., ^{68}Ga-DOTATATE [211]), ^{18}F-fluorothymidine [212], and other radiotracers that target IL-2, integrin receptors, and endothelial vascular cell adhesion molecule-1 [206,209,213]. These specific radiotracers are expected to have broad applications in the diagnostic detection and treatment monitoring of diabetes-associated coronary artery disease (CAD).

4.2. Imaging diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is an alteration of the cardiac structure and/or function in the absence of CAD, and valvular or hypertensive heart disease, and an important factor that increases cardiovascular morbidity and mortality associated with diabetes [214]. DCM is thought to be caused by the damage to the myocardial tissues associated with hyperglycemia, dyslipidemia, and inflammation in diabetes [215]. Echocardiographic techniques, such as tissue Doppler imaging and speckle tracking echocardiography, are the current gold standards for the diagnosis of structural cardiac disorders, and can provide reliable information for identifying structural abnormalities in the early stages of DCM [215,216].

Cardiac MRI is also useful for the diagnosis of structural and functional disorders of the myocardium. The temporal and spatial resolution provided by MRI is higher than that of echocardiography, which can provide additional information about myocardial fibrosis and subclinical ischemia, as premature markers of cardiac dysfunction [217]. Gadolinium-enhanced MRI, with spatial and contrast resolution superior to non-contrast-enhanced MRI, can detect unrecognized myocardial infarction and improve the risk stratification of diabetic patients without previous history of CAD, with normal electrocardiogram, and normal left ventricular systolic function [218].

Nuclear imaging using gated-SPECT or PET is another important tool for molecular imaging of cardiomyopathy, based on quantitative assessment of the myocardial blood flow of the injected radiotracers. Gated-SPECT imaging using ^{99m}Tc-sestamibi [219] or ^{201}Ti-chloride [219,220] can provide reliable and highly reproducible information on myocardial perfusion, and an assessment of the left ventricular global and regional function, although reports of its use in diabetic patients are currently limited [216,217]. PET imaging allows a more accurate quantitative assessment of the blood flow and myocardial metabolic abnormalities than SPECT, especially in obese diabetic patients or patients with CAD who cannot undergo gated-SPECT analysis [221]. ^{18}F-FDG PET imaging can also be used for the analysis of glucose metabolism in diabetic patients [220]. However, the main limitation of ^{18}F-FDG imaging is that it is influenced by metabolic impairments in the diabetic patients. Uptake of a potassium analogue PET radiotracer ^{82}Rb-chloride is not influenced by abnormal glucose metabolism, and is therefore more suitable for PET imaging of the myocardial blood flow in diabetic patients. In a recent study, ^{82}Rb-chloride PET/CT imaging was used to show that the myocardial blood flow reserve in patients with T2DM and systolic heart failure was lower than that in non-diabetic patients with systolic heart failure [222].

4.3. Imaging diabetic cardiac autonomic neuropathy

Cardiac autonomic neuropathy (CAN) is one of the most common diabetes-associated complications. It increases the risk of myocardial infarction and sudden cardiac death in diabetic patients. Early diagnosis of CAN, using either spectral analysis of the heart rate variability or imaging techniques, may improve patient management [223]. Among diabetic patients with the complication of CAN, the highest mortality rates are associated with advanced deficits of the cardiovascular sympathetic innervation. Therefore, PET and SPECT imaging, the only currently available direct approaches for assessing the cardiac sympathetic deficits, are highly desirable [224].

The use of several radiotracers, such as radiolabeled analogues of norepinephrine (e.g., ^{123}I-metaiodobenzylguanidine (MIBG) or ^{11}C-hydroxyephedrine), which can be actively taken up by the sympathetic nerve terminals of the heart, has been investigated for PET and SPECT imaging of CAN in diabetic patients [223]. Clinical studies using these tracers have provided valuable information on cardiac sympathetic dysfunction in diabetic patients [225]. For example, ^{123}I-MIBG imaging revealed that the cardiac sympathetic activity in diabetic patients with heart failure was lower than that in non-diabetic patients with heart failure [226]. Furthermore, ^{123}I-MIBG-imaged abnormalities were associated with left ventricular dysfunction in diabetic patients [227]. PET imaging using ^{11}C-hydroxyephedrine has also been used to characterize the left ventricular sympathetic innervation in diabetic patients by assessing regional disturbances in myocardial tracer retention and washout [228].

^{18}F-LMI1195 has been recently developed as a new PET radiotracer for cardiac neuronal imaging. It was designed as a benzylguanidine analogue, to act as a substrate for the noradrenaline transporter, enabling the evaluation of cardiac sympathetic neuronal function by PET imaging in animal models [229–231]. First-in-human study has revealed that ^{18}F-LMI1195 is well tolerated and yields a radiation dose comparable

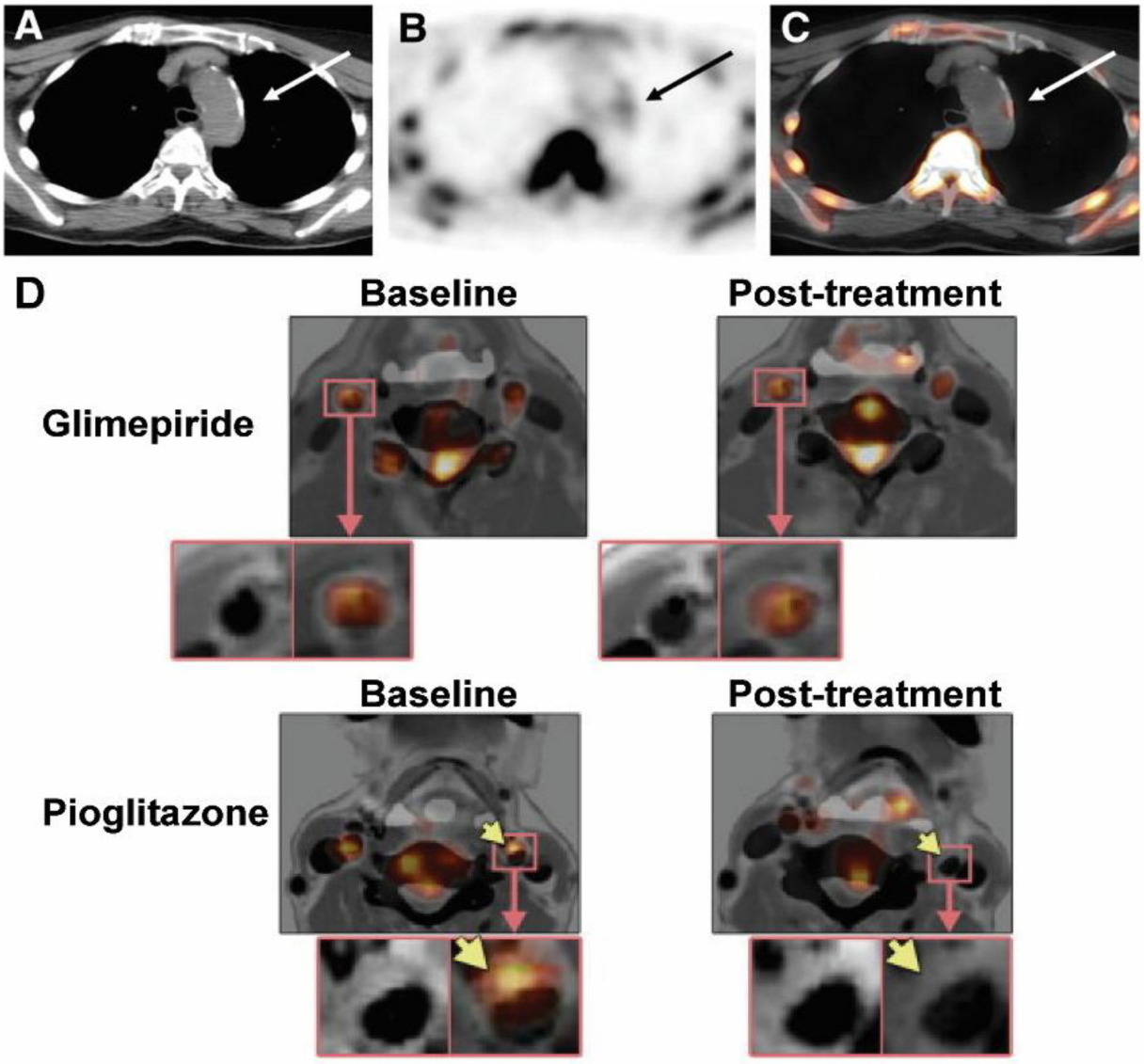

Fig. 4. Examples of PET imaging of coronary artery diseases. (A-C) Transaxial ^{18}F-NaF PET/CT imaging of calcification in the atherosclerotic lesion. (A) CT image. (B) PET image. (C) Fused PET/CT image. Arrows indicate calcified lesion. This research was originally published in [202] © SNMMI. (D) Treatment effects of pioglitazone and glimepiride on ^{18}F-FDG uptake in atherosclerotic plaques. Pioglitazone rather than glimepiride reduced atherosclerotic plaque inflammation, as evidenced by ^{18}F-FDG PET imaging. Adapted with permission from [208].

to that of other commonly used PET radiotracers. The kinetics of myocardial and adjacent organ activity demonstrated that ^{18}F-LMI1195 cardiac imaging with an acceptable patient radiation dose should indeed be feasible [232], suggesting that it might also be useful for the assessment of sympathetic innervation in diabetes.

Taken together, PET and SPECT imaging allows noninvasive and real-time assessment of cardiac autonomic innervation, and may become routine in diagnostic imaging, as well as monitoring the progression of CAN in patients with advanced diabetes mellitus to prevent myocardial infarction and sudden cardiac death.

Notably, the imaging modalities discussed above for noninvasive detection of CVDs are not specific to diabetic patients. However, the imaging approaches indeed allow early diagnosis and noninvasive visualization to facilitate improved management of diabetic CVDs.

4.4. Imaging diabetic kidney disease

Diabetic kidney disease (DKD) is one of the most common causes of end-stage renal disease, and significantly increases the morbidity and mortality of diabetic patients. Noninvasive detection of early stages of DKD is useful for a timely identification of patients at a greater risk of DKD progression, and can facilitate the evaluation of new therapies to treat DKD.

Kidney damage in diabetes is progressive. The kidney size may enlarge in the early stages of diabetic nephropathy because of hyperfiltration, and diminishes with the disease progression because of glomerulosclerosis [233]. Therefore, determination of the kidney size *via* ultrasound imaging can be used to predict the progression of renal disease in diabetic patients [234].

MRI is also an important tool for evaluating the structural and functional changes that accompany kidney damage in diabetic patients. In the past decade, several functional MRI strategies, such as blood oxygenation level-dependent MRI (BOLD-MRI), and diffusion weighted imaging (DWI) have been employed for the evaluation of DKD. Currently, most MRI studies focus on hypoxia using BOLD-MRI; fibrosis, using DWI; and tubular damage, using diffusion tensor imaging (DTI), which is a diffusion MRI approach that is more comprehensive than standard DWI [235]. For example, Lu et al. [236] compared the kidney DTI parameters in diabetic patients with those in healthy controls. They found that changes in medullary DTI assessments may serve as indicators of early

DKD [236], which warrants further larger clinical studies to refine and validate DTI parameters as biomarkers to identify diabetic patients at risk of DKD development.

In a recent study, a combination of Dixon imaging and DTI was performed for the evaluation of diabetic patients with early DKD. Renal lipid deposition and water molecule diffusion abnormalities in diabetic patients with early DKD were successfully detected, which suggested the possibility of noninvasive evaluation of early renal impairment in T2DM (Fig. 5A) [237]. Oxidative stress is a unifying cause for the onset and development of DKD. Keshari et al. [238] evaluated oxidative stress in the kidney in a diabetic mouse model using a hyperpolarized ^{13}C-dehydroascorbate, a novel endogenous redox sensor. The authors demonstrated that altered redox capacity was associated with diabetic renal injury, which suggested that such imaging approach might aid the prediction and early detection of DKD [238].

Currently, several radiotracers are used in preclinical or clinical studies to image the renal blood flow. These are ^{15}O-H_2O [239] and ^{82}Rb-chloride [240] for PET, and ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) [241] and ^{99m}Tc-mercaptoacetyl-triglycine (MAG3) [242] for SPECT, enabling noninvasive detection of the incidence of chronic kidney diseases, including DKD [243]. However, large-scale clinical studies are needed to investigate whether glomerular filtration rate determined by renal blood flow radiotracers is an early biomarker for the detection of DKD.

4.5. Imaging diabetic brain abnormalities

T2DM is associated with a high risk of cognitive dysfunction and dementia, although the mechanisms involved are not entirely clear [244]. Therefore, molecular imaging of the brain in diabetic patients or prediabetic subjects would facilitate the investigation of etiological factors that are associated with diabetic brain abnormalities. It would also enable early determination of the risk among patients, identifying early stages of disease progression for better management of diabetic patients.

MRI enables noninvasive evaluation of the anatomical and structural changes in the brain associated with diabetes. For example, total brain atrophy, white matter volume reduction, and smaller hippocampus, as well as cerebral infarcts and microbleeds can be detected in T2DM patients using MRI, demonstrating the role of MRI in monitoring the anatomical changes associated with T2DM [245]. The high spatial resolution of MRI allows definition of the regional distribution of brain atrophy in T2DM. In fact, MRI indicates that neurodegeneration rather than cerebrovascular lesions might be the primary driver of T2DM-related cognitive impairment. In a more recent study, Zhang et al. [246] performed structural network topological analysis using DTI in both T2DM patients and healthy controls. The authors demonstrated the occurrence of alterations of the white matter structural network, and the association between structural properties and cognitive state in T2DM patients before the onset of the complication [246].

Besides structural imaging, functional MRI and nuclear imaging (PET and SPECT) can also be used for molecular imaging of diabetic brain abnormalities, although the related studies are generally scarce [247]. For example, ^{1}H-MRS can be used to determine the resonance peaks of brain metabolites and neurotransmitters at different stages of cognitive impairment in T2DM patients [248,249]. Resting-state functional MRI (rs-fMRI) is also an important tool for *in vivo* studying brain functional connectivity, which showed disrupted default mode network, visual network and sensory motor network in diabetic patients compared with healthy controls (Fig. 5B) [250,251]. Blood flow radiotracers, such as ^{99m}Tc-HMPAO, have been used for SPECT imaging of the cerebral perfusions, and diminished blood flow has been shown in the brain of T2DM patients [252,253].

4.6. Imaging diabetes-related foot complications

The lifetime risk of developing foot complications for a patient with either T1DM or T2DM is estimated to be as high as 25% [254,255]. Ulceration is the most common diabetes-related foot complication, and it is related to the consequences of prolonged peripheral and autonomic neuropathy, as well as peripheral artery disease.

Diabetic foot lesions can become infected, which may be initially related to soft tissues, and then spread to the underlying bone, leading to diabetic foot osteomyelitis (DFO). DFO is the most serious complication of diabetic foot, which is responsible for the highest risk of lower extremity amputation and occasionally infection-related death [256]. Therefore, early identification and appropriate treatment of DFO are extremely important, and half of these amputations may be avoided by early diagnosis [60,257].

Although traditional plain X-ray is inexpensive and widely available, its sensitivity (approximately 60%) and specificity (approximately 80%) for the diagnosis of DFO are relatively low [256]. By contrast, the overall sensitivity and specificity of MRI are 90% and 80%, respectively [258]. However, the major limitation of MRI for DFO detection is that it cannot accurately differentiate infection from neuro-osteoarthropathy (Charcot foot) [60]. In addition, ^{18}F-FDG PET is superior to MRI for reliably differentiating Charcot's neuroarthropathy from osteomyelitis and when a foot ulcer is present [259]. ^{18}F-FDG has high uptake in inflammation sites, and ^{18}F-FDG PET/CT shows 74% sensitivity and 91% specificity in

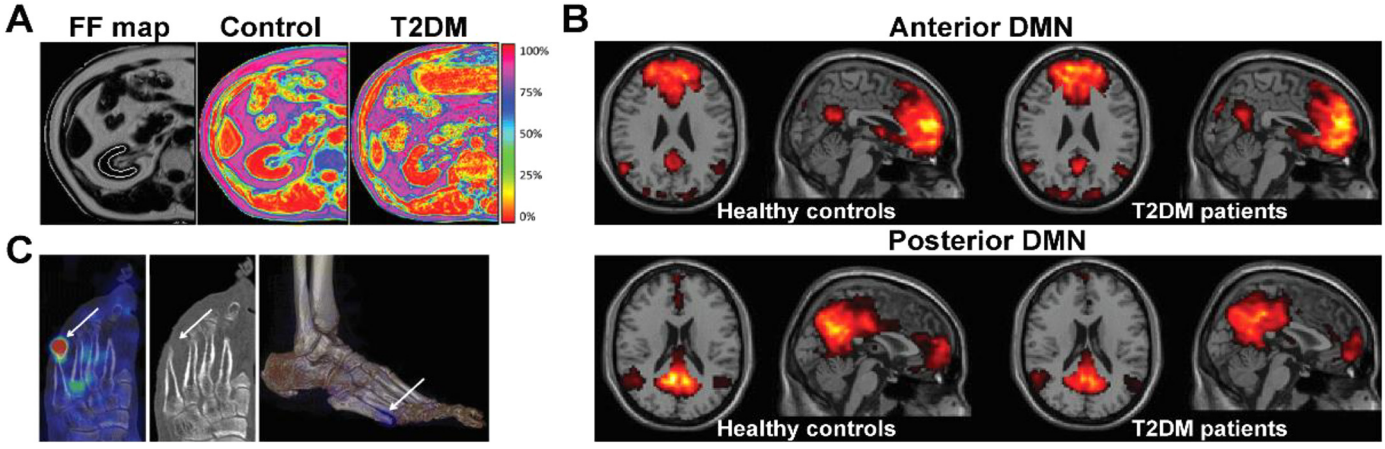

Fig. 5. Examples of noninvasive imaging of diabetes-associated kidney disease, brain abnormality, and foot complication. (A) Fat fraction (FF) map obtained from three-point Dixon imaging of the kidney and color-coded FF maps from a non-diabetic male and a T2DM male with microalbuminuria. Adapted with permission from [237]. (B) Representative resting-state functional MRI of the anterior default-mode network (DMN) (upper) and posterior DMN (lower) in healthy controls and T2DM patients. Adapted with permission from [251]. SPECT/CT imaging of ^{99m}Tc-labeled white blood cells in patients with diabetic foot osteomyelitis. Adapted with permission from [262].

patients with suspected DFO [260]. Notably, elevated blood glucose levels negatively influence the accuracy of ^{18}F-FDG PET imaging [256].

White blood cells (WBCs) can be radiolabeled with either ^{99m}Tc-HMPAO or ^{111}In-oxine for SPECT imaging of DFO in patients with diabetes. SPECT imaging using radiolabeled WBCs is highly specific for the accurate detection of DFO, and it can be used for predicting and guiding antibiotic therapy (Fig. 5C) [261–263]. Hybrid imaging such as SPECT/CT and SPECT/MRI can further increase DFO's sensitivity and specificity of radiolabeled WBCs due to the improved spatial resolution [264].

MRS can also be used for molecular imaging of diabetic food complications. For example, Suzuki et al. [265] developed ^{1}H- and ^{31}P-MRS and used them for clinical evaluation of the severity and extent of diabetic foot lesions. Patients with foot ulcer showed reductions in phosphocreatine-to-inorganic phosphate (PCr:Pi) ratios and peripheral nerve functions but an increase in fat-to-water ratio and intracellular pH compared with patients without foot ulcers. These findings indicate that ^{1}H- and ^{31}P-MRS can clarify the predisposing factors for foot ulcers [265].

Early detection of infection, as well as differentiating it from neuro-osteoarthropathy in the setting of a complicated diabetic foot, remains challenging. Advances in molecular imaging techniques are expected to play important roles in accurately identifying or excluding an infection and evaluating the extent of an existing infection to rationally design different treatments for DFO, soft tissue infection, or Charcot foot.

4.7. Imaging other abnormalities associated with diabetes

In addition to the conditions discussed above, diabetes is associated with several other complications, such as diabetic retinopathy, bone fragility, and even cancer. In most cases, these complications can be detected by routine imaging techniques designed for the imaging of a symptom in general, i.e., not specifically in relation to diabetes. For example, diabetic retinopathy can be detected by optical coherence tomography (OCT), and OCT angiography of the structural changes and vascular abnormalities of the retina [266]. Bone fragility and cancer can be detected by using routine imaging agents, as appropriate. The association of diabetes with the majority of ensuing complications is somewhat heterogeneous and nonspecific, and diabetic complications usually occur after the initiation of diabetes, with increasing duration of disease. Hence, noninvasive imaging of diabetic complications may play a limited role in the early diagnosis of diabetes. However, imaging of diabetes-associated complications would provide insight into the progression of changes associated with diabetes, which may help in tracking the progress of diabetes, exploring new treatment strategies, and informing better management of patients.

5. Conclusions and future perspectives

Development and refinement of imaging techniques that enable the early identification of risk factors for diabetes in special populations, monitoring diabetes progression noninvasively, as well as predicting or identifying acute and chronic diabetic complications are promising for the future management of this disease. For example, it has been suggested that molecular imaging of changes in BCM and β-cell function would be an ideal platform for making early diabetes diagnoses [24]. However, the accurate quantification of BCM *via* imaging, to date, remains elusive for many reasons, such as low affinity and selectivity of the available imaging probes for β-cells, the variability in subjects, and the very small populations and dispersed distribution of islet and β-cells in the pancreas [26,27,267]. Therefore, imaging approaches that target other cells or biomarkers mediating or affected by diabetes could represent alternative strategies for risk-stratifying patients with diabetes as well as aiding in better management of the disease.

Early detection of diabetes may lead to improved prognoses by providing opportunities for effective treatment or preventing its associated complications. The ideal approach to early detection of diabetes would be to identify patients at high risk of developing this disease before symptoms occur. For example, insulitis, which is characterized by the infiltration of activated T lymphocytes and macrophages in the pancreas, has been considered as a marker for early phase of T1DM, occurring before the development of its overt form [30]. Therefore, molecular imaging of insulitis could play an important role in identifying persons at high risk for developing T1DM, thereby allowing early interventions to delay or prevent the disease's clinical onset [22]. Unfortunately, the currently used approaches for molecular imaging of insulitis are primarily focused on MRI, PET, and SPECT imaging of the infiltrated lymphocytes and the vascular alterations associated with this condition. MRI using nanoparticles for insulitis imaging relies on the nonspecific accumulation of extravasated nanoparticles and phagocytosis by macrophages in an inflamed pancreatic islet; therefore, the specificity for insulitis using this methodology is generally limited. In addition, MRI has low sensitivity though it has very high spatial resolution in detecting individual islets. In contrast to MRI, both PET and SPECT have extremely high sensitivity; therefore, use of radiolabeled imaging agents with these technologies could quantitatively detect biomarkers *in vivo*. However, the biomarkers currently associated with insulitis are primarily focused on IL-2. Unfortunately, the IL-2 receptor is not specific for insulitis and is also expressed in pancreatic cancer cells. Moreover, the relatively low affinity of IL-2 to the IL-2 receptor makes radiolabeling of IL-2 unsatisfactory for PET or SPECT imaging. Therefore, biological research for new biomarkers associated with insulitis based on screening of genomic, epigenetic, proteomic, and metabolomic libraries is necessary for the eventual development of ideal agents for molecular imaging of insulitis.

In the past decade, advances in imaging technologies have provided real-time and dynamic images of glucose metabolism in various tissues, thereby extending our knowledge of the pathogenesis of diabetes and its complications substantially. Imaging technologies have unique advantages in identifying some important changes that precede diabetes and its complications, such as blood flow, glucose transporter translocation, hypothalamic and BAT activities, intracellular lipid content, muscle mass, and HGP. Therefore, combining imaging technologies with traditional methodologies for studying diabetes holds great promise for early diagnosis and treatment of diabetes and its complications.

Advances in delivery systems and imaging techniques have provided numerous opportunities to develop theranostic agents, which provide both diagnostic imaging and the means to deliver therapeutic agents for targeted therapy of several disorders, including diabetes and its complications [29]. For example, the development of targeted ultrasound technologies may allow guided specific delivery of microbubbles containing plasmid DNA for gene therapy to prevent DKD [268]. Further development of such theranostic agents may, therefore, facilitate more accurate image-guided diabetes therapies.

Notably, most of the imaging approaches currently used to detect diabetic complications, as discussed herein, are not specific for diabetes. However, advances in molecular imaging techniques could provide exceptional opportunities for detecting changes that precede the pathophysiological changes seen in diabetic complications. This would allow early identification of individuals at risk for developing diabetic complications. In addition, imaging techniques also allow noninvasive monitoring of the progression and development of diabetic complications at different stages. For example, longitudinal measurement of plaque inflammation in atherosclerosis can be obtained by repeated ^{18}F-FDG PET imaging [206], which holds promise for monitoring the progression of diabetes-associated CADs. Moreover, early identification of high-risk individuals could help guide the development of new anti-diabetic drugs. For example, an anti-diabetic drug that increased the risk of CVDs would not receive Federal Drug Administration approval [269]; therefore, real-time and dynamic imaging of CVDs could provide a house-keeping biomarker for evaluating side-effects, thereby speeding up the drug development process.

Currently, several imaging techniques have been extensively investigated for noninvasive imaging of diabetes and diabetic complications. Each imaging modality has its own advantages and disadvantages with respect to detection sensitivity, spatial resolution, and information provided (e.g., anatomical, cellular, or molecular). The combination of multiple modalities, such as PET, SPECT, MRI, MRS, ultrasound imaging, or CT, might provide a more complete picture of diabetes's characteristics. Therefore, integration of molecular, anatomical, and functional information to improve sensitivity, specificity, and accuracy for imaging the changes in diabetes and its complications, will be an important tool for future diabetes researchers targeting precise diabetes care.

Conflict of interest

All authors declare that they have no conflict of interest.

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