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Quantitative imaging biomarkers for the evaluation of cardiovascular complications in type 2 diabetes mellitus ☆

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a prevalent condition in aged populations. Cardiovascular diseases are leading causes of death and disability in patients with T2DM. Traditional strategies for controlling the cardiovascular complications of diabetes primarily target a cluster of well-defined risk factors, such as hyperglycemia, lipid disorders and hypertension. However, there is controversy over some recent clinical trials aimed at evaluating efficacy of intensive treatments for T2DM. As a powerful tool for quantitative cardiovascular risk estimation, multi-disciplinary cardiovascular imaging have been applied to detect and quantify morphological and functional abnormalities in the cardiovascular system. Quantitative imaging biomarkers acquired with advanced imaging procedures are expected to provide new insights to stratify absolute cardiovascular risks and reduce the overall costs of health care for people with T2DM by facilitating the selection of optimal therapies. This review discusses principles of state-of-the-art cardiovascular imaging techniques and compares applications of those techniques in various clinical circumstances. Individuals measurements of cardiovascular disease burdens from multiple aspects, which are closely related to existing biomarkers and clinical outcomes, are recommended as promising candidates for quantitative imaging biomarkers to assess the responses of the cardiovascular system during diabetic regimens.

1. Introduction

The cardiovascular system serves as the key infrastructure that delivers blood to the entire body, and it is vulnerable to metabolic diseases. A spectrum of cardiovascular diseases represent the major complications of diabetes and significant contributors to death and disability among people suffering from this endocrinological disorder (Polonsky, 2012). There are complicated pathological links between diabetes and cardiovascular diseases on the cellular and molecular levels. From an epidemiological perspective, diabetes has been weighted as an "equivalence" of preexisting coronary artery disease (CAD) in the risk assessment of clinical events (Haffner, Lehto, Ronnemaa, Pyorala, & Laakso, 1998). Patients with diabetes are considered to be at an early stage in the process leading to the development of heart failure (HF) even when there is no structural evidence of heart disease or any acute symptoms (Jessup et al., 2009). The prevalence of stroke in diabetic patients is significantly higher than in healthy controls (Janghorbani et al., 2007). Diabetic nephropathy, diabetic retinopathy and peripheral artery disease (PAD) are also frequently observed as severe and disabling manifestations of vascular damage in diabetic patients (Beckman, Creager, & Libby, 2002; de Boer et al., 2011; Zhang et al., 2010).

Current strategies for controlling the cardiovascular complications of diabetes primarily target a cluster of well-defined risk factors, such as hyperglycemia, lipid disorders and hypertension (Adler et al., 2000; Holman, Paul, Bethel, Matthews, & Neil, 2008; Saydah, Fradkin, & Cowie, 2004). For type 1 diabetes mellitus (T1DM), the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive interventions targeting those traditional cardiovascular risk factors satisfactorily resulted in a lower incidence of various clinical events compared to the conventional diabetic regimens (Nathan et al., 2005). However, type 2 diabetes mellitus (T2DM), which accounts for nearly 95% diabetes cases, seems to present different challenges. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) randomized clinical trial, aggressive glycemic intervention, strict lipid management and tight blood pressure control in patients with T2DM were unable to reduce the incidence of cardiovascular events or deaths to the extent that had been anticipated (Cushman et al., 2010; Gerstein et al., 2008; Ginsberg et al., 2010). These unexpected

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discrepancies between the observational studies and clinical trials led to debates regarding the efficacy and necessity of intensive therapies for T2DM. Because those disappointing clinical outcomes may possibly be due to irreversible organ damage in advanced T2DM patients, alternative clinical efficacy endpoints or biomarkers are highly desired to better evaluate the responses of the cardiovascular system to diabetes therapies.

Cardiovascular imaging is a powerful tool for quantitative cardiovascular risk estimation (Greenland et al., 2010). Both structural and functional imaging methods have been developed to noninvasively monitor the progression of various cardiovascular diseases (Wadwa, 2007). Recently, morphological changes associated with cardiovascular diseases have been accepted as primary endpoints in clinical trials assessing the effect of pharmacological treatments for atherosclerosis (Nicholls et al., 2011). Therefore, multi-disciplinary quantitative imaging methods are promising to provide new insights in the management of patients with T2DM from multiple aspects. Moreover, imaging biomarkers, which could be used to monitor the cardiovascular burden/risk and evaluate the benefits and harms of treatments, also have the potential to help to reduce the overall costs of health care for people with T2DM by facilitating the selection of optimal therapies.

In this review, we will focus on the recent findings of cardiac and vascular measurements associated with T2DM using state-of-the-art cardiovascular imaging techniques. By listing and comparing currently available noninvasive imaging approaches in clinical situations, we will also provide an overview of the progression of the cardiovascular complications in T2DM based on the usage of potential quantitative imaging biomarkers.

2. Noninvasive cardiovascular imaging techniques

2.1. Ultrasonography

Ultrasonography is a traditional method for imaging the cardiovascular system. Ultrasound imaging utilizes the interaction of high frequency (usually >20 KHz) sound waves with living tissue to produce an image of the structure or organ. Ultrasonography can also detect moving organs and blood flow in regions such as the heart based on Doppler effects. Combined with novel imaging reconstruction techniques, newer echocardiographic modalities have been introduced to clinics for the evaluation of cardiovascular diseases (Steeds, 2011). Tissue Doppler imaging (TDI) is a novel echocardiographic technique to measure the velocity of myocardial structures (Douglas et al., 2007). An new echo technique, speckle tracking echocardiography (STE), can track myocardial deformation (strain) during cardiac cycles to assess the function (both global and regional) of the left ventricle (LV) (Mondillo et al., 2011). Three-dimensional (3D) echocardiography (3DE) represents another advancement. This technique can acquire real-time 3D data for the comprehensive assessment of cardiac function and motion, including ventricular mass and ejection faction (EF) (Mor-Avi, Sugeng, & Lang, 2009). Contrast echocardiography is also applied to produce clear endocardial border definition for quantitative analysis of myocardial function, mass and blood flow (Olszewski et al., 2007; Tong et al., 2005). Intravascular ultrasound (IVUS) is an invasive imaging examination to put a special probe in the vascular lumen, such as coronary artery. It allows to detect vessel wall with a high resolution using ultrasound technology.

In addition to the application in the heart, ultrasonography also plays an important role in evaluating abnormalities in the whole vascular system. For surface vessels, such as the carotid artery and femoral artery, B-mode ultrasound may detect morphological changes, including thickening of the wall and occlusion (Schiano et al., 2012; Schulte-Altedorneburg et al., 2001). Transcranial Doppler (TCD) is a routine examination that helps diagnose intracranial vascular diseases by measuring the velocity of blood flow through the intracranial vessels (Nakae, Yokota, Yoshida, & Teramoto, 2011).

Ultrasound is generally considered safe. Currently, there are no reports of health risks associated with ultrasonography (except invasive procedures). However, not all tissues or structures in the body are suitable for the transduction of sound waves. Therefore, some tissue or organs cannot be reached by this examination because there is no optimal “acoustic window” (a pathway for sound waves between the probe and the target). Despite most ultrasonography examinations are cheap and convenient, IVUS is expensive and not available in some hospitals.

2.2. X-ray computed tomography (CT)

X-ray CT was first introduced to clinical practice in 1972. Tomographic imaging is a procedure of measuring the intensity attenuation of the X-ray beams from multiple orientations. A CT scanner is typically comprised of an X-ray source (X-ray tube) and a series of detectors arranged in a matrix sounding the target. Various imaging reconstruction algorithms are used to synthesize images from the distribution of X-ray beams from multiple projections. Over the past decades, CT has technically evolved and become one of the most common medical imaging methods in most hospitals.

Depicting the cardiovascular system requires fast imaging techniques. Taking advantages of spiral CT scanners equipped with multiple rows of detectors, an image can be obtained very quickly (less than 1 second) and such an advantage can “freeze” heartbeats and acquire images of the heart and its affiliated vessels. Therefore, Multidetector CT (MDCT) has wide applications in the cardiovascular system. For the heart, MDCT has been utilized for coronary CT angiography (CTA) to screen lumen stenosis, the major manifestation of CAD, in the coronary arteries (Miller et al., 2008).

Recent improvements in the hardware have further shortened the imaging time for the CT scan. For example, dual-source CT (DSCT) holds two X-ray tubes located at a 90° angle, allowing acquisition and reconstruction of cross-sectional images at 82.5 ms. MDCT with 320 row detectors has reached a coverage of 16 cm on the *z*-axis. Such a high speed and a large coverage are sufficient for cardiovascular imaging under most physiological circumstances.

Cardiac CT can be applied for scoring coronary calcification, a well-accepted quantitative imaging biomarker for overall cardiovascular risk estimation. In addition, CT can also be applied for detecting cerebral vascular disease, PAD and renal dysfunction.

However, the effects of ionizing radiation and iodinated contrast media are two major concerns for the safety of this method, especially in asymptomatic individuals at high risk of cardiovascular diseases.

2.3. Magnetic resonance imaging (MRI)

In general, body tissue contains a high concentration of protons. Water is the biggest source of H^+ ions in the body. The spin direction of protons will be aligned with the direction of a large static magnetic field (B0, provided by the scanner). When a radio frequency (RF) field (B1) at the resonance frequency is imposed, the protons will absorbed energy and flip the spin angle to precess synchronously (in phase). After the RF field is tuned off, the spins of the protons will be re-aligned in B0. This process is called longitudinal relaxation (T1 decay). T1 time is defined as the duration that it takes for the longitudinal magnetization to reach 63% of its final value, assuming a 90° RF pulse. At the same time, the protons also begin to dephase due to several effects including spin-spin interactions, magnetic field inhomogeneities, magnetic susceptibility and chemical shift effects. Such a dephasing is called transverse relaxation (T2 decay). T2 time is defined as the duration that it takes for the transverse magnetization to decay to 37% of its original value Bitar et al., 2006.