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MINIREVIEWS

Coronary atherosclerosis is already ongoing in pre-diabetic status: Insight from intravascular imaging modalities

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Abstract

Diabetes mellitus is a powerful risk factor of coronary artery disease (CAD), leading to death and disability. In recent years, given the accumulating evidence that prediabetes is also related to increasing risk of CAD including cardiovascular events, a new guideline has been proposed for the treatment of blood cholesterol for primary prevention of cardiovascular events. This guideline recommends aggressive lipid-lowering statin therapy for primary prevention in diabetes and other patients. The ultimate goal of patient management is to inhibit progression of systemic atherosclerosis and prevent fatal cardiovascular events such as acute coronary syndrome (ACS). Because disruption of atherosclerotic coronary plaques is a trigger of ACS, the high-risk atheroma is called a vulnerable plaque. Several types of novel diagnostic imaging technologies have been developed for identifying the characteristics of coronary atherosclerosis before the onset of ACS, especially vulnerable plaques. According to coronary angioscopic evaluation, atherosclerosis severity and plaque vulnerability were more advanced in prediabetic than in nondiabetic patients and comparable to that in diabetic patients. In addition, pharmacological intervention by statin therapy changed plaque color and complexity, and the dynamic changes in plaque features are considered plaque stabilization. In this article, we review the findings of atherosclerosis in prediabetes, detected by intravascular imaging modalities, and the therapeutic implications.

Key words: Diabetes; Prediabetes; Statin therapy; Coronary artery disease; Intravascular imaging modality

Core tip: Coronary artery disease is the principal cause of death and disability in not only diabetes but also prediabetes patients. Aggressive statin therapy is an established method of primary prevention of cardiovascular disease events in diabetic patients. According to the findings of coronary imaging modalities detecting atherosclerotic lesions, statin therapy in prediabetes may be beneficial for reducing atherosclerotic cardiovascular risk.

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INTRODUCTION

Diabetes is categorized as a metabolic disease char-acterized by hyperglycemia arising from abnormal insulin secretion from the pancreas and/or lack (or absence) of insulin action. Diabetes causes damage, dysfunction, or failure of various organs involving heart and blood vessels[1]. It is well known that diabetes promotes atherosclerotic disease of systemic and coronary arteries and increases the mortality rate from cardiovascular disease[2,3]. However, myocardial ischemia owing to coronary artery disease (CAD) is occasionally absent from the typical symptoms in patients with diabetes[4]. As a result, severe multivessel disease of the coronary arteries can manifest as silent myocardial ischemia before treatment is begun. A delayed recognition of CAD can worsen the prognosis in many diabetic patients[5]. Moreover, a recent study showed that impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are also causes of adverse cardiovascular events[6,7].

A goal of CAD management is to prevent cardiovascular diseases such as acute coronary syndrome (ACS). The principal pathogenesis of ACS is disruption of atheromatous coronary plaques and subsequent flow-limiting thrombus formation[8,9]. Plaque disruption, the trigger of this serious event, is pathologically classified as a rupture, and shallower intimal injury is termed erosion. Additionally, previous pathological studies showed that the majority of disrupted plaques have a large lipid core under a thin fibrous cap, hence the term thin-cap fibroatheroma (TCFA). Not only plaque rupture but also superficial calcified nodules are possible origins of ACS[10-12]. A vulnerable plaque is defined as a future high-risk plaque provoking ACS, and TCFA is representative of a vulnerable plaque. In recent years, novel intraco-ronary imaging modalities have been developed for detecting such vulnerable plaques.

Coronary angiography remains the gold standard for diagnosis of CAD and the following catheter intervention therapy. However, an angiogram represents a 2-dimensional silhouette of the coronary artery, and the angiogram does not supply certain information about the vessel wall components or the atherosclerotic plaque. Therefore, a coronary angiogram is not capable of detecting vulnerable plaques, including TCFA. Thus, supplemental CAD diagnostic modalities, including various intravascular imaging devices such as intravascular ultrasound (IVUS), coronary angioscopy (CAS), and optical coherence tomography (OCT), have been developed to discriminate each component of the plaque and to identify the presence of vulnerable plaques.

INTRACORONARY INVASIVE IMAGING MODALITIES

IVUS

IVUS is an intravascular imaging modality that supplies cross-sectional images of the coronary artery including the lumen and vessel wall. High-frequency (20-40 MHz) IVUS visualizes 3 layers of the vessel wall: the intima, media, and adventitia. IVUS allows *in vivo* qualitative measurements of the lumen and plaque area (and volume). Conventional grayscale IVUS images have major limitation of precise tissue characterization except calcification. Although a large plaque burden and microcalcifications, factors of plaque vulnerability, are detected by grayscale IVUS, this imaging system is not able to identify TCFA[13]. Because of these limitations, 3 modalities using radiofrequency analysis, virtual histology IVUS (VH-IVUS; Volcano Therapeutics, Rancho Cordova, CA, United States)[14], iMAP-IVUS (Boston Scientific, Santa Clara, CA, United States)[15], and integrated backscatter IVUS (IB-IVUS; YD Co., Nara, Japan)[16] are now available in clinical settings.

VH-IVUS takes into account detailed qualitative and quantitative assessment of the vessel wall components. The axial resolution of VH-IVUS is just about 150-250 μm. *Ex vivo* studies have shown that power spectrum-related parameters from raw backscattered ultrasound signals permit discrimination of plaque components[17]. These parameters are used in a classification scheme to yield a tissue color map for each plaque characteristic as follows: dark green indicates fibrous, yellow-green indicates fibrofatty, red indicates necrotic core, and white indicates dense calcium. VH-derived TCFA was defined as at least 3 consecutive frames with a plaque burden of at least 40% and without overlying fibrous tissue[18]. A recent prospective study using VH-IVUS, the PROSPET trial, has shown that the VH-derived TCFA with a minimal luminal area $\leqslant$ 4 mm^2 and a plaque burden $\geqslant$ 70% was the highest-risk plaque type leading to adverse cardiovascular events[19].

CAS

CAS using optic fibers is a technology that permits direct visualization of the lumen surface of the coronary artery and provides detailed information about plaque morphology and the presence of a thrombus with high resolution (50 μm). CAS clearly identifies irregularities of the lumen surface, such as ulceration, fissures, and tears. Disrupted plaques are involved in these plaques with irregularities (or complexity). In addition, CAS is an extremely sensitive detector of a thrombus. Angiographic stenosis of the lesion progresses despite healing of the silent plaque disruption in the nonculprit lesions[20].

Based on angioscopic analysis, an atherosclerotic plaque is defined as a nonmobile, protruding structure that can be clearly delimited from the adjacent vessel wall. Although a normal vessel wall appears glistening white, plaques can be yellow or white according to the surface color. The color of the plaque is classified semiquantitatively: (1) grade 0 is white; (2) grade 1 is

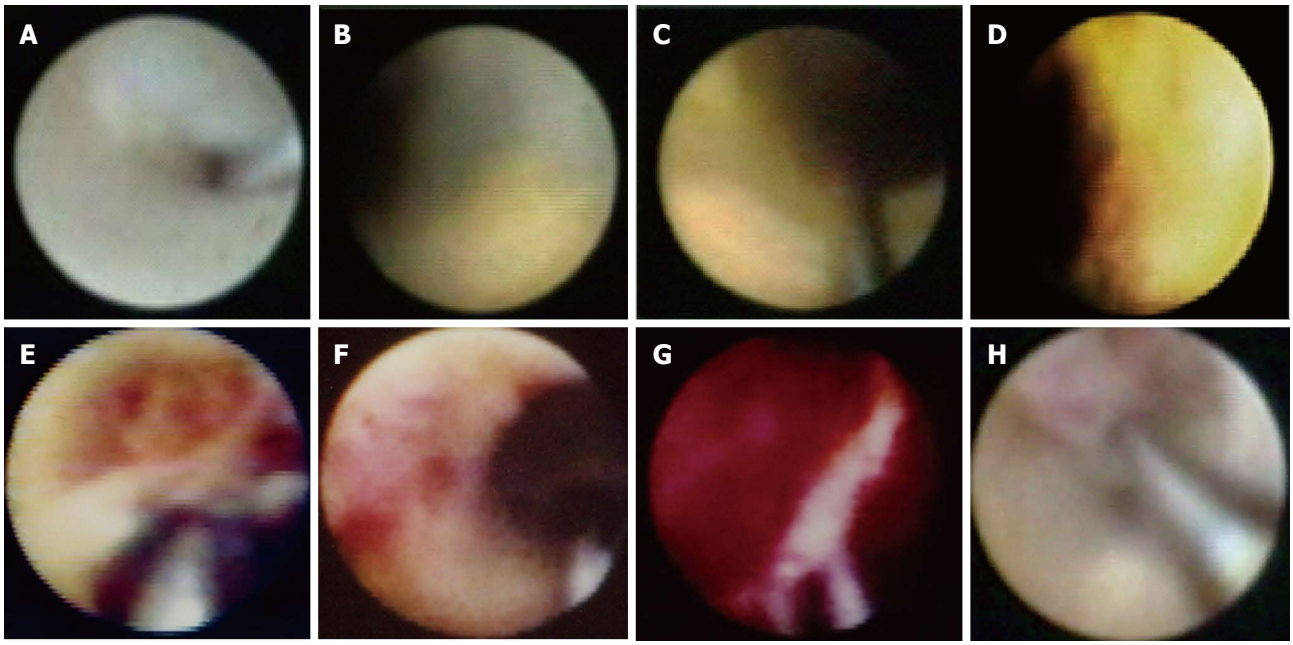

Figure 1 Classification of coronary angioscopic images. A: White plaque (yellow grade 0); B: Light yellow plaque (grade 1); C: Yellow plaque (grade 2); D: Intense yellow plaque (grade 3); E: Plaque rupture; F: Plaque erosion; G: Red thrombus; H: White thrombus.

light yellow; (3) grade 2 is medium yellow; and (4) grade 3 is intense yellow. The majority of yellow plaques contain lipid-rich tissue or a necrotic core according to comparative validation using OCT and IVUS. The grade of yellow plaques is affected by the thickness of the fibrous cap covering lipidic tissue. A high-intensity yellow plaque is identical to a TCFA. On the contrary, white plaques contain fibrous tissue or a thick fibrous cap covering the lipidic plaque[21-24]. Yellow plaques are detected not only in the culprit lesion but also in the nonculprit lesions of ACS[25-29]. Representative CAS images of plaques and thrombi are shown in Figure 1.

Prospective studies demonstrated that the incidence of ACS is higher in patients with intense yellow or multiple yellow plaques than in patients without yellow plaques[30,31]. These findings indicate that intense yellow or multiple yellow plaques detected by CAS might be vulnerable and could cause future coronary events.

OCT

OCT imaging employs a near-infrared range light source, at approximately 1300 nm. OCT has a 10-fold higher image resolution (10-15 μm) than IVUS, and its image quality is superior to that of other imaging devices. In addition, OCT provides accurate tissue characterization of the plaque. Normal vessel walls appear as a 3-layer structure on OCT images as well as IVUS. The vascular media is seen as a dark band delineated by the internal elastic lamina and external elastic lamina. Fibrous plaques consist of homogeneous and low-attenuation areas. Lipid-rich plaques exhibit a high-attenuation mass with a diffuse border. A calcified plaque is presented as high-attenuation mass with a clear border[32-36].

OCT is the only intravascular imaging technology with high spatial resolution that can measure the fibrous cap thickness[37,38].

CORONARY ATHEROSCLEROSIS INDUCED BY GLUCOSE METABOLISM DISORDER

Diabetes-associated coronary atherosclerosis as determined by imaging modalities

In diabetic patients, coronary angiograms characteristically reveal diffuse long lesions in multiple small vessels[39,40]. In an IVUS study, plaques in diabetic patients were characterized by an increased amount of dense calcium, a necrotic core, and a high frequency of VH-TCFA[41]. In addition, IVUS studies showed that the levels of hemoglobin A1c (HbA1c) was associated with atheroma volume and the severity of coronary atherosclerosis[42,43]. CAS showed that diabetes was an independent predictor of plaque disruption in the nonculprit vessel[44]. In an OCT study, patients with diabetes had large lipid plaque volumes and a high prevalence of calcified plaque and thrombus[45].

Possible mechanism of hyperglycemia-induced coronary atherosclerosis

Free fatty acids and insulin resistance, which are elevated by hyperglycemia, stimulate molecular mechanisms and alter the function and structure of blood vessels, including increased oxidative stress and activation of protein kinase C and the receptor for advanced glycation end products. Consequently, hyperglycemia decreases the availability of nitric oxide, increases the production of endothelin, and activates transcription factors such as

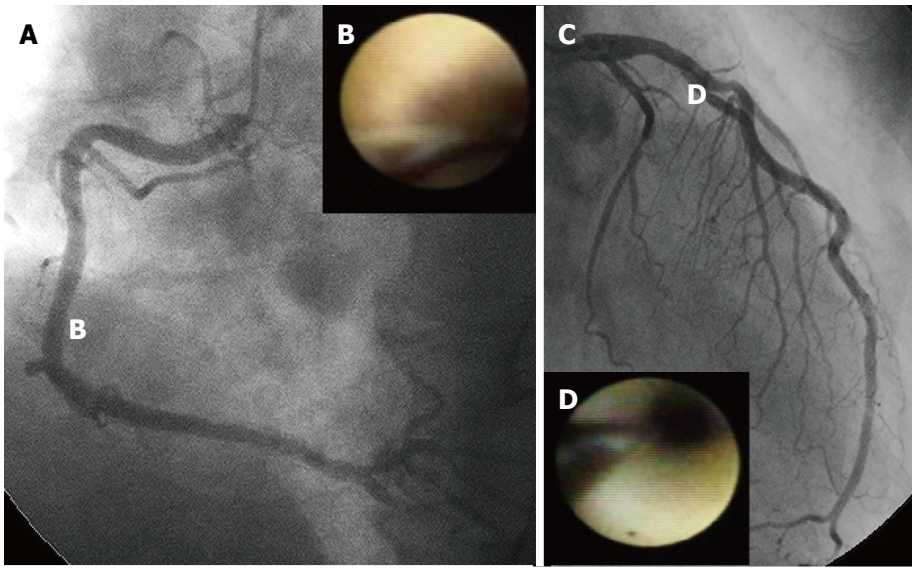

Figure 2 Representative images of nondiabetic patients. A and B: No angiographic stenosis was observed in the right coronary artery (A), whereas 1 yellow plaque was identified on angioscopy (B). The yellow intensity of these plaques was defined as grade 2; C: The left circumflex artery was too small to observe by coronary angioscopy, and a 75% stenosis was identified on angiography in the middle part of the left ascending artery; D: According to angioscopic findings, this lesion was evaluated as a grade 1 yellow plaque. In this case, the average number of yellow plaques per vessel was 1 (2 yellow plaques in 2 vessels), and the maximum yellow grade per coronary artery was 2.

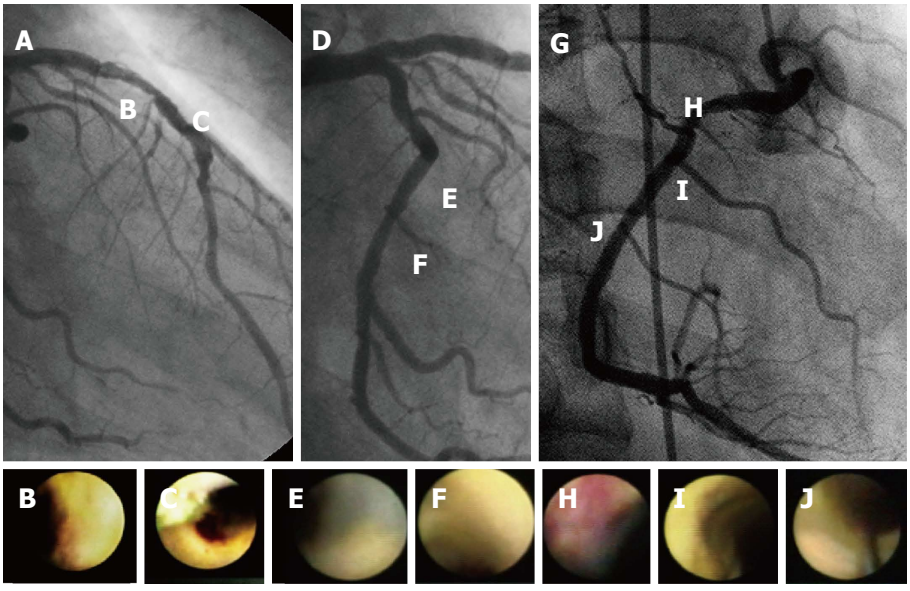

Figure 3 Representative images of prediabetes patients. A: A 50% stenosis and a 90% stenosis were identified on angiography in the middle part of the left ascending artery; B and C: According to angioscopic findings, both of these lesions were evaluated as grade 3 yellow plaques; D-F: No angiographic stenosis was observed in the left circumflex artery (D), whereas 2 yellow plaques were defined as grades 1 and 2, respectively (E and F); G-J: Significant stenosis was not observed in the right coronary artery (G), whereas an intramural red thrombus was observed at the proximal site (H), and 3 yellow plaques were identified on angioscopy (H–J). The yellow intensity of these plaques was defined as grades 1, 2, and 1, respectively. In this case, the average number of yellow plaques per vessel was 2.33 (7 yellow plaques in 3 vessels), and the maximum yellow grade per coronary artery was 3.

nuclear factor-κB and activator protein-1. These factors bring about systemic vasoconstriction and inflammation and promote systemic atherosclerosis[46-48]. A similar glucose metabolism disorder occurs in the prediabetic state[49,50].

The American Diabetes Association defines prediabetes as IFG, IGT, and HbA1c values ranging 5.7%-6.4%[1]. The patients with IFG and IGT should be informed of their increased risk for diabetes as well as CAD. The HbA1c value is more commonly used to diagnose diabetes, and an HbA1c level of 5.7%-6.4% also indicates a relatively high risk for future diabetes and CAD[1].

The low concordance in the relationships between IFG, IGT, and HbA1c, as well as the diagnoses of prediabetes using these parameters, accentuates the various dysfunctions of glucose metabolism. A dys-

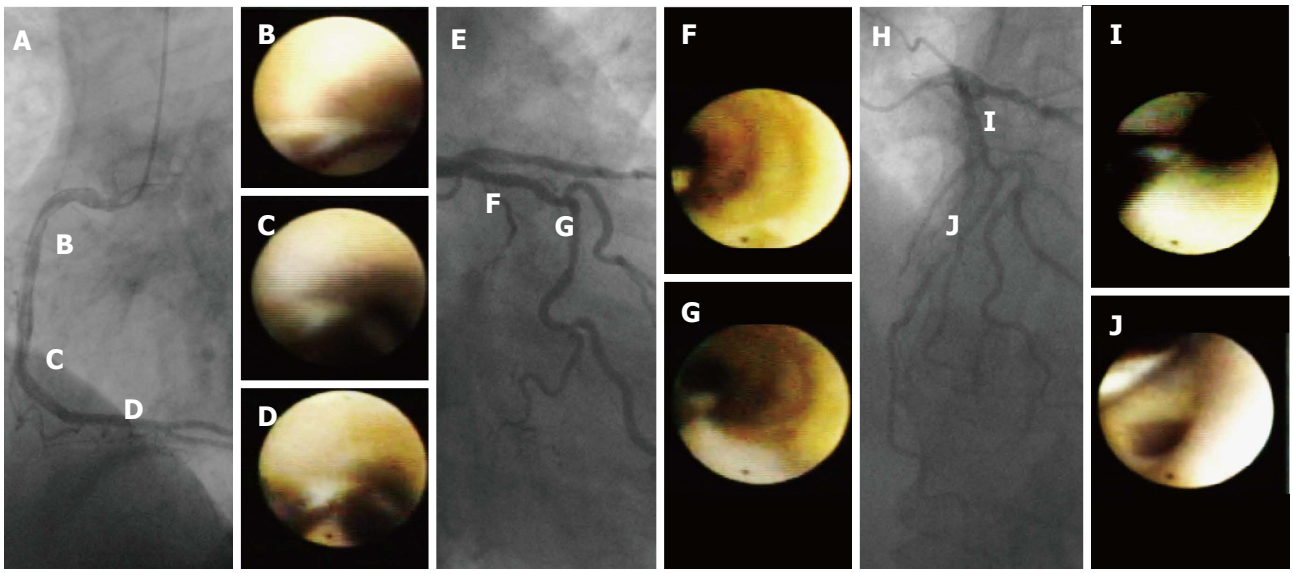

Figure 4 Representative images of diabetes patients. A-D: No angiographic stenosis was observed in the right coronary artery (A), whereas 3 yellow plaques were identified on angioscopy (B-D). The yellow intensity of these plaques was defined as grades 2, 1, and 2, respectively; E-G: Significant stenosis was not observed in the left circumflex artery (E), whereas 2 yellow plaques were identified on angioscopy (F and G). The yellow intensity of both of these plaques was evaluated as grade 3 (intense yellow); H: A 50% stenosis and a 90% stenosis were identified on angiography in the middle part of the left ascending artery; I and J: According to angioscopic findings, both these lesions were evaluated as light yellow plaques (grade 1). In this case, the average number of yellow plaques per vessel was 2.33 (7 yellow plaques in 3 vessels), and the maximum yellow grade per coronary artery was 3.

function in hepatic insulin resistance manifests as IFG, whereas muscle insulin resistance represents IGT[51]. Although data for IFG and IGT are provided by the daily glucose snapshot, HbA1c levels after chronic exposure (over 60-90 d) to basal and postprandial hyperglycemia reflects a combination of IFG and IGT[52].

Prediabetes-associated coronary atherosclerosis as determined by imaging modalities

An angiographic study revealed that atherosclerosis of coronary arteries developed not only in patients with diabetes but also in those with IGT[53]. An IVUS study showed that even patients with a prediabetic status detected by IGT and IFG exhibited abundant lipid-rich plaques in their coronary arteries[54]. Recently, we used CAS to identify yellow vulnerable plaques in the coronary arteries of patients with prediabetes and diabetes compared with controls. Representative images of patients without diabetes and with prediabetes and diabetes are shown in Figures 2-4. Our findings indicate that both the degree of coronary atherosclerosis and the plaque vulnerability were more advanced in patients with prediabetes than in those without diabetes, and were comparable to patients with diabetes. We showed that the number of yellow plaques (0.80 ± 0.64 *vs* 1.45 ± 0.81 *vs* 1.63 ± 0.99; $P = 0.011$) and yellow grade (1.44 ± 1.03 *vs* 2.00 ± 0.86 *vs* 2.30 ± 0.70; $P = 0.047$) in patients with prediabetes were greater than those in patients without diabetes, but similar to those in patients with diabetes (Figure 5)[55].

Prevention of atherosclerotic cardiovascular diseases

Recently, the American College of Cardiology and the American Heart Association proposed a new guideline for the treatment of hyperlipidemia to reduce the risk of cardiovascular events and recommended aggressive statin therapy for both primary and secondary prevention of atherosclerotic cardiovascular disease (ACVD) events in diabetes patients[56]. Moreover, for patients with diabetes without preexisting CAD, the American Diabetes Association currently recommends starting pharmacological therapy at a low-density lipoprotein cholesterol (LDL-C) level of ⩾ 130 mg/dL with a goal of < 100 mg/dL[57]. In an angioscopic investigation, lowering LDL-C by statin induces reduction of color intensity in yellow plaques, and the phenomenon is regarded as its effect on plaque stabilization[58].

Four major groups were identified that would benefit from statin therapy to reduce ACVD risk: (1) patients with clinical ACVD (secondary prevention); (2) patients with primary elevations of LDL-C ⩾ 190 mg/dL (primary prevention); (3) patients 40-75 years of age who have diabetes and LDL-C 70-189 mg/dL (primary prevention); and (4) patients up to 75 years of age without diabetes and with an estimated 10-year ACVD risk ⩾ 7.5% and LDL-C 70-189 mg/dL (primary prevention). Selected patients with < 5% 10-year ACVD risk who are < 40 or > 75 years of age may also benefit from statin therapy[56]. The 10-year ACVD risk was estimated from age, sex, race, blood cholesterol level, history of hypertension and diabetes, smoking habits, *etc*. In the group with 10-year ACVD risk < 7.5%, a benefit of statin therapy was not completely established. Regarding prediabetes, we should pay attention to this group and consider the benefit of statin therapy.

Because coronary atherosclerosis is already present

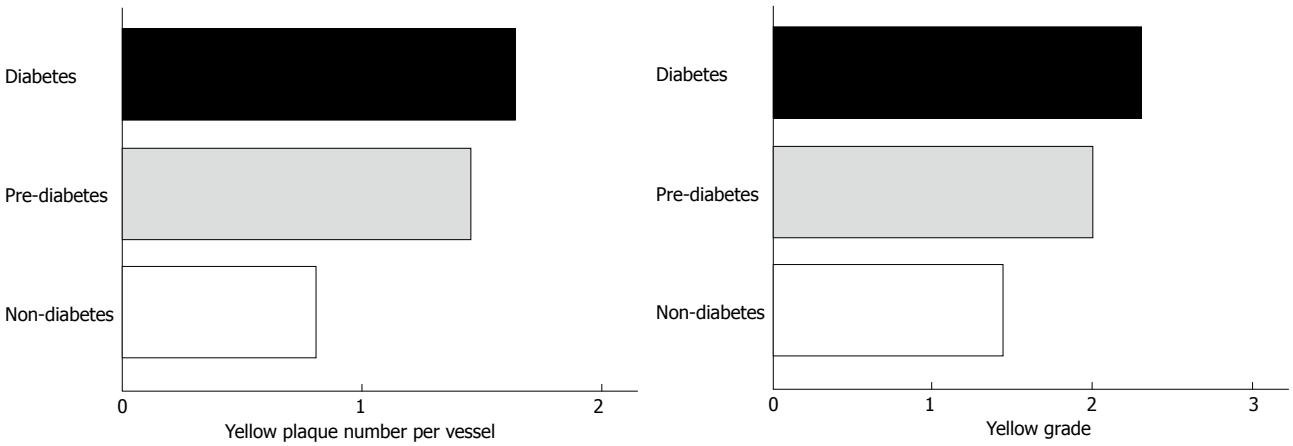

Figure 5 Comparisons of yellow plaque detected by coronary angioscopy among the 3 groups. A: Average number of yellow plaques per vessel; B: Average maximum yellow grade per coronary artery (MYG). The number of yellow plaques per vessel and maximum yellow grade per coronary artery in the prediabetic group were greater than those in the nondiabetic group ($P = 0.017$ and $P = 0.040$, respectively), whereas they were similar to those in the diabetic group ($P = 0.44$ and $P = 0.21$, respectively).

in prediabetes and our angioscopic examination revealed that the level of coronary atherosclerosis with prediabetes is almost equal to that in patients with diabetes, even for patients with prediabetes, earlier pharmacological therapy should be recommended.

CONCLUSION

We should consider the risk of CAD in the prediabetic state with mild glucose metabolism disorder, and further clinical investigations are required to establish an exact risk stratification and prevent future cardiovascular events in patients with prediabetes.

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