Diabetes is characterized by hyperglycemia and certainly indicates various micro- and macro-vascular complications. Macro-vascular complications include ischemic coronary artery disease due to atherosclerosis, which is a leading cause of mortality in diabetic patients. Diabetic retinopathy (DR) is considered as a specific marker of micro-vascular complications and is included in the criteria for diagnosis of diabetes. The ultimate goal of diabetes treatment is to inhibit the progression of systemic atherosclerosis and prevent fatal cardiovascular events like acute coronary syndrome (ACS). Although diabetes involves both micro- and macro-vascular diseases, the relationship between DR and severity of coronary atherosclerosis, fundamental to ACS, is unclear. Moreover, the correlation of the degree of glucose metabolism disorder with coronary atherosclerosis remains unclear. The American Diabetes Association considers prediabetes as a high risk for diabetes and cardiovascular events in the future. However, coronary atherosclerosis in prediabetic patients has not been fully investigated.

Coronary angioscopy (CAS) is a useful intravascular imaging modality for assessing the characteristics of atherosclerotic plaques and its severity in vivo. Recently, CAS has shown the above relationships. Herein, we review the angioscopic findings and subsequent therapeutic implications in patients with glucose metabolism disorders.

**Key words:** coronary angioscopy, coronary artery disease, glucose metabolism disorder, yellow plaque

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**Introduction**

Diabetes is a metabolic disorder characterized by fasting and/or post-prandial hyperglycemia resulting from a lack (or an absence) of insulin secretion and/or insulin action. Chronic hyperglycemia can cause dysfunction and damage or failure of systemic organs including eyes, kidneys, nerves, heart, and blood vessels as micro- and macro-vascular complications. The diagnosis of diabetes is based on the levels of hemoglobin A1c (HbA1c) or plasma glucose (PG) with the threshold defined by the prevalence of diabetic retinopathy (DR), which is one of the micro-vascular complications. Although DR is a major diabetic complication, DR itself does not cause a poor prognosis.

Diabetes is an intense risk factor of macro-vascular complications like coronary artery disease (CAD), which is a leading cause of mortality in diabetic patients. In addition, there is accumulating evidence that not only diabetes but also impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are correlated with a poor prognosis, owing to an increasing risk of cardiovascular events.

The final goal of the treatment for diabetes is prevention of the cardiovascular events like fatal acute coronary syndrome (ACS). ACS is caused by formation of a flow-limiting thrombus that adhered to the disrupted plaque in the coronary artery. Previous clinical and histopathological studies reported that the majority of ACS originated from disrupted plaques, especially thin-cap fibroatheromas (TCFA) composed of a large lipid core under a thin fibrous cap. A vulnerable plaque represented by the TCFA is defined as a plaque with a potential risk of ACS in the near future. In recent years, new intracoronary imaging modalities have been developed and use for detecting vulnerable plaques in daily
clinical practice. As one of the supplemental diagnostic methods of CAD, coronary angiography (CAS) has been utilized to discriminate plaque morphology and to identify vulnerable plaques and patients.

**Classification or Definition of Glucose Metabolism**

The American Diabetes Association defines diabetes as HbA1c (National Glycohemoglobin Standardization Program) ≥6.5%, or fasting PG ≥126 mg/dL, or 2-h PG ≥200 mg/dL during an oral glucose tolerance test (OGTT). Those diagnostic criteria of diabetes are based on the prevalence of DR with glycemic levels. In addition, the American Diabetes Association defines IFG as fasting PG level of 100–125 mg/dL and IGT as 2-h PG level of 140–199 mg/dL during an OGTT. Populations of IFG and/or IGT are thought that they frequently develop into diabetes in the future. HbA1c is commonly used to diagnose as diabetes, and its value of 5.7–6.4% also indicates an increased risk of diabetes. Therefore, the American Diabetes Association advocates the concept of prediabetes as patients with HbA1c 5.7–6.4%, IFG, and IGT.

**Glucose Metabolism and Atherosclerosis**

Hyperglycemia, free fatty acids, and insulin resistance in diabetes alter the function and structure of blood vessels through molecular mechanisms. These mechanisms include increased oxidative stress, activation of protein kinase C, and activation of the receptor for advanced glycation end products. Consequently, they decrease the availability of nitric oxide, increase endothelin production, and activate transcription factors, such as nuclear factor kappa B and activator protein-1. These substances provoke vasoconstriction and atherosclerosis as well as inflammation. Similar responses potentially arise in prediabetes characterized by disorders of glucose metabolism.

**Angioscopic Findings of Coronary Plaque**

In lumen observation by CAS, a normal coronary artery seems to be a milky white flat wall. On the contrary, an atherosclerotic plaque appears to be a protruding mass into the lumen with yellow or white color (yellow or white plaque, respectively). According to the surface color, the intensity (or grade) of the yellow plaque is semi-quantitatively classified as 0, white; 1, light yellow; 2, (medium) yellow; or 3, intense yellow (Fig. 1). The majority of yellow plaques contain lipid pool or necrotic core according to comparative validation using optical coherence tomography and intravascular ultrasonography. Moreover, the yellow grade is regulated by the thickness of fibrous cap covering the lipid pool, and the two indexes are conversely correlated with each other. Therefore, high-intensity yellow plaque identified by CAS is considered TCFA. Yellow plaque is frequently

**Glucose Metabolism and Vascular Complications**

Chronic hyperglycemia causes both micro- and macro-vascular complications, and evidence that diabetic population has increased risk of macro-vascular complications has been accumulated. Even though DR is a major micro-vascular complication of diabetes, the prognosis of diabetic patients with DR is not always poor. Controversially, presence of DR is associated with poor prognosis due to high incidence of cardiovascular events and mortality. Nevertheless, there are few investigations focusing on the relationship between the severity of coronary atherosclerosis and DR. In addition, whether mild disorder of glucose metabolism, prediabetes, causes coronary atherosclerosis remains unclear. Recently, non-diabetic status including IFG and IGT is reported to correlate with a high risk of cardiovascular events and a poor prognosis. However, morphology, vulnerability, and distribution of coronary plaque in prediabetes have not yet been fully validated.

**Fig. 1** Classification of yellow plaques. (A) White plaque (yellow grade 0). (B) Light yellow plaque (grade 1). (C) Yellow plaque (grade 2). (D) Intense yellow plaque (grade 3).
observed in the culprit lesion of ACS. Prospective angioscopic studies demonstrated that the incidence of ACS was higher in patients with intense yellow plaque and multiple yellow plaques than in patients without them. These findings suggest that patients with intense yellow or multiple yellow plaques may be vulnerable. In other words, yellow plaque, especially intense yellow plaque itself, indicates vulnerability.

Angioscopic Findings in Glucose Metabolism Disorder

Diabetes is well known to promote atherosclerotic disease including coronary artery disease and increase mortality rate resulting from cardiovascular events. Previous CAS studies showed frequent ulcerated plaque, adhering thrombus, and delayed healing process of the plaque in diabetes. It is common that diabetic patients have no ischemia-related symptoms. The absence of typical chest symptoms, so-called silent myocardial ischemia, entails late diagnosis and therapeutic intervention, and they lead to worsened prognosis of diabetes.

Another study using CAS showed that diabetes was an independent predictor of silent plaque disruption in the non-culprit lesion. With regard to the relationship between micro- and macro-vascular diseases in diabetes, patients with DR had larger number and higher grade of the yellow plaque than those without DR. As previously mentioned, the two indexes are angioscopically surrogate markers of patient or plaque vulnerability according to prospective studies. Therefore, the presence of DR indicates the prevalence of coronary atherosclerosis and advanced vulnerability of the plaque. This report suggested a direct link between micro- and macro-vascular complications such as DR and coronary atherosclerosis resulting into ACS. Catheter-based angioscopic procedure is relatively invasive, while an ophthalmoscope for the diagnosis of DR is less invasive and practical in the daily clinic. For diabetes management, it may be required to evaluate the presence of DR, to consider latent vulnerable plaque in the coronary artery, and to initiate early therapeutic intervention.

The present diagnosis of diabetes is based on DR, and the correlation between severity of glucose metabolism disorder and coronary atherosclerosis is still unclear. Prediabetes such as IFG and IGT has a poor prognosis following an increasing risk of cardiovascular events, according to recent evidence. We reported that the number and color grade of the yellow plaque in prediabetes were greater than those in non-diabetes. Moreover, they did not differ between prediabetes and diabetes. Therefore, both expansions of coronary atherosclerosis and plaque vulnerability were advanced in prediabetes as well as in diabetes. Three representative cases of non-diabetes, prediabetes, and DR are shown in Figs. 2-4.

Fig. 2 Representative coronary angiographic and angioscopic images in non-diabetic patients. (A) A 75% stenosis is identified on angiography in the middle part of the left ascending artery. (B) According to angioscopic findings, this lesion is a grade 1 yellow plaque. (C) No angiographic stenosis is observed in the right coronary artery. (D) On angioscopy, 1 yellow plaque is identified with an intensity grade of 2. The left circumflex artery is too small to be observed using coronary angioscopy. In this case, the average number of yellow plaques is 1 (2 yellow plaques in two vessels), and the maximum yellow grade is 2.
Fig. 3 Representative coronary angiographic and angioscopic images in prediabetic patients. (A) No angiographic stenosis is observed in the right coronary artery. (B) An intramural red thrombus is observed at the proximal site. (C) and (D) On angioscopy, three yellow plaques are identified with intensity grades of 1, 2, and 1, respectively. (E) Significant stenosis was not observed in the left circumflex artery. (F) and (G) Identification of two yellow plaques with grades 1 and 2, respectively. (H) A 50% stenosis and a 90% stenosis are identified on angiography in the middle part of the left ascending artery. (I) and (J) According to angioscopic findings, both lesions are grade 3 yellow plaques. In this case, the average number of yellow plaques is 2.33 (7 yellow plaques in 3 vessels), and the maximum yellow grade is 3.

Fig. 4 Representative coronary angiographic and angioscopic images in patients with diabetic retinopathy. (A) No angiographic stenosis was observed in the right coronary artery. (B–D) On angioscopy, three yellow plaques are identified with intensity grades 2, 3, and 2, respectively. (C) An intramural red thrombus was observed at the middle site. (E) Significant stenosis was not observed in the left circumflex artery. (F and G) Identification of 2 yellow plaques grades 2 and 1, respectively. (H) A 90% stenosis was identified on angiography in the proximal part of the left ascending artery. (I and J) On angioscopy, two yellow plaques are identified in the proximal and middle parts of the left ascending artery with intensity grades of 2 and 3, respectively. In this case, the average number of yellow plaques is 2.33 (7 yellow plaques in 3 vessels) and the yellow grade is 3.
Management of Glucose Metabolism Disorder

Sodium-glucose cotransporter-2 (SGLT-2) inhibitor demonstrated a clear benefit in reducing cardiovascular events and death in diabetes.\(^{30}\) In addition, a recent observational study demonstrated that SGLT-2 inhibitor might decrease particular cardiovascular events, myocardial infarction, and stroke.\(^{39}\) Further studies are needed to estimate the effect of glucose lowering drugs including SGLT-2 inhibitor.

By contrast, lipid-lowering therapy with statin is certainly beneficial to decrease all-cause mortalities in diabetes as many large-scale clinical trials revealed. Furthermore, the American College of Cardiology and the American Heart Association proposed guidelines for the treatment of hyperlipidemia to reduce the risk of cardiovascular events. Both guidelines recommend aggressive statin therapy for primary and secondary preventions of cardiovascular events for diabetes.\(^{40}\) Serial angioscopic examinations demonstrated that low-density lipoprotein cholesterol lowering therapy with the strong statin reduced yellow grade and complexity of the plaque. The phenomenon of the changes of plaque morphology is believed to be plaque stabilization caused by statin therapy.\(^{41, 42}\) The statin effects on plaque morphology in diabetes may be attenuated in mature plaques with large necrotic core.\(^{43, 44}\) We found that the reduction rate in the number and grade of the yellow plaque in patients with statin were lower than in those without statin. Therefore, statin therapy played an important role in inhibiting atherosclerotic progression in prediabetes.\(^{45}\) Previous clinical studies showed that the residual risk of ACS in diabetes was not very low despite statin therapy.\(^{46}\) Aggressive therapy may be required in the early stages of glucose metabolism disorders like as prediabetes. Since coronary atherosclerosis development can be promoted in prediabetes as in diabetes, effective intervention may be recommended in the early stages of glucose metabolism disorder.

Further clinical investigations focusing on the prevention of cardiovascular events in patients with glucose metabolism disorders are necessary.

Disclosure Statement

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