RESEARCH ARTICLE

Plaque Characteristics in Coronary Artery Disease Patients with Impaired Glucose Tolerance

Keishi Suzuki, Hitoshi Takano*, Yoshiaki Kubota, Keisuke Inui, Shunichi Nakamura, Yukichi Tokita, Koji Kato, Kuniya Asai, Wataru Shimizu

Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan

* htakano@nms.ac.jp

Abstract

Background

Impaired glucose tolerance (IGT) patients are known to have a high risk of cardiovascular events and their prognosis has been reported to be poor. The present study aimed to compare coronary plaque characteristics among coronary artery disease (CAD) patients with normal glucose tolerance (NGT), those with IGT, and those with diabetes mellitus (DM) by using optical coherence tomography (OCT).

Methods

The present study included 101 coronary artery disease patients (mean age, 67.9 ± 10.4 years; 82.4% male). OCT was performed for target and non-target vessels during percutaneous coronary intervention. The patients were divided into the following 3 groups: the NGT, IGT, and DM groups.

Results

A total of 136 non-target residual plaques were found in 101 patients (27, 30, and 44 in the NGT, IGT, and DM groups, respectively). The size of the lipid core expressed as the mean angle of the lipid arc was significantly greater in the IGT and DM groups than in the NGT group (163.0 ± 58.7˚, 170.1 ± 59.3˚, and 130.9 ± 37.7˚, respectively, P < 0.05). The fibrous cap covering the lipid core was significantly thinner in the IGT group than in the NGT group (77.0 ± 23.4 μm vs. 105.6 ± 47.0 μm, P = 0.040).

Conclusion

The coronary plaques in CAD patients are more vulnerable when having IGT compared to those with NGT, and similar to those with DM. This finding may explain the high risk of cardiovascular events in CAD patients with IGT.
Background

In addition to diabetes mellitus (DM), which is established as one of the most significant risk factors of coronary artery disease (CAD), prediabetic conditions such as impaired glucose tolerance (IGT) have also been reported to increase the risk of cardiovascular events and affect mortality rates [1, 2]. Previous studies have reported that severe atherosclerotic lesions are frequently observed in prediabetic patients suggesting the atherosclerotic formation starts at a very early stage [3–8]. As well as the severity and extent of atherosclerotic lesions, the morphology of atherosclerotic plaque is also considered to be one of the important factors responsible for the development of cardiovascular events [9, 10]. Vulnerable coronary plaques characterized by thin-cap fibroatheroma (TCFA), large lipid core, and macrophages infiltration are closely associated with the onset of acute coronary syndrome (ACS) [11–13]. Optical coherence tomography (OCT) is a high-resolution intravascular imaging modality that enables detailed assessment of coronary plaque morphology, which is considered to be superior to any other modalities currently available [14–16]. A previous study reported that DM patients have a larger lipid core in their coronary plaques and poorly controlled DM patients had more TCFA on OCT, which may be explaining the high risk of cardiac events [17]. The phenomenon similar to that observed in DM patients in their study can be also occurring even in CAD patients with IGT. Thus, the morphological assessment of atherosclerotic plaque by OCT may also be helpful to understand the mechanism of development of cardiovascular events in CAD patients with IGT.

In the present study, we aimed to evaluate the vulnerability of coronary plaques in CAD patients with IGT using OCT and compare it with those with normal glucose tolerance (NGT) or DM. The data will clarify whether the coronary plaques in CAD patients with IGT are more vulnerable than those in the patients with NGT and how different they are from those in the patients with DM.

Research Design and Methods

Patient population

There were 461 consecutive CAD patients who received PCI and were registered in our institutional PCI registry between August 2013 and December 2014 (Fig 1). Indication of PCI was determined when the patients have typical effort angina or positive stress-test findings (either ECG, nuclear scan, or stress echocardiogram), and suitable coronary stenotic lesion(s) for PCI. In this registry, the content of PCI procedure including the findings of intravascular imaging and clinical data including the result of 75-g oral glucose tolerance test (OGTT) were recorded. Thus all patients underwent 75-g OGTT except those already diagnosed as DM (Fig 1). 154 patients received OCT of the target and non-target vessels during percutaneous coronary intervention (PCI) by the intention of the operator (Fig 1). Patients with chronic total occlusion (n = 7), left main disease (n = 12), and poor image quality (n = 34) were excluded; therefore, 101 patients were included in the final analysis (Fig 1). Non-culprit lesions were defined as plaques angiographically confirmed but not treated during the session of PCI according to the results of stress test or ECG changes during the spontaneous ischemic attacks. Blood samples were obtained from the antecubital vein in the fasting state and before each OCT procedure. The patients were divided into 3 groups according to the results of a 75-g oral glucose tolerance test (OGTT). Glucose metabolism was assessed according to the American Diabetes Association (ADA) and World Health Organization (WHO) criteria [18].

NGT was defined as a fasting plasma glucose (FPG) level <110 mg/dL and 2-h plasma glucose (PG) level <140 mg/dL during an OGTT. IGT was defined as a 2-h PG level ≥140 mg/dL but <200 mg/dL during an OGTT. DM was defined as a history of DM, hemoglobin A1c
(HbA1c) value ≥6.5%, and FPG level ≥126 mg/dL or 2-h PG level ≥200 mg/dL during an OGTT[18]. Height and weight were measured at the time of discharge, and the body mass index (BMI; kg/m^2) was calculated as an index of obesity. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or the current use of antihypertensives. Dyslipidemia was defined as a total cholesterol (TC) level ≥220 mg/dL, low-density lipoprotein-cholesterol (LDL-C) level ≥140 mg/dL, high-density lipoprotein-cholesterol (HDL-C) level <40 mg/dL, or the current use of lipid-lowering agents. Chronic kidney disease was defined as a glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2 or proteinuria. The GFR was estimated using the simplified prediction equation derived from the Modification of Diet in a Renal Disease study [19].

**OCT imaging and analysis**

OCT images were obtained using frequency-domain OCT (C7-XRTM; LightLab Imaging). With the help of a 6 or 7-Fr guiding catheter, images were obtained using a continuous flush.
of contrast media or low molecular weight dextran at a rate of 4 mL/s from the guiding catheter, and the OCT wire was pulled back at a rate of 10 mm/s. Images were recorded at 100 frames/s, displayed with a color look-up table, and digitally archived.

We characterized the non-culprit lesions in CAD patients with DM and IGT using OCT imaging and compared them with those in the NGT patients. Each plaque was separated at least 5 mm from the edge of an implanted stent. The plaques were classified as fibrous (homogeneous with a highly backscattered region) or lipid (low signal region with a diffuse border). A thin-cap fibroatheroma (TCFA) was defined as the thinnest fibrous cap with a thickness ≤65 μm in a lipid-rich plaque on cross-sectional imaging. Macrophage infiltration was defined as signal-rich, distinct or confluent punctuate regions that exceed the intensity of background speckle noise [20–22]. Plaque disruption was defined as fibrous cap discontinuity with clear cavity formation inside the plaque [23]. Microchannel structures were defined as signal-poor voids that are sharply delineated in multiple contiguous frames [22]. Calcification was defined as well delineated and low backscattered heterogeneous regions [22]. A thrombus was defined as a well-delineated mass with a high signal attached to the luminal surface or floating within the lumen [22, 23]. OCT images were analyzed by 2 independent observers. The inter-observer reliability between the 2 observers measured by the Pearson coefficient was r = 0.97 (S1 Fig). The intra-observer reproducibility determined by the Pearson coefficient was r = 0.95 (S2 Fig).

The Medical Ethics Committee at Nippon Medical School Hospital approved the study protocol, and written informed consent was obtained from all the patients before the catheterization procedure.

**Statistical analysis**

Categorical variables were presented as frequencies, and these were compared using the Pearson chi-square test. Continuous variables are presented as means ± standard deviations, and these were compared using ANOVA. The relationships between the OCT findings, and lipid profiles or HbA1c levels were assessed using Pearson’s correlation. All statistical analyses were performed using SPSS software package ver. 20.0 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

**Results**

**Baseline characteristics**

The baseline characteristics of the patients are presented in Table 1. The NGT group included 27 patients (26.7%), the IGT group included 30 patients (29.7%), and the DM group included 44 patients (43.6%, 24 patients were known to have DM). The HbA1c level was significantly higher in the DM group (7.1 ± 0.8%) than in the IGT (5.9 ± 0.3%, P < 0.01) and NGT group (5.6 ± 0.5%, P < 0.01). There were no significant differences in the LDL-C level, HDL-C level, and statin use among the 3 groups.

**OCT findings**

The OCT plaque characteristics are presented in Table 2. Of the 136 non-target residual plaques, 72 were found to contain a lipid core on OCT (16, 28, and 28 in the NGT, IGT, and DM groups, respectively). The percentage of lipid-rich plaques was similar among the NGT, IGT and DM groups. Additionally, there were no differences in the percentages of TCFA, macrophage infiltration, plaque disruption, microchannels, calcification, and thrombi among the groups (Table 2).
Representative OCT images in each group are shown in Fig 2. A comparison of the quantitative OCT findings of the lipid plaques between the NGT, IGT, and DM groups is presented in Fig 3. The plaques had a significantly wider maximum lipid arc and mean lipid arc in the IGT and DM groups than in the NGT group (max lipid arc: 231.8˚ vs. 177.6˚, P = 0.019 and 223.6˚ vs. 177.6˚, P = 0.047; mean lipid arc: 163.0˚ vs. 130.9˚, P = 0.039 and 170.1˚ vs. 130.9˚, P = 0.009, respectively). There were no significant differences in these lipid plaque parameters between the IGT and DM groups. The fibrous cap thickness was lower in the IGT group than in the NGT group (77.0 μm vs. 105.6 μm, P = 0.040) (Fig 3). The relationships between the OCT findings, and lipid profiles or HbA1c level are shown in Fig 4. Max lipid arc positively correlated with HbA1c (y = 23.4x + 69.2, r = 0.244, P = 0.039). Fibrous cap thickness positively correlated with HDL-C (y = 0.544x + 58.3, r = 0.248, P = 0.039).

Table 1. Clinical characteristics of the study population.

| Characteristic          | NGT (n = 27) | IGT (n = 30) | DM (n = 44) | P-value |
|-------------------------|--------------|--------------|-------------|---------|
| Age, years              | 66.1 ± 9.8   | 69.3 ± 12.2  | 67.2 ± 9.2  | 0.485   |
| Male sex, n (%)         | 21 (81.5%)   | 23 (76.7%)   | 37 (84.1%)  | 0.73    |
| BMI, kg/m²              | 23.3 ± 2.7   | 25.0 ± 4.1   | 24.6 ± 4.5  | 0.277   |
| Hypertension, n (%)     | 25 (92.6%)   | 27 (90%)     | 40 (90.9%)  | 0.943   |
| Dyslipidemia, n (%)     | 18 (66.7%)   | 19 (63.3%)   | 27 (61.4%)  | 0.906   |
| Smoking, n (%)          | 10 (39.1%)   | 17 (58.7%)   | 28 (63.6%)  | 0.161   |
| ACS, n (%)              | 7 (25.9%)    | 8 (26.7%)    | 8 (18.2%)   | 0.676   |
| Prior MI, n (%)         | 12 (44.4%)   | 8 (26.7%)    | 15 (34.1%)  | 0.459   |
| HbA1c, %                | 5.6 ± 0.5    | 5.9 ± 0.3    | 7.1 ± 0.8   | <0.001  |
| FPG, mg/dL              | 90.6 ± 7.6   | 96.2 ± 13.3  | 106.7 ± 17.9| 0.003   |
| LDL-C, mg/dL            | 101.2 ± 32.0 | 96.7 ± 23.7  | 93.1 ± 26.9 | 0.489   |
| HDL-C, mg/dL            | 51.3 ± 13.6  | 51.1 ± 17.6  | 47.1 ± 12.8 | 0.383   |
| Statin use, n (%)       | 23 (88.5%)   | 23 (76.7%)   | 33 (75%)    | 0.389   |

The data are presented as mean ± standard deviation or actual number (percentage).

NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; ACS, acute coronary syndrome; MI, myocardial infarction; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

doi:10.1371/journal.pone.0167645.t001

Table 2. Clinical characteristics of the study population on optical coherence tomography.

| Characteristic                         | NGT (n = 27) | IGT (n = 30) | DM (n = 44) | P-value |
|----------------------------------------|--------------|--------------|-------------|---------|
| Total plaques observed by OCT, n       | 33           | 44           | 59          |         |
| Lipid-rich plaques, n                  | 16           | 28           | 28          |         |
| Patient with lipid-rich plaques, n (%) | 12 (44.4)    | 20 (66.6)    | 18 (40.9)   | 0.266   |
| Lipid-rich plaques/total plaques, %    | 48.5         | 63.6         | 47.5        | 0.227   |
| TCFA, n (%)                            | 5 (15.2)     | 9 (20.5)     | 11 (18.6)   | 0.839   |
| Macrophage infiltration, n (%)         | 0 (0)        | 4 (9.1)      | 6 (10.2)    | 0.177   |
| Disruption, n (%)                      | 2 (6.1)      | 4 (9.1)      | 4 (6.8)     | 0.862   |
| Microchannels, n (%)                   | 10 (30.3)    | 8 (18.2)     | 11 (18.6)   | 0.356   |
| Calcification, n (%)                   | 21 (63.6)    | 22 (50)      | 31 (52.5)   | 0.464   |
| Thrombus, n (%)                        | 4 (12.1)     | 4 (9.1)      | 6 (10.2)    | 0.912   |

Data are expressed as actual number (% of total plaques observed by OCT) otherwise specified.

doi:10.1371/journal.pone.0167645.t002
Fig 2. Representative cross-sectional OCT images for each of the 3 groups, NGT, IGT and DM (A, B, and C, respectively). We measured the thickness of the thinnest part (arrows) of the fibrous cap identified as a signal-rich homogenous region overlying a lipid core (*), which is characterized by a signal-poor region.

doi:10.1371/journal.pone.0167645.g002
The present study aimed to identify the coronary plaque characterization of CAD patients with IGT defined by the result of a 75 g OGTT. There were no significant differences in the percentage of coronary plaques or TCFAs between NTG, IGT and DM patients. However, a significant difference was observed in the quality of the plaque containing a lipid core. The lipid core in the coronary plaque of CAD patients with IGT was significantly larger and the fibrous cap covering the core was significantly thinner than those of NGT patients and equivalent to those of DM patients.

An increase in the size of the lipid plaque and thinning of the fibrous cap can cause ACS through an increase in atheroma vulnerability. OCT is an imaging modality characterized by clearly identifying plaque rupture, fibrous cap erosion, an intracoronary thrombus, a lipid plaque arc, and TCFA in vivo. OCT has been established as the modality for the detailed plaque morphological analysis, superior to other conventional imaging techniques such as intravascular ultra sound [24]. In a previous study, coronary tissue exhibited a larger number of lipid-rich atheromas, macrophage infiltrations, and thrombus among DM patients than among NGT patients, and patients with HbA$_{1C}$ $\geq$8% had a wide lipid arc, a long lipid length, thin fibrous caps, and high prevalence of TCFA and macrophage infiltration, which coincided with the typical pathological features of vulnerable plaques[17]. Kurihara et al. demonstrated that coronary atherosclerosis and plaque vulnerability assessed using angioscopy were more advanced in prediabetic patients than in nondiabetic patients[25]. A recent study showed that glucose fluctuations impact not only atherosclerosis, but also the formation of lipid-rich plaques and thinning of the fibrous cap in CAD patients [26]. In the present study, we performed 75g OGTT in all the patients who had not been diagnosed as DM to specify the patients with IGT and demonstrated that plaque vulnerability was more advanced in CAD patients with IGT than those with NGT using OCT.

The mechanisms of the development of vulnerable plaques in hyperglycemic status are not fully understood. Physiological studies have reported that hyperglycemia, excess free fatty acid,
Fig 4. Relationships between OCT findings (maximum lipid arc and fibrous cap thickness) and LDL-C (panels A and B), HDL-C (panels C and D) and HbA1c (panels E and F). Each panel illustrates individual values with closed circles. In the panels D and E, the linear regression lines are expressed. Fibrous cap thickness is positively and linearly correlated with HDL-C (panel D, $y = 23.4x+69.2$, $r = 0.248$ and $p = 0.039$). Maximum lipid arc was positively and linearly correlated with HbA1c (panel E, $y = 0.544x+58.3$, $r = 0.244$, $p = 0.039$). In other panels, only $r$ and $p$ values of linear regression analysis were expressed because correlation was not statistically significant.

doi:10.1371/journal.pone.0167645.g004
and insulin resistance in diabetes can cause metabolic disarray within endothelial cells, and the activation of these systems impairs endothelial function, augments vasoconstriction, increases inflammation, and promotes thrombosis[27]. These conditions may also affect vasoconstriction and inflammation, and thereby promote coronary atherosclerosis even in the prediabetic phase. Several in vitro investigations have reported that the development of oxidative stress and vascular injury are more strongly associated with glucose variability than exposure to a constant high glucose level [28, 29]. Schisano et al. reported that more detrimental conditions in terms of oxidative stress and DNA damage in endothelial cells were noted with prolonged exposure to oscillating glucose levels than exposure to constant high glucose levels, which were associated with hyperactivation of p53, in vitro[30]. These findings suggest that IGT could have an ominous impact on the function of endothelial cells to promote atherosclerosis, leading to an increase in plaque vulnerability.

In the present study we found that only 26.7% of the patients receiving PCI were defined as NGT according to the results of a 75 g OGTT performed for all the patients except known DM patients, and remaining patients had either DM or IGT. Kuhl et al have reported the percentage of NGT was 28% among 1062 ACS patients [31]. Lenzen et al confirmed 24% of NGT patients among 3940 CAD patients [32]. Thus, there have been many patients with potentially unidentified and untreated DM or IGT in this population [31, 32]. The Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) suggested that the treatment of IGT patients with an α-glucosidase inhibitor was associated with a significant reduction in the risk of cardiovascular disease [5]. This indicates that an abnormality in glucose metabolism should be corrected as early as possible and, therefore, early diagnosis of IGT or DM is essential. Taken together with the findings of the present study, the importance of 75-g OGTT is enhanced in CAD patients, which will allow the timely diagnosis of IGT or latent DM.

In the present study, we also found that fibrous cap thickness positively correlated with HDL-C. The findings similar to our study have been confirmed in the previous studies [33, 34]. Burke et al, have reported that the number of vulnerable plaques were significantly associated with lower serum HDL-C level [33]. Ozaki et al, have shown that HDL-C level is associated with fibrous cap thickness at the culprit lesion of ACS [34]. Although the precise mechanisms whereby HDL-C thicken the fibrous cap is unknown, one of the possible explanations we speculate is the inhibition of MMP-9 activity by HDL-C [35].

Study limitations
The present study had several limitations. First, this was a subanalysis from the institutional registry at a single hospital which was not conducted specifically to identify the differences of OCT findings, and it had a small sample size. Therefore, selection bias might be present and it may be difficult to make a definitive conclusion from this sample size. Type II error might also exist although we demonstrated no significant differences in clinical backgrounds between the 3 groups. Second, OCT was performed by the operator’s intention and only 1/3 received OCT during the study period. This may also bias the results. However, we think the influence was not significant because operators did not know the results of 75g OGTT at the time of PCI and OCT was mainly selected by the operators who were familiar with handling an OCT device and analyzing OCT images. Third, the exact measurements of the necrotic core and plaque burden on OCT were not possible because of a relatively shallow axial penetration. However, because the most important morphological determinants of plaque vulnerability were superficial, the region of greatest interest was within the imaging range of the current OCT systems. Forth, the OCT data were analyzed in the same institution not in core lab although those were analyzed by independent observers who did not know the clinical backgrounds of the patients.
Fifth, the study only included the patients having already developed CAD requiring PCI, which were not the representative patients simply having IGT, NGT, and DM. From the ethical viewpoint, however, it is impossible to perform OCT in patients who do not have significant CAD because of its invasive nature. Finally, the study was a cross sectional observational study which failed to examine the influence of glucose tolerance abnormality on the sequential changes of plaque morphology.

**Conclusion**

The vulnerability of coronary plaques of CAD patients having IGT is more significant than that of those having NGT and similar to that of those having DM. This finding may explain the high risk of cardiovascular events in CAD patients with IGT although further investigations such as a long-term follow up study are necessary.

**Supporting Information**

S1 Fig. Inter-observer reliability measured by the Pearson coefficient. Ten patients were randomly selected and their maximal lipid arch was separately measured. (TIF)

S2 Fig. Intra-observer reproducibility measured by the Pearson coefficient. The same observers re-measured the maximal lipid arch of the selected 10 patients 2 weeks later. (TIF)

S1 Table. All relevant data are available in this table. (XLSX)

**Acknowledgments**

The authors thank Dr. Atsushi Tanida and Dr. Rie Aoyama for their assistance in collecting patient data.

**Author Contributions**

Conceptualization: HT.

Formal analysis: KS YK.

Funding acquisition: WS KA.

Investigation: KS YK.

Methodology: KK.

Project administration: HT.

Resources: KS YK KI SN YT.

Supervision: WS KA.

Validation: HT WS.

Visualization: HT.

Writing – original draft: KS YK.

Writing – review & editing: HT.
References

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979; 241(19):2035–8. Epub 1979/05/11. PMID: 490798

2. Decode Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Archives of internal medicine. 2001; 161(3):397–405. PMID: 11176766

3. Rodriguez BL, Curb JD, Burchfiel CM, Huang B, Sharp DS, Lu GY, et al. Impaired glucose tolerance, diabetes, and cardiovascular disease risk factor profiles in the elderly. The Honolulu Heart Program. Diabetes Care. 1996; 19(6):587–90. Epub 1996/06/01. PMID: 8725856

4. Tomimaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care. 1999; 22(6):920–4. Epub 1999/06/18. PMID: 10372242

5. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karaki A, Laakso M, et al. Impaired glucose tolerance, diabetes, and cardiovascular disease risk factor profiles in the elderly. The Honolulu Heart Program. Diabetes Care. 1996; 19(6):587–90. Epub 1996/06/01. PMID: 8725856

6. de Vegt F, Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia. 1999; 42(8):926–31. Epub 1999/09/24. doi: 10.1007/s001250051249 PMID: 10491751

7. Meigs JB, Nathan DM, D’Agostino RB Sr., Wilson PW. Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care. 2002; 25(10):1845–50. Epub 2002/09/28. PMID: 12351489

8. Capaldo B, Di Bonito P, Iaccarino M, Roman MJ, Lee ET, Devereux RB, et al. Cardiovascular characteristics in subjects with increasing levels of abnormal glucose regulation: the Strong Heart Study. Diabetes Care. 2013; 36(4):992–7. Epub 2012/12/12. doi: 10.2337/dc12-1501 PMID: 23223343

9. Arbustini E, Dal Bello B, Morbini P, Burke AP, Bocciarelli M, Specchia G, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart. 1999; 82(3):269–72. PMID: 10455073

10. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation. 1996; 93(7):1354–63. PMID: 8641024

11. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation. 1995; 92(3):657–71. PMID: 7634481

12. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for noninvasive imaging. Nature clinical practice Cardiovascular medicine. 2008; 5 Suppl 2:S2–10.

13. Ahmadi A, Stone GW, Leipaisj J, Shaw LJ, Villines TC, Kern MJ, et al. Prognostic Determinants of Coronary Atherosclerosis in Stable Ischemic Heart Disease: Anatomy, Physiology, or Morphology? Circulation research. 2016; 119(2):317–29. doi: 10.1161/CIRCRESAHA.116.308952 PMID: 27990334

14. Inami S, Takano M, Kato K, Yoshida A, Nakamura S, Murai K, et al. Disruption of atherosclerotic neointima seven years after bare metal stent deployment. Int Heart J. 2012; 53(4):261–2. Epub 2012/08/11. PMID: 22222277

15. Takanu M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y, et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. Journal of the American College of Cardiology. 2009; 55(1):26–32. Epub 2010/02/02. doi: 10.1016/j.jacc.2009.08.032 PMID: 20117359

16. Kume T, Akasaka T, Kawamoto T, Okura H, Watanabe N, Toyota E, et al. Measurement of the thickness of the fibrous cap by optical coherence tomography. American heart journal. 2006; 152(4):755 e1–4. Epub 2006/09/26.

17. Kato K, Yonetsu T, Kim SJ, Xing L, Lee H, McNulty I, et al. Comparison of nonculprit coronary plaque characteristics between patients with and without diabetes: a 3-vessel optical coherence tomography study. JACC Cardiovasc Interv. 2012; 5(11):1150–8. Epub 2012/11/24. doi: 10.1016/j.jcin.2012.06.019 PMID: 23174639

18. Ryden L, Grant PJ, Anker SD, Beine C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013; 34(39):3035–87. Epub 2013/09/03. doi: 10.1093/eurheartj/eht108 PMID: 23996285
19. Levey AS, Bosch JP, Lewis JB, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Annals of internal medicine. 1999; 130(6):461–70. PMID: 10075613

20. Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. Circulation. 2003; 107(1):113–9. Epub 2003/01/08. PMID: 12515752

21. MacNeill BD, Jang IK, Bouma BE, Iftimia N, Takano M, Yabushita H, et al. Focal and multi-focal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. Journal of the American College of Cardiology. 2004; 44(5):972–9. Epub 2004/09/01. doi: 10.1016/j.jacc.2004.05.066 PMID: 15337206

22. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. Journal of the American College of Cardiology. 2012; 59(12):1058–72. Epub 2012/03/17. doi: 10.1016/j.jacc.2011.09.079 PMID: 22421299

23. Jang IK, Tearney GJ, MacNeill B, Takano M, Moseslewski F, Iftimia N, et al. In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. Circulation. 2005; 111(12):1551–5. doi: 10.1161/01.CIR.0000193934.43778.69 PMID: 15781733

24. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angiography. Journal of the American College of Cardiology. 2007; 50(10):933–9. Epub 2007/09/04. doi: 10.1016/j.jacc.2007.04.082 PMID: 17765119

25. Kurihara O, Takano M, Yamamoto M, Shirakabe A, Kimata N, Inami T, et al. Impact of prediabetic status on coronary atherosclerosis: a multivessel angioscopic study. Diabetes Care. 2013; 36(3):729–33. Epub 2012/12/12. doi: 10.2337/dc12-1635 PMID: 2323344

26. Kuroda M, Shinke T, Sakaguchi K, Otake H, Takaya T, Hirota Y, et al. Association between daily glucose fluctuation and coronary plaque properties in patients receiving adequate lipid-lowering therapy assessed by continuous glucose monitoring and optical coherence tomography. Cardiovasc Diabetol. 2015;14:78. Epub 2015/06/13. doi: 10.1186/s12933-015-0236-x PMID: 26062762

27. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002; 287(19):2570–81. Epub 2002/05/22. PMID: 12020335

28. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. Journal of the American College of Cardiology. 2012; 59(7):635–43. Epub 2012/02/11. doi: 10.1016/j.jacc.2011.08.080 PMID: 22322078

29. Ferrannini E, Gastaldelli A, Iozzo P. Pathophysiology of prediabetes. Med Clin North Am. 2011; 95(2):327–39. vii–viii. Epub 2011/02/02. doi: 10.1016/j.mcn.2010.11.005 PMID: 21281836

30. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295(14):1681–7. Epub 2006/04/13. doi: 10.1001/jama.295.14.1681 PMID: 16609090

31. Kuhl J, Jorneskog G, Wemminger M, Bengtsson M, Lundman P, Kalani M. Long-term clinical outcome in patients with acute coronary syndromes and dysglycaemia. Cardiovasc Diabetol. 2015; 14:120. Epub 2015/09/19. doi: 10.1186/s12933-015-0283-3 PMID: 26382578

32. Lenzen M, Ryden L, Ohrvik J, Bartnik M, Malmberg K, Scholte Op Reimer W, et al. Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. Eur Heart J. 2006; 27(24):2969–74. Epub 2006/11/09. doi: 10.1093/eurheartj/ehl363 PMID: 17090612

33. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. The New England journal of medicine. 1997; 336(18):1276–82. doi: 10.1056/NEJM199705013361802 PMID: 9113990

34. Ozaki Y, Tanaka A, Komukai K, Ishibashi K, Tanimoto T, Kitabata H, et al. High-density lipoprotein cholesterol level is associated with fibrous cap thickness in acute coronary syndrome. Circulation journal: official journal of the Japanese Circulation Society. 2013; 77(12):2982–9.

35. Noor R, Shuaib U, Wang CX, Todd K, Ghani U, Schwindt B, et al. High-density lipoprotein cholesterol regulates endothelial progenitor cells by increasing eNOS and preventing apoptosis. Atherosclerosis. 2007; 192(1):92–9. doi: 10.1016/j.atherosclerosis.2006.06.023 PMID: 16884727