Původní sdělení | Original research article

Non-infarct related chronically occluded coronary arteries and its association with diabetes and prediabetes

Mustafa Karanfil, Ahmet Akdi, Mustafa Bilal Ozbay, Meryem Kara, Ozcan Ozeke, Serkan Cay, Adnan Burak Akcay, Serkan Topaloglu, Dursun Aras

Department of Cardiology, Health Sciences University, Ankara City Hospital, Ankara, Turkey

ARTICLE INFO

Article history:
Submitted: 4. 2. 2019
Accepted: 24. 3. 2019
Available online: 25. 11. 2019

Klíčová slova:
Aterotrombóza
Diabetes mellitus
Chronické totální uzávěry koronárních tepen
Chronické totální uzávěry neinfarktových tepen
Koronární ateroskleróza
Prediabetes

SOUHRN

Kontext: Chronické totální uzávěry koronárních tepen (chronic coronary total occlusion, CTO) jsou většinou spojeny s infarktovou tepnou (infarct-related chronic coronary total occlusion, IRA CTO); ne všechny CTO však musejí vždy vést k rozvoji STEMI nebo být STEMI vyvolány. Klinický profil pacientů s neinfarktovou CTO (non-IRA CTO) by mohl představovat endogenní kardioprotektivní mechanismus aktivovaný v odpověď na ischemii myokardu vyvolanou rozvojem aterosklerózy.
Cíl: Naším cílem bylo posoudit klinický profil pacientů s non-IRA CTO z hlediska přítomných faktorů kardiovaskulárního rizika.
Metody: Prohlédli jsme naši databázi invazivních kardiologických výkonů, přičemž jsme pátrali po non-IRA CTO jakékoli významnější koronární tepny a snažili jsme se zjistit, zda byl v anamnéze pacienta uveden infarkt myokardu nebo zda byl nalezen elektrokardiografický (kmity Q, vymizení kmitu R), echokardiografický nebo ventrikulografický důkaz v tomto směru (abnormální kinetika segmentu stěny levé komory). Následně jsme porovnali incidenci non-IRA CTO u pacientů s diabetem, prediabetem a u kontrolních skupin jedinců bez diabetu nebo prediabetu.
Výsledky: Popisujeme průřezovou studii s 2 180 pacienty, u nichž byla v období mezi lednem a dubnem 2018 v nemocnici terciární péče provedena koronarografie pro zhodnocení stabilní ischemické choroby srdeční. Nalezli jsme 41 po sobě následujících pacientů s non-IRA CTO (1,9 %) s nízkou prevalencí kuřáctví (7 %). Většina jedinců s uvedeným nálezem (93 %) měla buď diabetes (61 %), nebo prediabetes (32 %); v tomto ohledu se statisticky významně lišili od jedinců bez diabetu nebo prediabetu ($p < 0,001$).
Závěr: Nalezli jsme vztah mezi non-IRA CTO a prediabetem a diabetem. Zatímco diabetes a prediabetes agresivně vyvolávají aterosklerózu, mohou aktivovat i endogenní kardioprotektivní mechanismy chránící kontraktilní funkci levé komory.

Keywords:
Atherothrombosis
Chronic total occlusions
Coronary atherosclerosis
Diabetes mellitus
Non-infarct related chronic total occlusions
Prediabetes

ABSTRACT

Background: Chronic coronary total occlusions (CTOs) are mostly associated with infarct-related artery (IRA CTO); however, all CTOs may not always lead to or be caused by STEMI. Clinical profile of patients with non-infarct-related artery related CTOs (non-IRA CTO) might give us endogenous cardioprotective mechanisms activated in response to myocardial ischemia caused by atherosclerotic process.
Objective: We aimed to evaluate the clinical profile of non-IRA CTO with regard to cardiovascular risk factors.
Methods: We reviewed our invasive cardiology database searching for the non-IRA CTO of any major coronary arteries, and assessed whether or not they have the clinical history or electrocardiographic (Q waves, loss of R wave), echocardiographic or left ventriculographic (segmental wall motion abnormality) evidence of previous myocardial infarction. The rates of non-IRA CTO were compared among diabetes, prediabetes and non-diabetic/prediabetic control groups.
Results: This was a cross-sectional study of 2180 patients who underwent coronary angiogram for the evaluation of stable coronary artery disease at a tertiary care hospital from January 2018 to April 2018. We detected 41 consecutive patients with non-IRA CTO (1.9%) with a low prevalence of smoking (7%). The most of patients (93%) had either DM (61%) or prediabetes (32%), and this was statistically different from non-diabetic/prediabetic patients ($p \leq 0.001$).
Conclusion: Non-IRA CTOs have been found to be associated with prediabetes and diabetes. Whereas the DM and prediabetes aggressively induces atherosclerosis, they can also activate some endogenous cardioprotective mechanisms protecting the left ventricular contractile function.

Address: Ozcan Ozeke, MD, Sağlık Bilimleri Üniversitesi, Ankara Şehir Hastanesi, Kardiyoloji Klinigi, 06800 Ankara, Turkey, e-mail: ozcanozeke@gmail.com
DOI: 10.33678/cor.2019.010

Please cite this article as: Karanfil M, Akdi A, Ozbay MB, et al. Non-infarct related chronically occluded coronary arteries and its association with diabetes and prediabetes. Cor Vasa 2019;61:e567–e572.

Introduction

Atherosclerosis is the leading cause of morbidity and mortality in the industrialized world and diabetes mellitus (DM) magnifies the risk of cardiovascular events.[1] Whereas "atherosclerosis" is a chronic and progressive process (causing stabile coronary artery disease, SCAD), the rupture of high-risk, vulnerable plaques is responsible for "atherothrombosis" (causing acute coronary syndrome, ACS).[2] Therefore, the presence of atherosclerosis is necessary but not sufficient for atherothrombosis. Whereas most coronary chronic total occlusions (CTO) are generally associated with late organization of an acute thrombotic total occlusion generated by vulnerable plaque rupture causing acute ST elevation myocardial infarction (STEMI)[3] (infarct-related artery related CTOs – IRA CTO), all total occlusions may not always lead to or caused by STEMI. Therefore, CTO are of two origins,

1. "IRA CTO" – those resulting from an STEMI and usually associated with a loss of viability and segmental wall motion abnormality (SWMA);
2. "Non-infarct-related artery related CTOs – non-IRA CTO" – those resulting from a progressive chronic stenosis that eventually evolves into a complete occlusion but with preserved viability and left ventricular contractility (Fig. 1). Although severe stenosis may progress to complete occlusion, the presence of collateral flow and other endogenous cardioprotective mechanisms may protect against the development of myocardial infarction (MI) and SWMA.[4–7]

Clinical profile of patients with non-infarct-related artery related CTOs might give us endogenous cardioprotective mechanisms activated in response to myocardial ischemia caused by atherosclerotic process. It has been previously reported an association between the non-IRA CTO and DM.[5] While, prediabetes is commonly an asymptomatic condition, there is always presence of prediabetes before the onset of DM.[8] Therefore, we examined the possible association of prediabetes with non-IRA CTO.

Methods

We reviewed our invasive cardiology database searching for the CTO of any major coronary arteries, and assessed whether or not they have the clinical history or electrocardiographic (Q wave, precordial R loss), echocardiographic or left ventriculographic evidence (SWMA) of previous MI. Conventional cardiovascular risk factors, including cigarette smoking, DM, hypertension, hyperlipidemia, and family history of early SCAD, were the targets for evaluation.

Patients were further stratified into three groups according to their HbA_{1c} levels: nondiabetic group (HbA_{1c} < 5.7%), prediabetic group (5.7 £ HbA_{1c} < 6.5%) and those with diabetes group (HbA_{1c} ³ 6.5%) according to 2019 ADA definition.[9] Patients with previous DM on antidiabetic or insulin therapy also included in the diabetic group.

We compared the frequency of non-IRA CTO rates among nondiabetic, prediabetic, and diabetic patients. Each coronary artery was displayed on at least 2 different

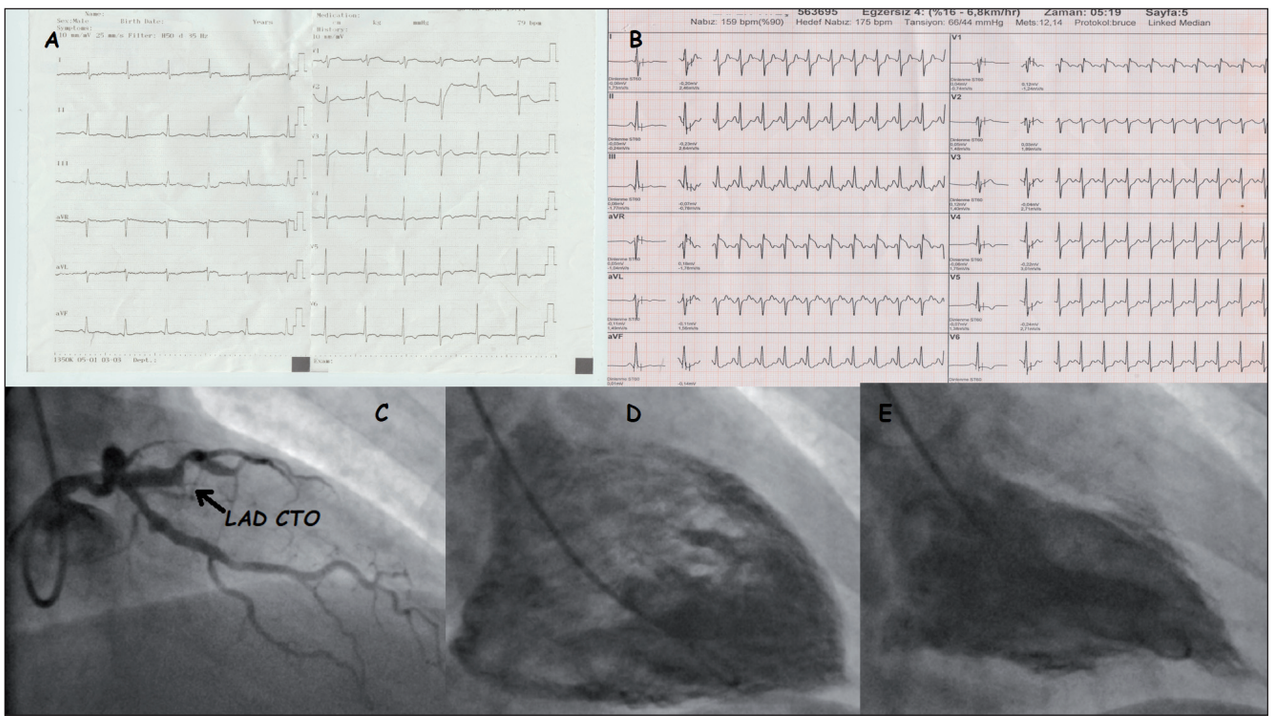

Fig. 1 – An example of non-IRA CTO in a 45-year-old patient with prediabetes presenting with stabile angina pectoris. 12-lead electrocardiogram (A) shows sinusal rhythm with lateral T wave inversions but without pathological q waves. Exercise testing at fourth stage (B) shows positive stress testing findings with ST elevation at leads avR and V_1 but ST depression at V_5–V_6 leads. Coronary angiogram at right anterior oblique position (C) shows CTO at LAD coronary artery. Left ventriculogram taken at diastole (D) and systole (E) shows no segmental wall motion abnormality. CTO – chronic total occlusion; LAD – left anterior descending coronary artery; non-IRA CTO – non-infarct-related artery CTOs.

Table 1 – Basal clinical and angiographic features of non-IRA CTO patients

	Non-IRA CTO patients (n = 41)
Age (years)	60.85 ± 4.92
Sex (male) Diabetes mellitus (%)	66% 61%
Prediabetes (%) Hypertension (%)	32% 54%
Current smoking (%)	7%
Family history	42%
CTO in LAD CTO in RCA CTO in Cx Good collateral circulation (%) LVEF	37% 56% 7% 100% 61.85 ± 2.09

CTO – chronic total occlusion; Cx – circumflex artery; LAD – left anterior descending artery; LVEF – left ventricular ejection fraction; non-IRA CTO – non-infarct-related artery CTO; RCA – right coronary artery.

planes. All measurements were performed by the same cardiology specialist blinded to the subjects' clinical and laboratory status. A CTO was defined as a non-IRA with 100% luminal narrowing before percutaneous intervention and without anterograde flow or with anterograde or retrograde filling through collateral vessels. The differentiation between a CTO and acute occlusion was based on a combination of the following factors: morphology of the occlusion (presence of fresh thrombus, bridge, and ipsi- or contra-lateral collaterals), the ECG recording, echocardiogram findings, and a possible history of prior documented MI in the same territory (Fig. 1). The collateral filling of the recipient artery was assessed according to modified Rentrop and Thrombolysis In Myocardial Infarction collateral grading system ("recipient filling grade").[10]

All analyses were performed using the SPSS 20.0 Statistical Package Program for Windows (SPSS Inc. Chicago, Illinois). The Kolmogorov-Smirnov test was used to assess normality of distribution. Continuous variables were expressed as mean plus standard deviation or median with interquartile range, while categorical variables were represented as numbers and percentages. Goodness of fit tests are used to compare any observed frequency distribution against an expected frequency distribution. Comparisons between groups were performed by one-way analysis of variance (ANOVA) followed by the Tukey test for parametric data, or by chi-square and Kruskal-Wallis test (for more than two group) for non-parametric data. Tukey test for normally distributed parametric data and Dunn's test for not normally distributed data was used for post hoc analysis between three groups. A p-value < 0.05 was considered statistically significant.

Results

This was a cross-sectional study of 2180 patients who underwent coronary angiogram for the evaluation of SCAD at a tertiary care hospital from January 2018 to August 2018. 410 patients with ACS (STEMI, NSTEMI or unstable angina) were not included to analysis. We detected 41 consecutive patients with non-IRA CTO (1.9 %) with a low prevalence of smoking (7%).The basal characteristics of total 41 patients with non-IRA CTO reported in Table 1. The most non-IRA CTO detected in right coronary artery (54%) and subsequently left anterior descending coronary artery (37%). The most of patients (93%) had either DM (61%) or prediabetes (32%), and this was statistically different from non-diabetic/prediabetic patients ($p \leq 0.001$) (Table 2). However, there was no statistically important difference between the diabetic and prediabetic patients ($p = 0.052$). The smoking rate was low (7%) in non-IRA CTO patients. Whereas most ECGs were completely normal, T wave abnormalities (biphasic or negative without R wave loss or q wave) were most abnormal finding (10/41, 24%) in non-IRA CTO patients.

Discussion

Whereas our group has reported an association of DM with non-IRA CTO,[5] the present study demonstrated that

Table 2 – Comparison of the frequency of non-IRA CTO with regard to diabetic status of patients

Groups	Diabetes (n = 25)	Prediabetes (n = 13)	Normal (n = 3)	p-value
Age (year)	61.6 ± 4.0	58.6 ± 4.9	64.7 ± 9.5	0.079
Family history (%)	36%	46%	67%	0.058
Hypertension (%)	64%	39%	33%	0.167
Current smoke (%)	4%	8%	33%	< 0.001
LDL (mg/dL)	106.24 ± 30.54	116.92 ± 43.51	148.67 ± 93.54	0.222
HDL (mg/dL)	42.64 ± 9.71	39.85 ± 9.21	39.33 ± 9.81	0.642
Triglyceride (mg/dL)	216.48 ± 76.99	236.31 ± 85.92	117.00 ± 32.05	0.071
HbA_{1c} (g/dL)	8.48 ± 1.82	5.98 ± 0.16	5.27 ± 0.06	< 0.001
LVEF (%) (median [min–max])	60 (60–66)	62 (60–65)	62 (60–66)	0.432
Non-IRA CTO (%)	61%	32%	7%	< 0.001

CTO – chronic total occlusion; HDL – high density lipoprotein; LDL – low density lipoprotein; LVEF – left ventricular ejection fraction; non-IRA CTO – non-infarct-related artery CTO.

the prediabetes was also associated with non-IRA CTO particularly in nonsmoker SCAD patients. Whereas the DM and prediabetes aggressively induces atherosclerosis and may be more susceptible to infarction; they can also activate some endogenous cardioprotective mechanisms protecting the left ventricular contractile function in the absence of smoking,[5,11] which might prevent endogenous cardioprotective mechanisms in these patients.

Diabetes is a powerful cardiovascular risk factor that is associated with more advanced and accelerated systemic and coronary atherosclerosis.[12] Prediabetic patients who subsequently develop diabetes are also considered to be high-risk subjects in terms of their cardiovascular mortality,[13,14] and some speculated that MI could be a prediabetes risk equivalent.[15] The European guidelines for diabetes, prediabetes, and cardiovascular disease recommend that all patients with cardiovascular disease manifestations are screened with an oral glucose tolerance test.[13]

Atherosclerotic plaques that lead to ACS often occur at sites of angiographically mild coronary-artery stenosis,[16] however, it is important to take into account that less severe stenotic plaques are 5–10 times more common than severely stenotic plaques.[17] There is growing interest in the possibility that identification and treatment of vulnerable plaques and vulnerable patients can enhance the progress made against coronary artery disease. Although emphasis on the vulnerable patient instead of vulnerable plaque is appropriate,[18] identifying these individuals in primary prevention is difficult. Future culprit lesions are difficult to identify and angiographic assessment of stenosis severity is prone to underestimation. We need to know which factors convert or protect stable patients to/from vulnerable ones. Whereas the rupture-prone vulnerable plaques in particular are thought to consist of a thin, fibrous cap covering an atheromatous, lipid-rich core (cholesterol and its esters),[19] the stable plaques at low risk of rupture have different characteristics, including a thick fibrous cap and macroscopic calcification.[2] Because severely stenotic plaques are more likely to stimulate collateral circulation to the post-stenotic segment, plaque rupture and thrombosis at such sites may be clinically silent.[17] Although severe stenosis may progress to complete occlusion, the presence of collateral flow and other endogenous cardioprotective mechanisms may protect against the development of MI and SWMA. In the setting of primary percutaneous coronary intervention, encountering with non-IRA CTOs is not a rare situation.[20] Among STEMI patients, about 50% have single vessel disease, while about 40% have multivessel disease (MVD) and near 10% have MVD with non-IRA CTO.[21] The occurrence of non-IRA CTO is present in approximately one-third of patients with non-ST elevation myocardial infarction (NSTEMI) and MVD.[22] The patients with NSTEMI and CTO probably had left ventricular dysfunction before their MI as a consequence of the greater extent of their SCAD. However it is interesting that more than 60% of the patients in the CTO group had not had a documented MI before admission.[22]

Enhancement of coronary collateral function is another important endogenous protective mechanism for the preservation of ischemic myocardium.[23] In adult organisms, the compensatory growth of blood vessels under ischemic conditions is an appreciated response, which can be achieved in two distinctive ways (i.e., arteriogenesis and angiogenesis).[24] While angiogenesis is induced by hypoxia and results in new capillaries, arteriogenesis is induced by physical forces, most importantly fluid shear stress. Consequently, chronically elevated fluid shear stress was found to be the strongest trigger under experimental conditions. Arteriogenesis describes the remodeling of pre-existing arterio-arteriolar anastomoses to completely developed and functional arteries.[25] It has been shown that the angiogenesis is regulated by a complex interplay of antiangiogenic and proangiogenic factors.[11,26,27] DM adversely affects coronary collateral development through multiple cellular mechanisms on arteriogenesis and angiogenesis, and the formation of coronary collaterals in patients with DM and CTO is influenced by various clinical, biochemical and angiographic factors.[28] The diabetic pathophysiology promotes an anti-angiogenic process and meanwhile mitigates pro-angiogenic factors in coronary vasculature during ischemia, jointly leading to impaired collateral growth.[28,29] Although the influence of the DM on collateral development is debatable,[11,30–34] it has been reported that diabetics and prediabetics generally have a poor acute collateral response because of the diffusely impaired endothelial function,[35–37] particularly in the presence of active smoking.[5,38,39]

Whereas the DM and prediabetes aggressively induces atherosclerosis and may be more susceptible to infarction; they can also activate some endogenous cardioprotective mechanisms protecting the left ventricular contractile function.[11] Despite more severe coronary calcification, including calcified nodules, potent pro-inflammatory, pro-oxidant, and pro-thrombotic stimuli in diabetic patients, these patients seem to experience their first event at a later stage in the process of CAD as compared with non-diabetic patients.[11] The severity of the coronary stenosis (CTO or not) plays a part in the intensity of arteriogenesis.[40] Moreover, the lower levels of lipids and higher levels of calcium in diabetic patients could help to identify plaque characteristics which might be less thrombogenic.[11] Whereas the brief episodes of ischemia can have a negative effect on the heart by stunning, they have a protective effect via preconditioning. Although some have been reported that preconditioning protection against infarction and stunning do not develop in diabetic hearts.[41] Niccolli et al. hypothesized that there might be, besides an increased presence of collaterals, also other as yet unidentified protective factors operating in DM patients, which is an intriguing finding.[11] Therefore, the majority of coronary plaque rupture events appear to be clinically silent, resulting in plaque growth rather than MI.[2] In patients with stable CAD, a gradual development of complete CTO may lead to a sufficient compensation of blood supply via collateral circulation induced by angiogenesis to prevent myocardial damage from ischemic insults.[42] This mechanism may be important in increasing the capacity of a poorly developed collateral circulation over time, particularly in CTO patients due to progressive occlusion of a long-term high-degree stenosis.[43] It can protect and preserve myocardium around the time of coronary occlusion, contribute to better residual myocardial contractility, and lessen symptoms and it is

compatible with better survival if adequately exist.[23] The revascularization decision of a CTO should be based not only on clinical manifestation of the patients but also on the morphology of occluded coronary lesions, the quality of collaterals, and myocardial viability.[28] Current evidence favors coronary artery bypass grafting as the preferred revascularization modality for diabetic patients with MVD/CTO, which is likely to reflect the more complete revascularization and global protection provided by arterial conduits against rapid atherosclerosis progression in percutaneous coronary intervention and untreated segment.[28]

In the current study, we found that the prediabetes beyond the DM was also associated with non-IRA CTO. The present definition of DM is based on the level of glucose at which retinopathy occurs, but macrovascular complications such as coronary artery disease appear earlier and, using current glycemic criteria are often present at the time when DM is diagnosed.[13] The development of metabolic risk goes through a continuum from normoglycemia to prediabetes and DM. The progression from prediabetes to DM occurs over many years, strong evidence to support intervention to delay the progression from prediabetes to DM.[8] However, several issues in the management of prediabetes remain controversial, such as the role of pharmacotherapy and when to escalate treatment.[44] Therapeutic promotion of collateral growth[42] and exercise[45] is a valuable treatment strategy in those patients. Furthermore, the future challenge is how to minimize the stunning phenomenon and maximize the preconditioning phenomenon in clinical practice.[45] Since smoking cessation has not been found associated with an increased risk of prediabetes or DM,[46] health professionals should strongly recommend smoking cessation with focus on limiting weight gain after quitting particularly in diabetic and prediabetic patients.

An inherent incongruity exists between how DM is diagnosed in clinical practice and how DM cases are identified in epidemiologic studies.[47] Despite complete interruption of antegrade coronary artery flow in the setting of a CTO, clinical recognition of MI is often challenging.[48] The use of HbA_{1c} to diagnose DM has limitations as any factor affecting the quantity or quality of the hemoglobin molecule can result in measurement inaccuracies. When using HbA_{1c} to diagnose DM, it is important to recognize that A_{1C} is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia including age, race/ethnicity, erythrocyte lifespan and anemia/hemoglobinopathies.[49] This has not been accounted for in our study.

Conclusion

In conclusion, the non-IRA CTO have been found to be associated with prediabetes and diabetes in current study. Despite more earlier and progressive atherosclerosis in diabetic and prediabetic patients,[32] some endogenous protective mechanisms also might be more effective in these patients particularly in the absence of smoking.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

The authors report no financial relationships regarding the content herein.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

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