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Review Article

Coronary artery disease and diabetes mellitus

Mansour M. Al-Nozha, FACC [a,*], Hussein M. Ismail, MD [b] and Omar M. Al Nozha, MD [a]

[a] *Department of Medicine, School of Medicine, Taibah University, Almadinah Almunawwarah, KSA*
[b] *Cardiology Department, School of Medicine, Suez Canal University, Ismailia, Egypt*

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لملخص

أهداف البحث: هناك علاقة وطيدة بين مرض السكري ومرض الشرايين التاجية. ولا تعد الإصابة بمرض السكري مجرد عامل خطورة للإصابة بأمراض الشرايين التاجية، وإنما تعتبر مساوية لمن هو فعلا مصاب بأمراض الشرايين التاجية. نسب انتشار المرضين في ازدياد، ويُعزى ذلك بالدرجة الأولى إلى زيادة انتشار السمنة. ويلعب التغير السريع في نمط الحياة، لاسيما في الدول النامية، دورا رئيسا في الإصابة بالمرضين.

طرق البحث: قمنا بدراسة استرجاعية للأدبيات بهدف تلخيص واستكشاف العلاقة بين مرض السكري وأمراض الشرايين التاجية، مع تركيز خاص على الدول العربية في ما يخص عوامل الخطورة ونسبة الانتشار. كما نقترح اتجاهات مستقبلية لمنع الزيادة في انتشار المرضين في الدول العربية.

الاستنتاجات: يجب أن يشتمل أي برنامج وقائي لأمراض الشرايين التاجية على استراتيجيات للوقاية من مرض السكري، وغيره من عوامل الخطورة الأيضية المصاحبة له مثل السمنة. كما ينبغي التشجيع على الإجراءات الوقائية مثل التمارين الرياضية في الفئات المجتمعية المعرضة للإصابة.

الكلمات المفتاحية: العالم العربي؛ مرض السكري؛ السمنة؛ أمراض الشرايين التاجية؛ التمارين الرياضية

Abstract

Objectives: Diabetes mellitus (DM) and coronary artery disease (CAD) are closely related. DM is a risk factor for CAD, but it is also equivalent to established CAD. The prevalence of DM and CAD is growing primarily due to the rising prevalence of obesity. The rapidly changing life style, especially in developing countries, plays major role in the occurrence of these diseases.

Methods: We performed a literature review to summarize and explore the relationship between CAD and DM with a special focus on Arab countries in terms of risk factors and prevalence. We suggest future directions to prevent escalation in the incidence of DM and CAD in Arab countries.

Conclusion: An important part of any preventive program for CAD should include clear prevention strategies for DM and other associated metabolic risk factors, such as obesity. Preventive measures, such as physical exercise in high-risk groups, at the population level should be encouraged.

Keywords: Arab world; Coronary artery disease; Diabetes mellitus; Obesity; Physical exercise

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Introduction

Coronary artery disease (CAD) is a major cause of death in Western countries, and it is becoming a major cause of death in developing countries. This increase may be due to the rising prevalence of many CAD risk factors, such as diabetes, which is one of the most important of these risk factors. The prevalence of diabetes is increasing globally, and it has reached pandemic levels in the Middle East and worldwide.[1]

* Corresponding address: Department of Medicine, School of Medicine, Taibah University, P. O. Box: 30088, Almadinah Almunawwarah, 41477, KSA.
E-mail: malnozha@hotmail.com (M.M. Al-Nozha)
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The prevalence of diabetes in patients with CAD is up to 50% in many countries.[2] The impact of tighter control of diabetes on cardiovascular morbidity and mortality has been controversial with conflicting results, which attracted special attention in current diabetes management guidelines. The measurement of this impact remains an active area of research.

Diabetes and atherosclerosis

Type 2 diabetes mellitus (DM) is a strong risk factor for CAD, and experts consider DM an equivalent to established CAD risk.[3] Patients with diabetes have 2- to 4-fold greater risk of developing CAD than non-diabetic patients.[4,5]

Diabetic patients exhibit an increased risk for development of atherosclerotic CAD for many reasons, including metabolic factors, like hyperglycaemia, dyslipidemia and insulin resistance, which lead to endothelial cell, vascular smooth muscle dysfunction,[6,7] impaired platelet function and abnormal coagulation.[8] Diabetic patients tend to exhibit other risk factors for CAD, like hypertension and obesity. Patients with diabetes have lipid-rich atherosclerotic plaques, which are more vulnerable to rupture than the plaques seen in non-diabetic patients.[9,10] Yoo et al. described an overall increase in atherosclerotic burden and a 3.5-fold higher risk of coronary stenosis that was independent of other cardiovascular risk factors in diabetic patients.[11]

Inflammation plays an important role in atherosclerosis. Inflammation activation in type 2 DM results from obesity and insulin resistance, in which an acute phase reaction occur, and a large number of inflammatory and pro-inflammatory cytokines are released from adipose tissue.[12] Endothelial dysfunction is generally present in diabetic patients with CAD, as evidenced by high levels of endothelin 1 and low levels of nitric oxide.[13] Vascular endothelial (VE)-cadherin was identified recently as an updated marker of endothelial function that is well-correlated with endothelin 1 in diabetic patients with CAD.[14]

Enhanced thrombus formation occurs in type 2 DM because of increased platelet activity and blood coagulability.[15] Pathological alterations in fibrinogen and plasminogen activation inhibitors are primarily relevant for the short-term incidence of cardiovascular events in patients with type 2 DM.[16]

Notably, not all diabetic patients develop cardiovascular disease despite the presence of the same risk factors. However, recent studies focused on biomarkers of CVD in diabetic patients, such as serum phospholipids and their role in the progression of CVD. Beatriz García-Fontana and colleagues recently found low serum levels of 4 phospholipids in diabetic patients with CVD compared to diabetic patients without CVD.[17]

A recent study found a new biomarker in type 2 DM complicated with CAD that was significantly elevated and positively correlated with the degree of CAD stenosis. This new biomarker is called Osteonectin Secreted Protein Acidic and Rich in Cysteine (SPARC). The mechanism by which SPARC may cause CAD development requires further research.[18]

Palazhy et al. evaluated oxidative stress in CAD patients on statins in a cross-sectional study of 3 groups: Group 1, healthy control; Group 2, patients with DM and CAD on statins; Group 3, only diabetic patients. They found that oxidative stress was higher in the CAD and DM group despite statin therapy. These results highlighted the importance of oxidative stress.[19]

Diabetes as a risk factor for CAD

The prevalence of DM is increasing globally, and the International Diabetes Federation (IDF) estimated that there were 387 million people with DM in 2013, and this incidence is expected to rise to 592 million by 2035. An estimated 1 in 10 people have DM in the Middle East and North Africa (MENA) region.[20] Six of the top ten countries with a high estimated prevalence of DM were Arab countries in the 2011 IDF global estimate: Kuwait, Lebanon, Qatar, KSA, Bahrain and United Arab Emirates.[21] Three of the top 10 countries with a high estimated prevalence of DM were Arab countries in the updated 2014 IDF estimate: KSA, Kuwait and Qatar.[20] (Table 1 and 2).

The overall prevalence of DM was 23.7%, (26.2% in males & 21.5% in females) in a study of the prevalence of diabetes in KSA,[22] which was part of the Coronary Artery Disease in Saudis Study (CADISS),[23] and the impaired fasting blood glucose was 14.1% for males and females combined. A total of 27.9% of diabetics were unaware of having diabetes,[22] and 34% of diabetic patients were hypertensive compared to 21.4% without DM ($P < 0.001$).[24] These factors further contribute to the risk of CAD in the KSA population.

CADISS is a national community-based study that examined 17,232 KSA subjects aged 30–70 years from randomly selected households. The primary objective was to estimate the prevalence of CAD and its risk factors in KSA. The overall prevalence of CAD was 5.5% (6.6% in males, 4.4% in females).[23]

The prevalence of type 2 DM in KSA is expected to rise because of the high prevalence of obesity. The overall prevalence of obesity was 35.6% in CADISS with a higher prevalence in females (44%) compared to males (26.4%) ($P < 0.0001$).[25]

Another important factor in the high prevalence of DM in KSA is the high prevalence of physical inactivity, with an overall prevalence of 96.1% (98.1% in females vs. 93.9% in males) ($P < 0.001$).[26]

The prevalence of metabolic syndrome in KSA is also very high (39.3%), and it is higher in females (42%)

Table 1: The adjusted prevalence of diabetes in some Arab counties in 2011 [adopted from Top 10 countries/territories for prevalence (%) of people with diabetes (20–79 years), 2011 and 2030[a]].

Country	The adjusted prevalence (%)	Rank in top 10 countries for prevalence
Kuwait	20.7	3
Qatar	19.8	5
KSA	19.6	6
Lebanon	19.6	7
Bahrain	19.5	8
United Arab of Emirates	18.8	10

[a] Adopted from The IDF Diabetes Atlas 2011[21].

Table 2: Top 10 countries/territories for prevalence[a] (%) of people with diabetes (20–79 years), 2013 and 2035[b].

2013		2035	
Country/territory	%	Country/territory	%
Tokelau	37.5	Tokelau	37.9
Federated States of Micronesia	35.0	Federated States of Micronesia	35.1
Marshall Islands	34.9	Marshall Islands	35
Kiribati	28.8	Kiribati	28.9
Cook Islands	25.7	Cook Islands	25.7
Vanuatu	24.0	KSA	24.5
KSA	24.0	Vanuatu	24.2
Nauru	23.3	Nauru	23.3
Kuwait	23.1	Kuwait	23.2
Qatar	22.9	Qatar	22.8

[a] Comparative prevalence.
[b] Adopted from The IDF Diabetes Atlas 2014[20].

compared to males (37.2%). The prevalence of DM in patients with metabolic syndrome was 67.8% compared to 15.7% in DM patients without metabolic syndrome.[27]

A recent cross-sectional community-based Indian study published in January 2016 estimated the prevalence of CAD and its risk factors and found that the age-adjusted prevalence of definite CAD was 3.5% in the entire study population, 4.8% in males, and 2.6% in females. DM was found in 15% of the population, hypertension in 28%, smoking in 28%, and overweight or obesity in 59%.[28]

A recent study investigated the prevalence of CAD risk factors in 1056 healthy adults in Brazil and found that the prevalence of DM was 11%, systemic hypertension was 40%, family history of CAD was 50%, smoking was 23%, dyslipidemia was 43%, and overweight/obesity was 68%.[29]

Diabetes in CAD patients

Several studies in the Arabian Gulf region had limitations because a large proportion of expatriates were included in the population. This inclusion was reflected in the results that revealed a similar prevalence in their country of origin. Therefore, we excluded many of these studies from the current review.

The World Health Organization (WHO) initiated a cross-sectional study, the Prevention of Recurrences of Myocardial Infarction and Stroke (WHO-PREMISE), of 10,000 patients in 10 countries, primarily the Middle East, which exhibits coronary heart disease in approximately 85% of the population and cerebrovascular disease (CVD) in approximately 15%. The working group found a high prevalence of some risk factors, and DM was found in approximately one third of the patients (31.5%).[30]

National data from Lebanon are scarce. The Lebanese Interventional Registry provided data of the cardiovascular risk factors of patients who presented for coronary angiography. The risk factors included DM (29%), hypertension (60%), smoking (50%), and dyslipidemia (29%).[31]

The INTERHEART study is a case-control study of modifiable risk factors in acute myocardial infarction patients. The investigators studied 15,152 patients and 14,820 controls, which included more than 1500 patients and 1700 controls from the Middle East. Subgroup analysis of the Middle East group revealed a diabetes prevalence of approximately 15%, hypertension was present in approximately 9%, and current smokers included approximately 45% of cases. Dyslipidemia and abdominal obesity were present in 70% and 25% of cases, respectively.[32]

The Gulf Registry of Acute Coronary Events (Gulf RACE) is the first multi-national acute coronary syndrome registry in the Middle East. These investigators studied patients with in the United Arab Emirates, Kuwait, Bahrain, Oman, Qatar and Yemen. A total of 1484 ACS patients were recruited. Myocardial infarction formed the majority of cases (approximately 69%), and DM prevalence was relatively high (38%). Hypertension was present in 46% of the study population, hyperlipidaemia in 31%, and smoking in 45%.[33]

The Second Gulf Registry of Acute Coronary Events (Gulf RACE 2) is a registry studying the effects of DM and new-onset hyperglycaemia on cardiovascular outcomes in ACS patients from Arabian Gulf countries. More than 7000 patients were recruited from 6 Arabian Gulf countries: KSA, Bahrain, Qatar, Oman, United Arab Emirates, and Yemen. The prevalence of DM was high; 49.2% of the study patients had been diagnosed previously with DM (23% on insulin, and 76% treated with oral anti-diabetic agents and/or diet control). New-onset hyperglycaemia was estimated at 8.8%.[2]

The DM prevalence reported in Gulf RACE 2 was very high compared to the Western data in the Global Registry of Acute Coronary Events (GRACE) registry (approximately 24%)[34] and the Asian data found in treatment and outcomes of ACS in an Indian registry (about 30%).[35]

Hersi et al. examined the gender difference between patients with ACS from 17 participating centres in KSA. More than 5000 patients were recruited, and the prevalence of DM in the entire study population was even higher at 58%, 73% in the female subgroup, and 41% in the male subgroup.[36] Mobeirek and co-workers found a relatively high prevalence of risk factors in the SPACE registry (the KSA Patients Admitted with acute Coronary syndromes registry) in KSA: DM (57%), overweight or obesity (72%), hypertension (56.6%), dyslipidemia (42%), and smoking (32.4%).[37]

A total of 16,736 patients with acute coronary syndrome were studied in a 20-year registry (1991 to the end of 2010) from Hamad Medical Corporation (HMC) in Qatar. This centre provides medical services to different ethnicities in the area, and the results should be interpreted carefully. The prevalence rates of DM were 65.7% and 37.4% in females and males, respectively, and hypertension prevalence was estimated as 68.1% in females and 36.5% in males.[38]

Abdelmoneim and colleagues published the results of their cross-sectional observational study of the demographic of ACS in Egypt in 2014. They studied 795 ACS patients divided into 2 groups: group 1 (270 patients), ST segment Elevation Myocardial Infarction (STEMI) and group 2 (525 patients), Unstable Angina/Non-ST Segment Elevation Myocardial Infarction (UA/NSTEMI). The prevalence of DM in these groups was 34% and 45%, respectively. Other reported risk factors in these groups were hypertension (33% and 59%, respectively), dyslipidemia (29% and 39%, respectively), smoking (51% and 38%, respectively), family history (16% and 7%, respectively), and male gender (72% and 64%, respectively).[39]

Another Egyptian study recruited 142 patients with STEMI and classified patients into 2 groups according to waist circumference. The prevalence of diabetes was (53/142) 37.3% in the entire study population. The prevalence of other risk factors was hypertension 41.5%, current smoking 49.3%, and family history of coronary artery disease 16.2%.[40]

Jain et al. (2015) investigated the risk factors for post-myocardial infarctions and assessed coronary artery anatomy using coronary angiography. They found that the prevalence of DM was 28.2%, hypertension was 31.4%, dyslipidemia was 37.5%, and current smoker was 44.9%.[41]

Screening of diabetic patients for CAD

The 2015 American Diabetes Association (ADA) recommendations suggest that diabetic patients who are candidates for advanced investigations that may include coronary angiography are patients with cardiac symptoms (either typical or atypical) or patients with abnormal resting electrocardiogram (ECG). Routine screening of asymptomatic patients is not recommended[42] because high-risk diabetic patients for CAD should receive optimal medical therapy (OMT) to reduce the incidence of cardiovascular events, even if they are asymptomatic. A large body of evidence confirms that OMT provides similar benefits as percutaneous coronary intervention (PCI) in stable CAD. This evidence came from 2 landmark trials: the first trial, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[43]; and the second trial, the "Bypass Angioplasty Revascularization Investigation 2 Diabetes" (BARI 2D) Trial.[44]

Other studies also demonstrate that the coronary artery calcium score (CACS) provides refined risk stratification for high-risk patients,[45] but coronary computed tomography angiography (CCTA) provides a more detailed assessment of subclinical CAD and had a better prognostic value than CACS.[46]

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study assessed cardiac autonomic neuropathy in 1119 asymptomatic type 2 DM patients using autonomic heart rate, blood pressure, and heart rate variability. Cardiac autonomic neuropathy predicted adverse cardiac events in 8.4% of the studied population who developed symptomatic cardiac disease during the 5 years of follow-up.[47]

The COURAGE trial examined 2287 patients with stable CAD with objective evidence of ischaemia who were randomised to PCI with OMT versus OMT alone. The primary outcome endpoint was a composite of death from any cause and non-fatal myocardial infarction. There was no significant difference in the primary outcome at the mean follow-up of 4.6 years. Therefore, the addition of early PCI to OMT did not reduce the long-term risk of death or myocardial infarction (MI) in COURAGE patients regardless of diabetes status.[48] The BARI-2D trial examined the coronary revascularization using PCI or Coronary Artery Bypass Grafting (CABG) versus intensive medical therapy in patients with type 2 diabetes. The research group found no significant difference in the all-cause mortality or the composite endpoints of death, MI or stroke (BARI-2D trial).[44]

A total of 1123 diabetic patients were recruited in the DIAD study, and 522 patients were randomised for adenosine-stress myocardial perfusion imaging screening. A total of 358 patients underwent repeat adenosine-stress myocardial perfusion imaging 3 years after the first evaluation. Fifty-six of the 71 patients with abnormal studies during the initial evaluation (79%) had resolution of ischaemia on the myocardial perfusion scan after 3 years. Fifteen (21%) patients had abnormal studies at follow up. There were more patients using aspirin, statins, and angiotensin-converting enzyme inhibitors (ACEIs) at the 3-year follow up than the initial evaluations. This increase supports the evidence that silent myocardial ischaemia may resolve over time with OMT. This result undermines the strategy of routine aggressive screening of asymptomatic diabetic patients and emphasises the importance of the use of evidence-based OMT for high-risk patients.[49] The benefits of newer non-invasive CAD screenings, such as computed tomography angiography, are not well established, and their use as a routine screening tool in asymptomatic diabetic patients may lead to undue radiation exposure and interventional procedures.[42]

Management of CAD in diabetes

Reduction of diabetic macrovascular disease

Diabetics are at increased risk of developing cardiovascular disease and total death compared to non-diabetics.[50,51]

The United Kingdom Prospective Diabetes Study (UKPDS) is a landmark study of modifiable risk factors in more than 3000 type 2 diabetics: increased levels of low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) cholesterol, hypertension, and smoking. The median follow-up period was approximately 8 years. Coronary artery disease was significantly associated with these risk factors.[52]

Reduction of macrovascular complications in type 2 DM was confirmed using good blood pressure control, but tight glycaemic control was not conclusively demonstrated as beneficial.[53] Intensive glycaemic control in type 1 DM demonstrated long-term benefits on macrovascular complications and mortality in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.[54]

A meta-analysis on cardiovascular risk reduction found that smoking cessation was the most important intervention in reducing mortality compared to other interventions. This study concluded that smoking cessation may prolong life in a 45-year-old male diabetic patient for a mean of 3 years and a mean of 4 years in non-diabetic male patients.[55]

The Veteran Affairs Diabetes Trial (VADT) demonstrated in its extended follow-up arm that intensive glycaemic control group had a significant lower risk of primary outcomes compared to the standard therapy group. The absolute risk reduction was 8.6 major cardiovascular events per 1000 person-years. However, there was no reduction in cardiovascular mortality or total mortality.[56] These researchers found a 17% relative risk reduction in the rate of cardiovascular events in the intensive medical therapy group. The results of the follow up study of the Action to Control Cardiovascular Risk in Diabetes blood pressure trial (the ACCORD trial) exhibited a similar result with

fewer non-fatal cardiovascular events, and the conclusion from the extended follow-up arm was not very different from the original trial, especially that the overall mortality remained higher in the intensive glycaemic control group.[57]

Use of anti-platelet drugs in DM

The recent recommendations of American Diabetes Association (ADA) published in 2015 suggest aspirin (75–162 mg) for secondary prevention of CAD and primary prevention in patients with high cardiovascular risk, with an estimated 10-year risk of more than 10%. This group includes males older than 50 years or females older than 60 years with one or more of the following risk factors: hypertension, dyslipidemia, family history of cardiovascular disease, smoking, and albuminuria.[42] Clopidogrel is indicated for patients with cardiovascular disease and documented aspirin allergy.[58]

Blood pressure control

The UKPDS confirmed in early 1998 that tight treatment of hypertension in diabetic patients was associated with better outcomes than less tight control. The mean achieved BP was 144/82 mmHg in the tight control group versus 154/87 mmHg in the less tight control group. The tight BP control arm exhibited a risk reduction of 24% in any related DM endpoints, 32% in diabetes-related death, 44% in strokes, and 37% in microvascular complications.[59]

The Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) trial demonstrated that major macrovascular and microvascular events were reduced significantly in the active BP intervention arm (a single pill, fixed-dose combination of perindopril and indapamide), and this result was associated with reductions in all-cause mortality and cardiovascular mortality. A blood pressure of 136/73 mmHg was the level attained in the active treatment arm.[60] Reductions in all-cause mortality and cardiovascular mortality was attenuated in the 6-year follow-up of the ADVANCE-BP study, but it continued to be significant.[61]

Several of the major guidelines for the management of hypertension, including the Eighth Joint National Committee (JNC-8)[62] and the European Societies of Hypertension and Cardiology (ESH/ESC),[63] suggested that the goal of blood pressure control in diabetics should be less than 140/90 mmHg. Previous guidelines recommended blood pressure control to less than 130/80 mmHg.

The Action to Control Cardiovascular Risk in Diabetes blood pressure trial Blood Pressure (ACCORD-BP) arm recruited a total of 4733 patients who were randomly assigned to intensive (systolic BP goal below 120 mmHg) versus standard (systolic BP goal below 140 mmHg) blood pressure control and followed up to 4.7 years. There was a statistically significant reduction in the annual incidence of stroke (total stroke and non-fatal stroke) in the intensive BP control group, but there was no significant difference between the two groups in the primary composite endpoint of non-fatal MI, non-fatal stroke or death from cardiovascular causes. There was also no difference in all-cause mortality. Serious side effects were reported in the intensive BP arm, such as a significant rise in serum creatinine of more than 1.5 mg/dl, hyperkalemia, hypotension, and syncope.[64]

A meta-analysis of ACCORD-BP, Appropriate Blood Pressure Control in NIDDM Trial (ABCD), and The Hypertension Optimal Treatment (HOT) trials reported that intensive BP control in diabetic patients significantly reduced the risk of stroke but failed to reduce the incidence of myocardial infarction or total mortality.[65]

The JNC-8 in white adult ($\geq$18 years) patients suggested that the initial antihypertensive regimen should include thiazide diuretic, a calcium channel blocker (CCB), and ACEI or angiotensin receptor blockers (ARBs). However, the initial treatment in black adult ($\geq$18 years) patients should include a thiazide diuretic or CCB. ACEI or ARB should be included in the treatment of patients with chronic kidney disease (CKD), regardless of diabetes status or race[62].

The Heart Outcomes Prevention Evaluation (HOPE) trial investigated a total of 9297 patients with diabetes or evidence of vascular disease (high-risk group) and randomised patients to ramipril or placebo control groups. Ramipril significantly reduced the primary endpoint of myocardial infarction, stroke or death from cardiovascular disease.[66]

Statins in DM

A meta-analysis of 14 randomised trials of statins involved 18,686 diabetic patients who were followed up for 4.3 years. There was a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each one mmol/l reduction of LDL-cholesterol.[67]

The ADA standard of medical care of diabetes in 2015 states that diabetic patients aged $\geq$40 years should receive moderate intensity statins with life-style modifications, but high-dose statins are indicated in patients with cardiovascular diseases or other risk factors.[42] Cannon and colleagues investigated an intensive lipid-lowering regimen (atorvastatin 80 mg/day) versus a moderate regimen (pravastatin 40 mg/day) in 4162 ACS patients. The high-intensity regimen of atorvastatin provided significantly greater protection against death and cardiovascular events compared to the moderate regimen of pravastatin after a 2-year follow up.[68] There is scarce data on the use of statins in diabetics under the age of 40 years, and the current recommendations do not indicate statin use for diabetic patients below 40 years of age without overt cardiovascular disease or other risk factors.[42]

Coronary revascularization in diabetics

Selection of the optimal method of coronary revascularisation for diabetic patients often requires a multidisciplinary team meeting (i.e., a heart team). The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial was a landmark trial that addressed the treatment of diabetic patients with stable CAD. A total of 2368 patients with type 2 DM and stable CAD were enrolled and randomised to a revascularization, coronary artery bypass graft (CABG) or PCI group, according to individual physician's preference, plus intensive medical therapy (IMT) versus IMT alone. The primary endpoints were the rate of death and the composite

cardiovascular events of death, MI or stroke. There was no significant difference in the primary endpoints at the 5-year follow-up. The cardiovascular events were significantly lower in the CABG subgroup compared to the medical treatment group, but mortality was not significant. There was no significant difference in the risk of death and the cardiovascular events between the PCI group plus IMT and IMT alone.[44]

Diabetic patients are at an increased risk of progressive coronary artery disease and coronary artery re-stenosis after stent implantation. The predictors of coronary artery re-stenosis are small vessel coronary artery, long lesion, and lower body mass index.[69,70]

Drug-eluting stents (DES) are used preferentially used over bare metal stents (BMS) in diabetic patients because DES significantly reduce the incidence of re-stenosis and target vessel revascularisation (TVR). Bangalore and colleagues published a meta-analysis of 42 trials with more than 22,000 patient-years of follow up and found that DES significantly reduced the TVR compared to BMS (37–69%, respectively). There was no increased risk of any safety outcomes in the DES group, such as death, MI, or stent thrombosis.[71]

The recent 5-year follow-up of (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) SYNTAX trial investigated the cause of death following PCI versus CABG in complex CAD. Most death after PCI was due to a cardiovascular cause (67%), and myocardial infarction death accounted for approximately 29%. Post-CABG deaths included 49% due to cardiovascular cause. The cumulative incidence rates of all-cause death were not significantly different between CABG and PCI, but cardiovascular and cardiac deaths were significantly higher in PCI group. A difference between PCI and CABG in MI mortality was found in diabetic patients, three-vessel CAD, and high SYNTAX score. It was concluded that treatment with PCI versus CABG was an independent predictor of cardiac death in patients with complex CAD (hazard ratio: 1.55; 95% confidence interval: 1.09 to 2.33; $P = 0.045$).[72]

Anti-diabetic agents and the risk of cardiovascular events

The hypothesis linking anti-diabetic agents with cardiovascular disease is not new. The 2007 meta-analysis that linked rosiglitazone to increased cardiovascular risk and the possibility of increasing cardiac events further added to this concern.[73] The decision of the Food and Drug Administration (FDA) in the United States (U.S.) to restrict the use of rosiglitazone because of this postulated link resulted from this study. The chairman of the same committee from the U.S. FDA wrote a perspective paper in the New England Journal of Medicine (NEJM) to explain the process of the FDA decision and announcement, and he clarified his personal opinion about this decision, which further added to this debate and controversy.[74] The FDA subsequently modified these restrictions in 2013 after their re-evaluation of the results of the **R**osiglitazone **E**valuated for **C**ardiovascular **O**utcomes and **R**egulation of Glycemia in **D**iabetes (**RECORD**) trial, which concluded that these trends were not statistically significant, and the re-evaluation confirmed the initial results of the original study.[75] The FDA recently eliminated the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone and rosiglitazone-containing hypoglycaemic agents in 2015 and stated "The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks".[76] Many concerns were raised about other agents and classes intended to treat hyperglycaemia following the rosiglitazone story. These concerns triggered a series of trials on newer classes and agents and changed the process of approving new anti-diabetic agents, at least by the U.S. FDA.

Conclusion and recommendations

Diabetes is a very important major risk factor for CAD, and it is becoming a global health problem with increasing prevalence in a pandemic form. Many Arab countries, especially the Arabian Gulf region, are at the top of the international prevalence list. However, many Arab countries do not possess updated prevalence data from the community or maintain a registry of DM, CAD or other DM complications. Therefore, there is a great need to collect these data in all Arab countries.

There is an urgent need for interventions at the population level and in high-risk groups to reduce the incidence of DM by promoting physical activity and controlling the obesity epidemic. The prevalence of CAD will continue to rise in these countries if no action is taken to control DM and other risk factors for CAD, like hypertension and dyslipidemia.

International agencies, such as the WHO, IDF, ADA, European Association for the Study of Diabetes (EASD), American College of Cardiology (ACC) and the European Society of Cardiology (ESC), should play an active role to assist Arab countries to establish basic data and registries and the promotion of health interventional programs to ultimately control the rising incidence of DM and CAD.

All efforts, governmental and non-governmental, including all health organisations and scientific societies, should come together locally in each country to combat this epidemic of DM and CAD instead of individual scattered efforts. We need uniformed programs at the national level to win this battle.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

All authors contributed equally in both reviewing available evidence and writing up this manuscript.

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