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Original article

Non-diabetic hyperglycaemia correlates with angiographic coronary artery disease prevalence and severity

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Abstract

Aim. – The role of glycaemia as a coronary artery disease (CAD) risk factor is controversial, and the optimal glucose level is still a matter of debate. For this reason, we assessed the prevalence and severity of angiographic CAD across hyperglycaemia categories and in relation to haemoglobin A_{1c} (HbA_{1c}) levels.

Methods. – We studied 273 consecutive patients without prior revascularization undergoing coronary angiography for suspected ischaemic pain. CAD severity was assessed using three angiographic scores: the Gensini's score; extent score; and arbitrary index. Patients were grouped, according to 2003 American Diabetes Association criteria, into those with normal fasting glucose (NFG), impaired fasting glucose (IFG) and diabetes mellitus (DM).

Results. – CAD prevalence was 2.5-fold higher in both the IFG and DM groups compared with the NFG group. Deterioration of glycaemic profile was a multivariate predictor of angiographic CAD severity (extent score: $P=0.027$; arbitrary index: $P=0.007$). HbA_{1c} levels were significantly higher among CAD patients ($P=0.016$) and in those with two or more diseased vessels ($P=0.023$) compared with the non-CAD group. HbA_{1c} levels remained predictive of CAD prevalence even after adjusting for conventional risk factors, including DM (adjusted OR: 1.853; 95% CI: 1.269–2.704).

Conclusion. – Non-diabetic hyperglycaemia, assessed either categorically by fasting glucose categories or continuously by HbA_{1c} levels, correlates with the poorest angiographic outcomes.

Keywords: Impaired fasting glucose; Coronary artery disease; Haemoglobin A_{1c}; Non-diabetic hyperglycaemia

Résumé

L'hyperglycémie non diabétique est en corrélation avec la prévalence et la sévérité des lésions coronaires angiographiques.

Objectif. – Le rôle de la glycémie comme facteur de risque de coronaropathie et l'objectif glycémique optimal restent controversés. Nous avons quantifié la prévalence et la sévérité des lésions coronaires angiographiques en fonction des différentes catégories d'hyperglycémie et des taux d'HbA_{1c}.

Méthodes. – Nous avons étudié 273 patients consécutifs sans antécédents de revascularisation qui avaient bénéficié d'une coronarographie pour suspicion de douleur d'origine ischémique. La sévérité de la coronaropathie a été quantifiée en utilisant trois scores angiographiques différents : le score de Gensini, l'extent score et un indice arbitraire. Les patients ont été repartis selon les critères 2003 de l'American Diabetes Association en trois groupes : glycémie à jeun normale, hyperglycémie à jeun non diabétique, diabète.

Résultats. – La prévalence de la coronaropathie était 2,5 fois plus élevée chez les patients atteints d'hyperglycémie à jeun non diabétique et les patients diabétiques par rapport aux patients normoglycémiques. L'aggravation du profil glycémique était en analyse multivariée un prédicteur de la sévérité de la coronaropathie à l'angiographie (score extent, $P=0,027$; indice arbitraire, $P=0,007$). Le taux d'HbA_{1c} était significativement plus élevé chez les patients atteints de coronaropathie ($P=0,016$) et chez ceux qui présentaient une atteinte bitronculaire ou plus sévère ($P=0,023$). Le taux d'HbA_{1c} prédisait la prévalence de coronaropathie même après ajustement sur les facteurs de risque conventionnels, y compris le diabète (OR ajusté : 1,853 ; intervalle de confiance de 95 % : 1,269-2,704).

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Conclusions. – L'hyperglycémie non diabétique définie soit par la glycémie à jeun soit par l'HbA_{1c} est associée à des altérations coronaires à l'angiographie.

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Mots clés : Hyperglycémie à jeun ; Angiographie coronaire ; Coronaropathie ; HbA_{1c} ; Hyperglycémie non diabétique

1. Introduction

Diabetes mellitus (DM) is associated with a two- to three-fold increased cardiovascular morbidity [1] and mortality [2,3]. Indeed, DM is considered a coronary artery disease (CAD) equivalent, as individuals with DM and no prior history of myocardial infarction have the same risk for future myocardial infarction and death due to CAD as have patients without DM, but with a positive history of myocardial infarction [4]. Diabetic patients also present with a cluster of metabolic abnormalities such as high triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), hypertension, increased insulin resistance and abdominal obesity [5,6]. However, the excess risk associated with DM is only partly explained by the above-mentioned traditional CAD risk factors [7]. There is evidence to suggest that hyperglycaemia *per se* may be related to atherosclerotic disease. Hyperglycaemia is associated with endothelial barrier injury [8], mitochondrial overproduction of reactive oxygen species [9], nuclear factor- κ B activation [10], impaired endothelial-dependent vasodilatation [11] and overexpression of adhesion molecules such as Inter-Cellular Adhesion Molecule (ICAM), Vascular Cell Adhesion Molecule (VCAM) and E-selectin [12]. In addition, sustained exposure of proteins and lipids to high glucose concentrations leads to non-enzymatic glycation of these molecules and the formation of advanced glycation end products which, *via* their endothelial surface receptors, can regulate gene expression [13] and stimulate the production of superoxide in endothelial cells [14]. All of these derangements ultimately contribute to increased atherogenesis and atherosclerosis progression.

The link between hyperglycaemia and microvascular diabetic complications is well documented, and clinical trials have demonstrated that better glycaemic control is associated with a lower incidence of retinopathy, nephropathy and neuropathy [15,16]. With regard to the relationship between glucose homeostasis and cardiovascular disease, there is ample epidemiological evidence that hyperglycaemia is an independent predictor of cardiovascular mortality among both patients with DM [17] and non-diabetic individuals [18]. Moreover, the risk associated with hyperglycaemia appears to extend well beyond the diabetic threshold [19,20]. In the face of such mounting data, the American Diabetes Association (ADA) reviewed its earlier definition of impaired fasting glucose (IFG), released in 1997 [21], and, in 2003, further reduced the lowest fasting glucose cut-off point from 110 to 100 mg/dL [22].

The aim of the present study was to explore whether or not non-diabetic hyperglycaemia, assessed either categorically by fasting glucose categories or continuously by haemoglobin A_{1c} (HbA_{1c}) levels, is associated with angiographic CAD prevalence

and severity. In addition, we sought to compare the sensitivity and specificity of the 2003 *versus* 1997 ADA definitions of IFG in predicting CAD prevalence.

2. Methods

2.1. Study subjects

The present study population included a consecutive sample of 273 individuals who were referred to our centre for coronary angiography. These patients had either stable angina or angina-like chest pain and a positive exercise test. None of these patients had an acute coronary syndrome or a history of revascularization procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting). The medical ethics committee of Aristotle University of Thessaloniki approved the study protocol, and all participants provided their written informed consent.

Before entering the catheterization laboratory, a detailed medical history was obtained from each patient for demographic data, socioeconomic status, educational level, lifestyle habits, current and past medical conditions, and concomitant medications. Also, all participants underwent a physical examination. Blood pressure was measured with a mercury sphygmomanometer in the right arm of the patient while seated, and the average of three recordings was used for analysis. Hypertension was defined as blood pressure $\geq 140/90$ mmHg or treatment with antihypertensive drugs. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m²). Waist circumference was measured at the level of the highest point of the iliac crest, with the patient standing and just after a full expiration. Presence of the metabolic syndrome was diagnosed according to the modified National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III) criteria [23]. A family history of CAD was considered to be present if a subject had any first-degree relatives with a history of CAD or sudden cardiac death prior to age 55 years for males and age 65 years for females. Normal fasting glucose (NFG), IFG and DM were defined as fasting glucose levels <100 mg/dL, 100–125 mg/dL and ≥ 126 mg/dL, respectively. Individuals with a documented history of DM and/or receiving antidiabetic treatment were also considered to be diabetic, irrespective of their fasting glucose levels.

2.2. Coronary angiography

CAD was defined as $\geq 50\%$ luminal narrowing of at least one major epicardial vessel. According to the number of diseased arteries, patients were considered to have no disease, or one-, two- or three-vessel disease. Given the small number of patients

Table 1
Demographic, clinical and biochemical characteristics of the patients according to glycaemic status.

Characteristic	NFG	IFG	DM	<i>P</i>
Age (years)	60.35 ± 1.10	62.05 ± 1.35	64.88 ± 0.84	0.005
BMI (kg/m ²)	28.41 ± 0.37	29.39 ± 0.46	28.78 ± 0.36	0.266
HbA _{1c} (%)	4.66 ± 0.03	4.90 ± 0.06	6.62 ± 0.17	<0.001
TC (mg/dL)	175.20 ± 4.00	181.83 ± 5.29	168.20 ± 4.46	0.128
TG (mg/dL)	117.02 ± 4.65	134.63 ± 5.60	139.26 ± 6.94	0.029
HDL-C (mg/dL)	48.33 ± 1.41	46.52 ± 1.58	46.68 ± 1.36	0.613
LDL-C (mg/dL)	103.46 ± 3.65	108.38 ± 4.82	93.77 ± 3.62	0.033
Non-HDL-C (mg/dL)	126.87 ± 3.84	135.30 ± 4.96	121.67 ± 4.07	0.101
Pack × years ^a	49.74 ± 4.62	53.24 ± 6.32	79.74 ± 11.60	0.098
Male gender	78 (76.5)	54 (85.7)	68 (63.0)	0.003
Family history of CAD	21 (21.0)	17 (27.4)	24 (22.6)	0.634
Metabolic syndrome	22 (23.2)	47 (75.8)	86 (82.7)	<0.001
Hypertension	72 (71.3)	54 (85.7)	93 (86.9)	0.009
Smoking	78 (76.5)	43 (68.3)	60 (55.6)	0.005

NFG: normal fasting glucose; IFG: impaired fasting glucose; DM: diabetes mellitus; BMI: body mass index; HbA_{1c}: haemoglobin A_{1c}; TC: total cholesterol; TG: triglycerides; CAD: coronary artery disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. Data are presented as means ± standard error of the mean (SEM) or frequencies (%) within each glucose category. *P* values refer to comparisons across all study groups, and statistically significant differences are in bold.

^a Product of the number of cigarettes per pack × the period of smoking (in years). This variable was computed only for current smokers.

with three-vessel disease, the last two categories were grouped together into one, including left main coronary artery involvement as a two-vessel disease. For a more detailed description of the patients' atherosclerotic burden, three angiographic scores were employed: the Gensini's score [24]; extent score [25]; and arbitrary index [26]. All angiograms were visually evaluated by two experienced interventional cardiologists who were unaware of both the scope of the study and of each other.

2.3. Blood tests for lipids

After fasting for at least 8 h, all patients had venous blood drawn through the antecubital vein, without the use of a tourniquet, at approximately 30 min before the catheterization procedure. The blood samples were centrifuged at 3000 g for 10 min at ambient temperature. Serum triglycerides, total cholesterol, HDL-C and glucose were determined by standard enzymatic procedures. Serum low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula.

2.4. Statistical analyses

All scalar data were expressed as means ± standard error of the mean (SEM), while categorical data were expressed as absolute values and proportions. Scaled variables were tested for normality using the Kolmogorov–Smirnov test. For normally distributed variables, a comparison of means between two or more groups was made using Student's *t* test or analysis of variance (ANOVA), respectively. In cases of non-normally distributed variables, non-parametric Mann–Whitney *U* and Kruskal–Wallis *H* tests were applied. Comparisons between proportions were carried out by the Chi² test. Logistic-regression analysis was used to test the independent contribution of either glycaemic status or HbA_{1c} levels in predicting CAD prevalence after controlling for the effect of conventional risk factors. Linear-regression analysis was used to explore the relation-

ship between fasting glucose categories and angiographic scores after adjusting for confounders. In the multivariate analyses, all covariates were entered simultaneously in one block. A *P* value of 0.05 or less was considered statistically significant. All statistical analyses were done using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 273 patients studied, 102 (37.4%) had NFG, 63 (23.1%) had IFG and 108 (39.6%) had previously known or newly diagnosed DM. Coronary angiography revealed that 188 (68.9%) had angiographically severe CAD, while 85 (31.1%) had non-obstructive or no coronary atherosclerotic lesions. Table 1 outlines the demographic, clinical and biochemical characteristics of the patients according to glycaemic status. Age, triglycerides and HbA_{1c} levels as well as the metabolic syndrome and hypertension prevalences were progressively increased, while smoking progressively decreased, from the NFG through IFG to DM groups. Individuals with IFG had the highest LDL-C levels, and female gender was much more prevalent in the DM group.

3.1. Glycaemic status and coronary artery disease prevalence

Fig. 1A depicts CAD prevalence in relation to glycaemic status. Individuals with NFG had the lowest CAD prevalence (56.9%), while those with IFG and DM had significantly higher prevalences (76.2% [*P* = 0.012] and 75.9% [*P* = 0.003], respectively). Using the NFG group as reference, individuals with either IFG or DM had more than a twofold increase in CAD prevalence, while the odds ratios (OR) remained virtually unchanged even after adjusting for a number of CAD risk factors (Table 2). HbA_{1c} levels and the metabolic syndrome, although significantly different among the study groups, were

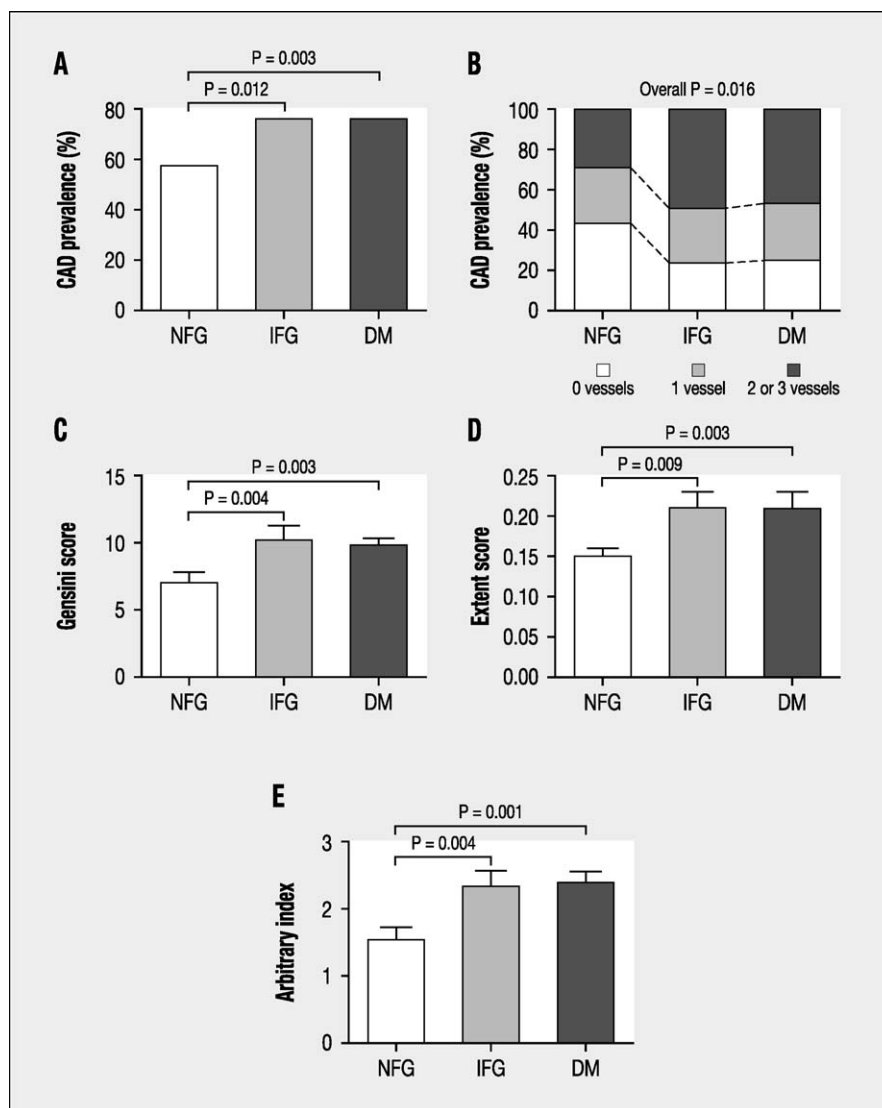


Fig. 1. Coronary artery disease (CAD) prevalence (%) in relation to glycaemic status (A), the number of diseased vessels in each glycaemic group (B), the Gensini's score (C), extent score (D) and arbitrary index (E). NFG: normal fasting glucose; IFG: impaired fasting glucose; DM: diabetes mellitus; bars represent mean values, and error bars represent ± 1 standard error of the mean (SEM).

not included in the multivariate analysis to avoid intercorrelation with independent variables.

3.2. Glycaemic status and coronary artery disease severity

On exploring the relationship between glycaemic status and number of diseased vessels, both IFG and DM individuals had higher rates of two or more diseased vessels (49.2 and 46.7%,

respectively) than the NFG group (29.4%; Fig. 1B). The same was true when the three angiographic scores were employed. Those with IFG levels and DM had scores comparable to each other, but both were significantly higher than in the NFG group (Fig. 1C, D, E). Linear-regression analysis revealed that glycaemic status was still associated with the extent score and arbitrary index, despite adjusting for conventional CAD risk factors (Table 3).

Table 2

Coronary artery disease (CAD) prevalence (%) in each glucose category, with crude and adjusted odds ratios (OR) for CAD prevalence in relation to glycaemic status, adjusted for age, gender, hypertension, smoking, triglycerides and low-density lipoprotein cholesterol.

Patients	CAD (N=188)	Crude OR (95% CI)	Adjusted OR (95% CI)
Normal fasting glucose	58 (56.9)	1 (reference)	1 (reference)
Impaired fasting glucose	48 (76.2)	2.428 (1.206–4.887)	2.567 (1.187–5.551)
Diabetes mellitus	82 (75.9)	2.393 (1.326–4.316)	2.454 (1.238–4.861)

Table 3
Beta coefficients and *P* values derived from linear-regression analysis to assess the impact of glycaemic status on angiographic scores, after adjusting for age, gender, hypertension, smoking, triglycerides and low-density lipoprotein cholesterol.

	Gensini's score		Extent score		Arbitrary index	
	Beta	<i>P</i>	Beta	<i>P</i>	Beta	<i>P</i>
Glycaemic status	0.121	0.059	0.142	0.027	0.173	0.007

Statistically significant *P* values are shown in bold.

3.3. Haemoglobin A_{1c}, and coronary artery disease prevalence and severity

HbA_{1c} levels were significantly higher among CAD patients and those with two or more diseased arteries compared with the group without CAD (Fig. 2). For every unit increase in HbA_{1c}, there was a 1.4-fold increase in CAD prevalence (OR: 1.4; 95% CI: 1.094–1.791). Logistic-regression analysis revealed that HbA_{1c} levels were still predictive of CAD prevalence even after considering the effects of age, gender, DM, family history of CAD, hypertension, smoking, triglycerides, and HDL-C and LDL-C levels (adjusted OR: 1.853; 95% CI: 1.269–2.704).

3.4. 1997 versus 2003 American Diabetes Association definition of impaired fasting glucose for coronary artery disease prevalence

On applying the ADA 1997 criteria for IFG, fewer patients (*N*=25, 9.2%) were assigned to the IFG group compared with the 2003 definition. Also, as expected, the prevalence of DM remained the same regardless of the IFG definition (*N*=108, 39.6%). In contrast to the 2003 IFG criterion, the 1997 IFG definition was not significantly associated with CAD prevalence (OR: 1.929; 95% CI: 0.725–5.137). Receiver operating characteristics curve analysis revealed that the 2003 classification of IFG predicted obstructive CAD prevalence with better sensitivity and specificity than did the older definition (area under the curve [AUC]: 0.604 ± 0.038; *P*=0.006 versus AUC: 0.580 ± 0.037; *P*=0.034, respectively).

4. Discussion

According to the present study results, poor glycaemic control was associated with progressive worsening of the CAD risk profile, while increases in fasting glucose levels were associated with advanced age, higher levels of HbA_{1c} and triglycerides, and greater prevalences of the metabolic syndrome and hypertension. These findings are in concordance with other studies in which patients with IFG [27] or impaired glucose tolerance [28], or both [29], had a significantly higher burden of CAD risk factors compared with normoglycaemics. Significant differences in CAD risk factor prevalence have been reported even among patients of similar glucose category. Subjects with high NFG levels compared with those with low NFG levels were more insulinresistant, and had higher triglyceride levels, lower HDL-C concentrations and smaller LDL particle size independent of age, gender and adiposity [30].

4.1. Coronary artery disease prevalence and severity across fasting glucose categories

Individuals with IFG had a more than twofold increase in CAD prevalence (OR: 2.428; 95% CI: 1.206–4.887) compared with the NFG group. Yet, these individuals had odds for CAD similar to those in the DM group (OR: 2.393; 95% CI: 1.326–4.316). This finding persisted even after adjusting for conventional CAD risk factors such as age, gender, hypertension, smoking, LDL-C and triglycerides (adjusted OR: 2.567; 95% CI: 1.187–5.551), and is in agreement with a previous study reporting a gradual increase in angiographic CAD prevalence along with higher fasting glucose levels beginning in the nor-

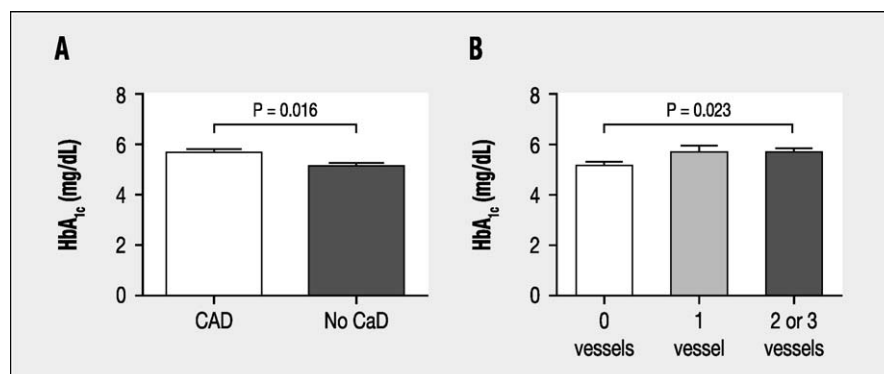


Fig. 2. Haemoglobin A_{1c} (HbA_{1c}) levels according to coronary artery disease (CAD) prevalence (A) and the number of diseased vessels (B). Bars represent mean values, and error bars represent ± 1 standard error of the mean (SEM).

moglycaemic range [31]. Others report that the prevalence of $\geq 50\%$ coronary stenoses increased significantly from patients with NFG through patients with IFG to those with DM [6]. In a study of a high-risk Chinese cohort that also recruited non-diabetics, those with IFG compared with those with NFG had significantly greater odds of having CAD. Also, the coronary artery stenosis score and percentage of stenosis in the left anterior descending branch increased in association with increasing fasting glucose levels [32].

According to the present study results, around half the patients with IFG (49.2%) and half of those with DM (46.7%) had multivessel (two or more) CAD, while only one-third (29.4%) of the normoglycaemic subjects did ($P=0.016$ for trend). In addition, all three angiographic scores were significantly higher among the IFG and DM patients compared with the NFG group. In a small angiographic study that recruited asymptomatic members of high-risk families, fasting glucose levels correlated significantly with the atheroma burden index among both patients with normal glucose tolerance and those with impaired glucose tolerance or DM; however, fasting glucose levels failed to predict angiographic severity when incorporated into a multivariate model [33]. This was also true for HbA_{1c} levels and post-load glycaemia which, although significantly correlated with the number of diseased vessels in the univariate analysis, were not so when conventional risk factors were taken into account [34]. Our study, however, demonstrates that deterioration of the glycaemic profile is still positively and significantly associated with the extent score (beta = 0.142; $P=0.027$) and arbitrary index (beta = 0.173; $P=0.007$), even after adjusting for conventional CAD risk factors. Thus, according to our results, hyperglycaemia – even in the non-diabetic range – is an independent determinant of angiographic CAD prevalence and severity.

4.2. Haemoglobin A_{1c} levels, and coronary artery disease prevalence and severity

HbA_{1c} reflects the average glycaemia over the past 3 months and is, therefore, a more reliable marker than fasting glucose in the assessment of the effects of long-term glycaemia on the arterial wall. HbA_{1c} levels are significantly higher among CAD subjects and those with two or more diseased vessels compared with those with no or non-obstructive atherosclerotic lesions. In addition, our findings are in concordance with other studies reporting a positive correlation between HbA_{1c} levels and CAD prevalence [35], the number of diseased coronary arteries [36] and carotid plaque prevalence [37]. In our study, each unit increase in HbA_{1c} correlated with an 85.3% increase in CAD prevalence in the multivariate analysis independent of conventional CAD risk factors, including DM (OR: 1.853; 95% CI: 1.269–2.704). This finding is further supported by a study reporting that, when HbA_{1c} and DM status were analyzed together in the same multivariate model, only the HbA_{1c} level, but not DM, remained a significant determinant of carotid intima-media thickness (IMT) [38].

4.3. 2003 versus 1997 American Diabetes Association definition of impaired fasting glucose

Using the 2003 ADA definition, 63 (23.1%) patients were assigned to the IFG group. On applying 1997 ADA criteria, only 25 (9.2%) individuals were considered to have IFG, and they also showed a trend towards higher CAD prevalence (OR: 1.929; 95% CI: 0.725–5.137) compared with the NFG group, although this finding failed to reach statistical significance. Reducing the fasting glucose criterion for IFG from a lower limit of 110 to 100 mg/dL was associated with a greater AUC for prevalent CAD. This finding suggests that the updated definition of IFG can identify individuals with prevalent CAD with better sensitivity and specificity than did the earlier, 1997 definition.

5. Limitations

The present study is limited by the small number of patients enrolled. Also, given its cross-sectional design, a causal relationship between glycaemic indices and CAD prevalence cannot be inferred. In addition, our results cannot be extrapolated to the general population, as our study participants were a highly selected group of individuals referred for coronary angiography for evaluation of suspected ischaemic pain. Furthermore, CAD was assessed by coronary angiography, which does not provide information on the arterial wall and may, therefore, underestimate the proportion of patients with a significant atherosclerotic burden and preserved lumen (expansive remodelling). Intravascular ultrasound would provide a more accurate representation of the atherosclerotic burden. However, the present study was focused on patients with angiographically severe CAD, and these patients are not underestimated by angiography. Moreover, a significant proportion of our patients were taking antihypertensive medications, such as beta-blockers and thiazide diuretics, which are known to interfere with glucose homeostasis. Finally, the diagnosis of DM was based solely on fasting glucose levels and medical records (conventional DM), and no oral glucose tolerance test was undertaken. Thus, the true prevalence of DM may have been underestimated.

6. Conclusion

Our study demonstrates that non-diabetic hyperglycaemia, as assessed either categorically by fasting glucose categories or continuously by HbA_{1c} levels, is a significant determinant of angiographically verified CAD prevalence and severity. Hyperglycaemia is correlated with the coronary atherosclerotic burden independent of traditional CAD risk factors, including DM. The study findings also suggest that hyperglycaemia should be treated even in the absence of clinical diabetes, although more interventional studies are needed to establish the optimal glucose level.

Conflicts of interest statement

No potential conflicts of interest relevant to this article were reported.

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