Hypertensive target organ damage predicts incident diabetes mellitus

Raffaele Izzo1, Giovanni de Simone1*, Valentina Trimarco2, Eva Gerdtst1,3,4, Renata Giudice1, Olga Vaccaro5, Nicola De Luca1, and Bruno Trimarco6

1Department of Translational Medical Sciences, Federico II University Hospital, via S. Pansini 5, 80131 Naples, Italy; 2Department of Neurosciences, Federico II University, Naples, Italy; 3Institute of Medicine, University of Bergen, Bergen, Norway; 4Department of Heart Disease, Haukeland University Hospital, Bergen, Norway; 5Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; and 6Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy

Received 3 January 2013; revised 20 June 2013; accepted 27 June 2013; online publish-ahead-of-print 23 July 2013

See page 3395 for the editorial comment on this article (doi:10.1093/eurheartj/eht281

Aims

Whether patients with hypertensive preclinical cardiovascular disease (CVD) are at higher risk of incident diabetes has never been studied.

Methods and results

We assessed incident diabetes in 4176 hypertensive non-diabetic patients (age 58.7 ± 8.9 years, 58% male) with ≥1 year follow-up (median: 3.57 years; inter-quartile range: 2.04–7.25). Left ventricular (LV) hypertrophy (LVH) was defined as LV mass index (LVMi) ≥ 51 g/m². Carotid atherosclerosis (CA) was defined as intima-media thickness > 1.5 mm. During follow-up, diabetes developed in 393 patients (9.4%), more frequently in those with than without initial LVH or CA (odds ratio = 1.97 and 1.67, respectively; both P < 0.0001). In the Cox regression, the presence of either initial LVH or CA was associated with higher hazard of diabetes [hazards ratio (HR) = 1.30 and 1.38, respectively; both P = 0.03], independently of the type and number of anti-hypertensive medications, initial systolic blood pressure (P < 0.001), body mass index, fasting glucose, family history of diabetes (all P < 0.0001), and therapy with β-blockers. The presence of one of the, or both, markers of preclinical CVD increased the chance of incident diabetes by 63 or 64%, respectively (both P < 0.0001). In the Cox model.

Conclusion

Initial LVH and CA are significant predictors of new onset diabetes in a large population of treated hypertensive patients, independently of initial metabolic profile, anti-hypertensive therapy, and other significant covariates. This sequence may be attributable to risk factors common to preclinical CVD and diabetes, but a vascular origin of diabetes cannot be excluded.

Keywords

Diabetes • Hypertension • Target organ damage • Metabolic syndrome

Introduction

A large body of epidemiological and pathological data indicates that type 2 diabetes mellitus (diabetes) is an independent risk factor for preclinical cardiovascular (CV) disease (CVD), including carotid atherosclerosis (CA) and left ventricular (LV) hypertrophy (LVH), as well as for overt CVD in both men and women. Diabetes also worsens survival in patients who develop clinical CVD.

We have previously demonstrated that uncontrolled blood pressure (BP) is associated with a two-fold increased risk of incident diabetes in treated hypertensive subjects, extending previous observations indicating that incident diabetes is more frequent in hypertensive than in normotensive subjects, and that combinations of hypertension, obesity, and abnormal lipid profile, which often coexist with diabetes, are associated with preclinical cardiovascular abnormalities. Interestingly, clusters of metabolic abnormalities and the presence of LVH are also reported to increase the probability of uncontrolled hypertension.

These findings raise questions regarding the temporal sequence of these abnormalities and development of both hypertension and diabetes.
It is unclear whether the presence of hypertensive preclinical CVD (target organ damage), such as LVH and/or CA, is associated with increased risk of incident diabetes, independent of metabolic risk factors and arterial hypertension. Accordingly, the present study was designed to test whether or not prevalent hypertensive preclinical CVD increases the risk of incident diabetes in the hypertensive participants of the Campania Salute Network Registry.

**Methods**

**Participants**

Hypertensive patients without diabetes and known CVD were studied, with at least 1-year follow-up, within the Campania Salute Network Registry. The Campania Salute is an open registry collecting information from a network of general practitioners and community hospitals networked with the Hypertension Center of the Federico II University Hospital. The database generation of the Campania Salute Network was approved by the Federico II University Hospital Ethics Committee. Signed informed consent was obtained from all the participants to use data for scientific purposes. Detailed characteristics of this population have been previously reported.

Exclusion criteria for the present analysis were: pre-existing CVD, diabetes, secondary hypertension, chronic kidney disease more than grade 3 (GFR by simplified MDRD < 30 mL/min/1.73 m<sup>2</sup>), aortic and/or mitral regurgitation more than mild, any degree of aortic stenosis, and follow-up < 1 year. Pre-existing CVD was defined as the history of previous myocardial infarction, angina, coronary revascularization, stroke, transitory ischaemic attack, and congestive heart failure at the time of the admission visit in our outpatient clinic. Thus, from the initial population of 10 254 hypertensive patients, 3157 patients were excluded due to the presence of pre-existing CVD or diabetes, 2392 for insufficient follow-up period or poor quality echocardiographic windows, and 529 because of the lack of same-day baseline echocardiogram and carotid ultrasound. Thus, the present analysis included 4176 hypertensive non-diabetic participants free of pre-existing CVD and renal failure, with at least 1-year follow-up.

During initial and follow-up visits, BP, heart rate, body mass index (BMI), fasting glucose, and lipid profile were measured for each patient by standard methods. All hypertensive patients of the network underwent baseline echocardiogram and carotid ultrasound.

**Measurements and definitions**

Impaired fasting glucose and diabetes were defined according to 1997 ADA criteria (fasting glucose > 110 mg/dL, or > 125 mg/dL or anti-diabetic treatment, respectively). Family history of diabetes (in > 1 family member) was recorded at the time of the first visit.

Obesity was defined as a BMI ≥ 30 kg/m<sup>2</sup>. Metabolic syndrome (MetS) was defined according to modified ATPIII criteria, changing waist circumference with BMI ≥ 30 kg/m<sup>2</sup>, as previously done when waist girth was not available.

Fasting glucose and lipid profile were measured by standard methods. Systolic and diastolic BP were measured by standard aneroid sphygmomanometer after 5 min rest in the supine position, according to current guidelines. Three BP measurements were obtained in the sitting position at 2 min intervals. The averages of these measurements were used for the analysis. Incident diabetes was adjudicated based only on detection of abnormal fasting glucose.

**Echocardiography**

Echocardiograms were recorded in videotapes, using commercial machines and a standardized protocol, were digitally mastered and read offline by one expert reader under the supervision of a senior faculty member, using dedicated work-stations (MediMatic). Measurements were made according to the American Society of Echocardiography/European Association of Echocardiography recommendations. Left ventricular mass was calculated from a necropsy-validated formula and normalized for height in metres to the power of 2.7 (LVMi).

Left ventricular hypertrophy (LVH) was defined as LVMi ≥ 51 g/m<sup>2</sup>. Carotid ultrasound

**Carotid ultrasound**

Carotid ultrasound was carried out in the supine position with the neck extended in mild rotation. The scanning protocol was performed with an ultrasound device (SONOS 2500/5500, HP, Philips) equipped with a 7.5 MHz high-resolution transducer with an axial resolution of 0.1 mm. Examinations were recorded on S-VHS videotapes and analysed as previously described. The maximal arterial intima-media thickness (IMT) was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation, and proximal internal carotid artery, and using an image-processing dedicated workstation (MediMatic). Evidence of IMT value higher than 1.5 mm was considered as ‘plaque’. The presence of carotid plaque was considered a marker of CA.

**Statistical analysis**

Data were analysed using SPSS (version 20.0; SPSS, Chicago, IL, USA) and expressed as mean ± 1 SD. Variables not normally distributed were log-transformed. Descriptive comparison between patients with or without initial LVH and/or evidence of CA was performed using t-test. Unadjusted prevalence of specific conditions in population subgroups was compared using the χ<sup>2</sup> distribution, and Monte Carlo simulation to generate exact P-values.

To account for therapy, single classes of medications, including anti-renin–angiotensin system drugs (anti-RAS, including ACE inhibitors and/or AT1 receptor antagonists), calcium channel blockers (CCBs), β-blockers, and thiazide diuretics, were dichotomized according to their overall use during the individual follow-up, based on the frequency of prescriptions during the control visits, considering as the end of follow-up time of diabetes diagnosis for patients with incident diabetes. Thus, all medications used for more than 50% of control visits were considered as covariates in proportional hazards analysis, a method that has been previously reported.

Incident diabetes in relation to the presence of either initial LVH or CA was assessed using two models of the Cox regression analysis (one for each marker), controlling for demographic, haemodynamic, and metabolic variables participating to the phenotypes of MetS (age, sex, reported duration of hypertension, initial BP, heart rate, BMI, fasting glucose, HDL-cholesterol, triglycerides) and number and type of anti-hypertensive medications that were significantly different in exploratory statistics. In alternative Cox models, we assessed the effect of the generic presence of either one of the two markers of preclinical CVD (LVH or CA) or both, adjusting for the same covariates. Finally, the latter Cox model was also run by substituting individual risk factors (i.e. glucose, HDL-cholesterol, BP, BMI, and triglycerides) with MetS, in the whole, as well as in subsets of, study population.

A two-tailed α-value of < 0.05 was used to reject the null hypothesis.

**Results**

Among the 4176 non-diabetic hypertensive outpatients included in this analysis (mean age 58.7 ± 8.9 years, 58% male), 992 (24%) were obese and 1158 met the criteria for the diagnosis of MetS.
than in those without initial LVH (14.1 and 7.7%, respectively; odds ratio (OR) = 1.97, 95% confidence interval (CI): 1.59–2.45, P < 0.0001) and similarly, the incidence of diabetes was significantly more frequent among patients with baseline evidence of carotid plaque (12.3 vs. 7.7%; OR = 1.67, 95% CI: 1.36–2.06, P < 0.0001). Hypertensive patients developing diabetes during follow-up were given more often β-blockers and CCB than patients without incident diabetes (32.6 vs. 26.1%; 30.0 vs. 21.7%, respectively; both P < 0.006), whereas no difference was found for the other classes of antihypertensive meds. Patients with incident diabetes also took a greater number of antihypertensive meds (1.8 ± 0.98) than those free of incident diabetes (1.5 ± 0.95, P < 0.0001). No difference was found in the number of visit per year in patients with or without incident diabetes (1.29 ± 1.02 vs. 1.39 ± 1.03, respectively; P = 0.620).

In the Cox regression, the presence of initial LVH remained associated with 30% higher risk of incident diabetes [hazards ratio (HR) = 1.30; (95% CI 1.02–1.64); P = 0.03], independently of the type and number of anti-hypertensive medications, initial higher systolic BP (P = 0.001), BMI, fasting glucose, and family history of diabetes (all P < 0.001). Similarly, the presence of CA was associated with nearly 40% higher risk of incident diabetes [HR = 1.38; (95% CI 1.11–1.70); P = 0.003], independently of the type and number of anti-hypertensive medications, initial higher systolic BP, BMI, fasting glucose, and family history of diabetes (all P < 0.001).

The presence of either of the two markers of preclinical CVD (n = 1582) increased the chance of incident diabetes by more than 60% [HR = 1.63; (95% CI 1.27–2.08); P < 0.0001], a risk that remained

### Incident diabetes

During follow-up (median: 3.57 years; inter-quartile range: 2.04–7.25), incident diabetes was adjudicated in 393 patients (9.4%). Diabetes developed near two-fold more frequently in patients with than in those without initial LVH [14.1 and 7.7%, respectively; odds ratio (OR) = 1.97, 95% confidence interval (CI): 1.59–2.45, P < 0.0001].

| Table 1 | Baseline demographic and clinical characteristics of participants with or without initial LV hypertrophy (LVH) |
|---------|-----------------------------------------------------------------------------------------------------------|
|         | Non-LVH (n = 3040) | LVH (n = 1136) | P ≤ |
| Age (years) | 57.61 ± 8.9 | 61.69 ± 8.3 | 0.0001 |
| Sex (M/F %) | 56.6/43.4 | 61.6/38.4 | 0.003 |
| BMI (kg/m²) | 26.84 ± 3.6 | 29.77 ± 4.4 | 0.0001 |
| Hypertension duration (years) | 5.13 ± 6.0 | 7.39 ± 7.3 | 0.0001 |
| Systolic BP (mmHg) | 140.14 ± 15.8 | 146.54 ± 19.1 | 0.0001 |
| Diastolic BP (mmHg) | 89.37 ± 9.9 | 91.48 ± 11.2 | 0.0001 |
| Heart rate (b.p.m.) | 74.97 ± 11.4 | 73.09 ± 11.4 | 0.0001 |
| Fasting plasma glucose (mg/dL) | 93.36 ± 12.0 | 95.90 ± 12.0 | 0.0001 |
| HDL Cholesterol (mg/dL) | 50.83 ± 12.7 | 48.99 ± 12.4 | 0.0001 |
| Triglycerides (mg/dL) | 130.9 ± 71.9 | 141.5 ± 79.2 | 0.0001 |
| Metabolic syndrome (%) | 28.2 | 46.9 | 0.0001 |
| Family history of diabetes (%) | 30.2 | 29.8 | 0.809 |
| CCB (%) | 18.8 | 32.2 | 0.0001 |
| β-Blockers (%) | 26.5 | 27.3 | 0.614 |

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; CCB, calcium channel blockers.

| Table 2 | Baseline demographic and clinical characteristics of participants with or without initial carotid atherosclerosis (CA) |
|---------|-----------------------------------------------------------------------------------------------------------|
|         | Non-CA (n = 2628) | CA (n = 1548) | P ≤ |
| Age (years) | 53.57 ± 8.9 | 62.37 ± 7.7 | 0.0001 |
| Sex (M/F %) | 56.2/43.8 | 60.9/39.1 | 0.004 |
| BMI (kg/m²) | 27.64 ± 4.1 | 27.62 ± 3.9 | 0.891 |
| Hypertension duration (years) | 5.03 ± 5.9 | 6.95 ± 7.2 | 0.0001 |
| Systolic BP (mmHg) | 140.92 ± 16.3 | 143.50 ± 18.0 | 0.0001 |
| Diastolic BP (mmHg) | 90.38 ± 10.0 | 89.21 ± 10.6 | 0.0001 |
| Heart rate (b.p.m.) | 74.87 ± 11.5 | 73.76 ± 11.5 | 0.002 |
| Fasting plasma glucose (mg/dL) | 93.27 ± 11.8 | 95.38 ± 12.4 | 0.0001 |
| HDL Cholesterol (mg/dL) | 50.51 ± 12.8 | 50.03 ± 12.3 | 0.233 |
| Triglycerides (mg/dL) | 131.0 ± 74.0 | 138.5 ± 74.2 | 0.001 |
| Metabolic syndrome (%) | 33.1 | 33.5 | 0.780 |
| Family history of diabetes (%) | 30.0 | 30.1 | 0.954 |
| CCB (%) | 20.4 | 26.0 | 0.0001 |
| β-Blockers (%) | 26.9 | 26.4 | 0.680 |

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; CCB, calcium channel blockers.
similar in the presence of both markers (n = 551; HR = 1.64; (95% CI 1.19–2.23); P = 0.002), and was independent of initial higher systolic BP [HR = 1.05/5 mmHg; (95% CI 1.02–1.11); P = 0.001], greater BMI [HR = 1.05/kg/m²; (95% CI 1.02–1.08)], higher fasting glucose [HR = 1.08/mg/dL; (95% CI 1.07–1.09)], family history of diabetes [HR = 1.59; (95% CI 1.29–1.96); all P < 0.0001], and type and number of anti-hypertensive medications (not significant). The last model of the Cox regression was repeated clustering all the components of MetS in a single variable as initial presence or absence of MetS. In this analysis, incident diabetes was independently predicted by initial presence of one or both markers of preclinical CVD, with additional significant effects for MetS, older age, and family history of diabetes, with no detectable effect for the other covariates (Table 3).

The Cox regression, adjusting for age, family history of diabetes, heart rate, duration of hypertension, number of anti-hypertensive meds, and use of CCB or β-blockers, was also run in specific subpopulations, based on the presence or absence of obesity or impaired fasting glucose. Patients with BMI ≥ 30 were younger, had higher baseline glucose, triglycerides, systolic and diastolic BP, heart rate and duration of hypertension, lower HDL cholesterol, and more frequent MetS and family history of diabetes (all P < 0.04) than those without obesity. In the obese sub-population (n = 992), incident diabetes was independently predicted also by the initial presence of one of the markers of preclinical CVD (Table 4; Figure 2A). In the non-obese sub-population (n = 3184), incident diabetes was independently predicted also by the initial presence of one of the markers of preclinical CVD (Table 4; Figure 2B). Similarly, incident diabetes was independently predicted by the initial presence of one of the markers of preclinical CVD either in the presence (n = 1389) or in the absence of MetS (n = 2787, all P < 0.02, Table 4).

Patients with impaired fasting glucose were older and more frequently men, had higher BMI, triglycerides, longer duration of hypertension, lower HDL cholesterol, and more frequent MetS and family history of diabetes (all P < 0.01) than those with normal fasting glucose. In patients with impaired fasting glucose (n = 453), the presence of one of the markers of preclinical CVD was associated with more than 1.6-fold greater risk of incident diabetes and the presence of both markers increased the risk to 1.7 folds (both P < 0.001, Table 4; Figure 3A). In patients with normal fasting glucose, incident diabetes was associated with more than 1.7-fold greater risk of incident diabetes in patients with either LVH or CA and more than two-fold in patients with both LVH and CA (both P < 0.001, Table 4; Figure 3B). No interaction was found between the presence of one or two markers of preclinical CV and BMI, MetS, or fasting plasma glucose at the first available visit, after adjusting for age, family history of diabetes, heart rate, duration of hypertension, number of anti-hypertensive meds, and use of CCB or β-blockers.

Finally, we compared the risk of incident diabetes in patients with different follow-up period (1, 2, and 5 years). The odds of diabetes referred to initial preclinical CVD increased with longer period of follow-up, but was already evident at a 2-year follow-up (Table 5).

### Table 3 Baseline predictors of incident diabetes including either one of or both markers of preclinical CV disease

|                          | HR  | CI 95.0% HR  | P ≤  |
|--------------------------|-----|--------------|------|
| Age (years)              | 1.02| 1.00–1.03    | 0.028|
| MetS (n/y)               | 2.73| 2.21–3.37    | 0.0001|
| Family history of diabetes (n/y) | 1.85| 1.51–2.27    | 0.0001|
| LVH or CA (n/y)          | 1.70| 1.33–2.17    | 0.0001|
| LVH and CA (n/y)         | 1.93| 1.42–2.63    | 0.0001|
| Heart rate (b.p.m.)      | 0.99| 0.99–1.01    | 0.762 |
| Duration of hypertension (years) | 1.01| 0.99–1.02    | 0.270 |
| Number of antihypertensive drugs | 1.09| 0.95–1.24    | 0.213 |
| CCB (n/y)                | 0.99| 0.78–1.27    | 0.920 |
| β-Blockers (n/y)         | 1.04| 0.82–1.32    | 0.749 |

MetS, metabolic syndrome; LVH, left ventricular hypertrophy; CA, carotid atherosclerosis; CCB, calcium channel blockers; β-blockers, beta-blockers.

### Discussion

This study indicates for the first time that the presence of hypertensive target organ damage (preclinical CVD), specifically LVH or CA or the combination of both, significantly increases the risk of future development of diabetes, independent of metabolic profile, BP, antihypertensive treatment and MetS, in a large outpatient-based cohort of clinically healthy, treated, non-diabetic hypertensive patients. This finding could be confirmed in the subgroups of non-obese patients.
whereas in obese subjects, only the combination of both markers could add to the risk of diabetes. The explanation of the difference between non-obese and obese participants relies in the higher absolute risk of diabetes in the presence of obesity, which also tracks significant preclinical CVD, making reasonable that only the combination of both markers adds to the risk of incident diabetes, already high in the condition of obesity. In the non-obese subpopulation, the exposure is substantially lower and, therefore, the condition of preclinical CVD can better modulate risk, according to severity.

Compared with the hazard of incident diabetes in the Cox model including single components of MetS, the risk related to preclinical CVD increased when MetS was accounted for in the Cox regression, suggesting that hypertensive target organ damage is particularly discriminating when MetS is present. This finding is consistent with the evidence that MetS significantly increases CV risk, independently of the effect of its single components. The common vision about the temporal relations between these abnormalities and diabetes was that diabetes is a cause or a concurrent cause of them. Similarly, both impaired fasting glucose and diabetes have been demonstrated to be independently associated with increased carotid IMT, a subclinical measure of atherosclerosis, independently of several potentially important metabolic and coagulation

Table 4  Cox’s regressions performed for subgroups stratified by BMI (obese vs. non-obese), presence or absence of MetS or impaired fasting glucose, adjusting for age, family history of diabetes, heart rate, duration of hypertension, number of anti-hypertensive meds, and the use of CCB or β-blockers

| HR  | CI 95.0% | P≤  |
|-----|----------|-----|
| BMI ≥ 30 (n = 992) | | |
| LVH or CA | 1.40 | 0.91 | 2.17 | 0.126 |
| LVH and CA | 1.76 | 1.06 | 2.92 | 0.030 |
| BMI < 30 (n = 3184) | | |
| LVH or CA | 1.73 | 1.28 | 2.33 | 0.0001 |
| LVH and CA | 1.83 | 1.22 | 2.74 | 0.003 |
| With MetS (n = 1389) | | |
| LVH or CA | 1.50 | 1.08 | 2.08 | 0.015 |
| LVH and CA | 1.68 | 1.12 | 2.52 | 0.012 |
| Without MetS (n = 2787) | | |
| LVH or CA | 1.97 | 1.37 | 2.83 | 0.001 |
| LVH and CA | 2.29 | 1.41 | 3.72 | 0.001 |
| First fasting glucose ≥ 110 mg/dL (n = 453) | | |
| LVH or CA | 1.63 | 1.10 | 2.41 | 0.015 |
| LVH and CA | 1.70 | 1.05 | 2.76 | 0.029 |
| First fasting glucose < 110 mg/dL (n = 3723) | | |
| LVH or CA | 1.73 | 1.27 | 2.36 | 0.001 |
| LVH and CA | 2.00 | 1.34 | 2.99 | 0.001 |

MetS was also added as a covariate in the models using BMI or impaired fasting glucose.

Figure 2  Hazard of incident diabetes in subgroup with (A) or without obesity (B), according to the initial presence of one (dotted line) or both markers (continuous black line) of preclinical cardiovascular disease (left ventricular hypertrophy, carotid atherosclerosis), compared with the absence of preclinical cardiovascular disease (continuous grey line).
factors. Similar to the temporal relation found with LVH, also CA could be demonstrated to precede diabetes, a finding contributing to overlook scenarios different from the traditional cause-effect relation. The association between preclinical CVD and incident diabetes was not inflated by the presence in the study population of patients with impaired fasting glucose, as it could also be confirmed in the subpopulation without impaired fasting glucose, using the most conservative approach proposed by the ATPIII in the 2002.

Our findings may be conciliated with the evidence that endothelial dysfunction precedes and predicts incident diabetes, to raise the hypothesis that vascular disease precedes the β-cell failure, which signs the shift from a condition of insulin resistance to diabetes. Endothelial dysfunction and impaired nitric oxide-mediated vasodila
tation have also been suggested to directly lead to reduced insulin delivery to skeletal muscles, resulting in peripheral insulin resistance and hyperglycaemia.

The association of insulin resistance with arterial hypertension further suggests that a vascular impairment might precede development of diabetes. The ability of arterial hypertension to predict incident diabetes also confirms that the vascular changes associated with diabetes cannot be simply considered as a consequence of the disease. These findings are eventually reinforced by the evidence that poor therapeutic control of BP further increases the risk of incident diabetes in hypertensive subjects. Considering this evidence, it is not surprising that we found that conditions of preclinical CVD, such as LVH and CA, precede and predict incident diabetes.

This scenario is also consistent with the evidence that most vascular damage associated with diabetes seems to be related to the coexisting MetS, more than to diabetes itself. Taken together with our findings, this evidence also suggests that the potent atherogenic effect of insulin resistance might be part of the biological mechanism yielding β-cell failure. Under this scenario, diabetes might be at least in part a consequence more than a cause of vascular impairment.

Microvascular disease has been hypothesized as a possible pathogenic factor in development of diabetes. This hypothesis is largely based on observations of microvascular abnormalities, such as arteriolar narrowing and impaired microvascular blood flow in the skin and skeletal muscles of persons with, or at high risk of, diabetes (e.g. those with impaired glucose tolerance and a family history of diabetes). Retinal arteriolar narrowing and hypertension have been associated with incident diabetes, independent of known risk factors. Parallel pancreatic microvascular disease might also precede clinical manifestation of diabetes. The hypothesis that diabetes might be the consequence of pancreatic microvascular dysfunction and ischaemia has been raised, but never proven. However, this hypothesis is supported by the experimental evidence of massive necrosis (but not apoptosis) associated with development of diabetes in diabetes-prone rats.

Limitations

We need to highlight some limitations of this study. First of all, this analysis has been performed in an observational registry, with the potential limitation related to this type of data repository. As a consequence, the frequency of follow-up visits was not standardized. However, we show that the number of visit/year was not different between patients developing or not developing diabetes. In addition, follow-up time was very variable, ranging from 1 to more than 20 years. However, sub-analyses performed at fixed duration of follow-up (1, 2, 5 years) could exclude a substantial bias related to the wide range of follow-up (Table 5), being the difference in incidence already significant after 2 years. Although the number of patients lost to follow-up is very low in the Campania Salute network (< 9%), the possibility of a bias related to patients lost to follow-up cannot be excluded with certainty. β-Blockers were more used in patients developing diabetes than in those without incident diabetes. However, the proportion of patients taking β-blockers was not statistically different in the presence or absence of markers of preclinical

Figure 3 Hazard of incident diabetes in subgroup with (A) or without impaired fasting glucose (B) according to the initial presence of one (dotted line) or both markers (continuous black line) of preclinical cardiovascular disease (left ventricular hypertrophy, carotid atherosclerosis), compared with the absence of preclinical cardiovascular disease (continuous grey line).
Table 5  Risk of incident diabetes in patients with different follow-up period (1, 2, and 5 years) with the initial presence of one or both markers of preclinical cardiovascular disease

|                          | No LVH (n = 3040) | LVH (n = 1136) | P< | OR | CI 95.0% OR |
|--------------------------|-----------------|----------------|----|----|------------|
| Incident diabetes after 1 year follow-up | 8 (0.3%)        | 7 (0.6%)       | 0.14 | 1.00 | 1.00 | 1.01 |
| Incident diabetes after 2 years follow-up | 23 (0.8%)       | 21 (1.8%)      | 0.003 | 1.01 | 1.00 | 1.02 |
| Incident diabetes after 5 years follow-up | 106 (3.6%)      | 74 (6.5%)      | 0.0001 | 1.03 | 1.01 | 1.05 |
| Incident diabetes after 1 year follow-up | 6 (0.2%)        | 9 (0.6%)       | 0.104 | 1.00 | 1.00 | 1.01 |
| Incident diabetes after 2 years follow-up | 21 (0.8%)       | 23 (1.5%)      | 0.041 | 1.01 | 1.00 | 1.01 |
| Incident diabetes after 5 years follow-up | 92 (3.5%)       | 88 (5.7%)      | 0.001 | 1.02 | 1.01 | 1.04 |
| Incident diabetes after 1 year follow-up | 10 (0.3%)       | 5 (0.9%)       | 0.038 | 1.01 | 1.00 | 1.01 |
| Incident diabetes after 2 years follow-up | 33 (0.9%)       | 11 (2.0%)      | 0.039 | 1.01 | 1.00 | 1.02 |
| Incident diabetes after 5 years follow-up | 144 (4.0%)      | 36 (6.5%)      | 0.009 | 1.03 | 1.00 | 1.05 |

CVD, making unlikely a confounding effect, which was in fact excluded in the Cox models.

Finally, direct assessments of endothelial function, β-cell function, or sympathetic activity could have helped substantially the understanding of our findings and should track future research.

Conclusions

We provide first evidence that initial LVH and CA are significant predictors of new onset diabetes in a large population of treated, relatively healthy hypertensive patients, independently of initial metabolic profile, anti-hypertensive therapy, and other significant covariates. This temporal sequence is likely to be attributable to risk factors both affecting CV system and yielding to diabetes, for which LVH and CA represent a more severe and advanced stage, but a vascular origin of diabetes cannot be excluded.

There are important implications of these findings for primary CV prevention, because they help identifying hypertensive patients at high risk of incident diabetes, a condition that would enormously increase CV risk in the setting of arterial hypertension. The possibility of refining identification of hypertensive patients at high risk to develop diabetes, by pooling ultrasound with clinical information, increases the chance to target individuals who might benefit from more aggressive pharmacological management, even independently of BP control, to reduce their vascular burden. Further studies are warranted to evaluate mechanisms explaining the reverse causation suggested by our findings.

Authors’ contributions

R.I., G.d.S., and N.D.L. conceived the study, made the analysis, and wrote the manuscript. V.T. and R.G. gave substantial help in data management, contributed to the analysis, and edited the manuscript. E.G., B.T., and O.V. gave substantial conceptual help in writing, editing, and finalizing the manuscript. R.I. and G.d.S. edited the final version of the manuscript. B.T. and G.d.S. gave final approval for submission. The guarantors of the study are G.d.S., N.D.L., and B.T.

Funding

This work has been supported in part by grant AIFA (Italian Agency for Drugs): AIFA/FARM5STRH9.

Conflict of interest: none declared.

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