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Importance of glycemic control on the course of glomerular filtration rate in type 2 diabetes with hypertension and microalbuminuria under tight blood pressure control

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Abstract *Background and aims:* To evaluate the role of glycemic control on the evolution of glomerular filtration rate (GFR) in type 2 diabetes (T2DM) with mild-moderate hypertension under tight blood pressure control, and to address the current controversy whether diabetic nephropathy worsens, independently of blood pressure, proportionally to HbA1c at any physiological level or only when HbA1c is above a 7.5–8% threshold.
Methods and results: T2DM ($N = 127$) during early stage diabetic nephropathy characterized by microalbuminuria were followed during a 2 year multicenter study. Individual GFR profiles were accurately obtained by $^{51}Cr-EDTA$ bolus injections and analyzed with linear statistical mixed-effects models. GFR at baseline was significantly negatively correlated with age and plasma creatinine concentration ($P \leq 0.0001$), and GFR declined, on average, by 4.0 ml/min 1.73 m^2/year ($P = 0.001$). A significant correlation was found between individual GFR decline rate and average systolic (SBP) and diastolic (DBP) blood pressures (−0.254 (0.736) ml/min 1.73 m^2/year per mmHg increase in SBP (DBP), $P = 0.041$ (0.014)) and % of glycated hemoglobin (HbA1c) (−1.78 ml/min 1.73 m^2/year per % increase in HbA1c, $P = 0.048$). This implies a 44% increase/reduction in GFR decline rate for 1% HbA1c increase/reduction around 7.0% (i.e. 5.79 and 2.24 ml/min 1.73 m^2/year at 8% and 6% HbA1c, respectively).

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Conclusions: This study demonstrates that, despite tight blood pressure control, an accurate glycemic control till very low patterns of HbA1c (from 10—11% to 5—6%) is needed to delay the progression of GFR decay in Mediterranean T2DM in south Europe with microalbuminuria.

Introduction

Type 2 diabetes (T2DM) has become the main cause of renal function impairment and can ultimately lead to end stage renal disease (ESRD) requiring dialysis or renal transplant [1]. The progression of renal disease in T2DM is characterized by an initial increase of glomerular filtration rate (GFR) during the early stage followed by a steady decline [2]. The major symptom of the inversion of the trend towards hyperfiltration is the appearance of microalbuminuria, identified also as risk factor of ESRD [2]. The decline of GFR over time has been associated with increased levels of glucose and glycated hemoglobin (HbA1c) and hypertension [3,4], and it has been demonstrated that levels of systolic and diastolic blood pressure have a strong association with microvascular and macrovascular complications in T2DM [3,4]. As regards the relationship between blood pressure levels and renal complications, an increase of 5—6 mmHg in both systolic and diastolic blood pressure levels is associated with a significant increase of the occurrence of ESRD [5].

Several well designed prospective studies have shown that blood pressure control through ACE-inhibition has an additional protective effect on renal function lowering urinary albumin excretion rate (AER), e.g. ref. [6]. It has also been claimed that drugs inhibiting the renin angiotensin system prevent the progression of microalbuminuria to proteinuria in the majority of type 2 diabetic Caucasian patients in whom blood pressure was steadily maintained in the range of 135—140 mmHg for the systolic value and 85—90 mmHg for the diastolic value [2,4]. Interestingly, also creatinine clearance after a slight decrease of 4—5 ml/min 1.73 m^2 (from a starting value of 108—110 ml/min 1.73 m^2 in the first 3 months of treatment) remained steadily stable at 105 ml/min 1.73 m^2 from the 6th—12th month in the groups of patients treated with irbesartan, whose HbA1c ranged from 7.1 to 7.3% [7].

However, it is still unclear how AER is related to renal function expressed in terms of GFR. For instance, it has been reported that GFR declines inexorably in Pima Indians with diabetic nephropathy despite careful therapy with ACE inhibitors [8]; and that in microalbuminuric type 2 diabetic patients normalization of AER by antihypertensive treatment and improved glycaemic control decelerates, but does not prevent, GFR decline [9].

In type 1 diabetes according to the DCCT the onset of renal complications was prevented or delayed when HbA1c was kept around 7.5% [10], while Warram and colleagues demonstrated that only levels of HbA1c above 8.0% increase significantly the risk to develop renal complications in Caucasian type 1 diabetes [11]. In T2DM a decrease of HbA1c from 7.9 to 7.1% reduced the incidence of renal complications [12]. Previous data of ours from a multicenter study in Italy were in agreement with Warram et al. [11] as a significant decrease of GFR was observed in T2DM with micro-macroalbuminuria only when HbA1c was steadily higher than 7.5—8.0% during a follow-up period between 2 and 8 years despite tight blood pressure control [13,14].

Given these relationships between renal complications and HbA1c in different conditions, we wanted to examine GFR decline under tight blood pressure control. Therefore, the aim of the present study was to investigate the independent role of glycemic control on the course of GFR in T2DM patients, whose HbA1c was maintained below 7.5—8% and whose blood pressure was tightly controlled.

Methods

A multicenter 24-month study in 127 microalbuminuric (MA) and mild-moderate hypertensive T2DM was designed to study primarily the effects of tight blood pressure control on changes in GFR over time. The present analysis investigates the effects on GFR of secondary parameters, such as AER, blood pressure, HbA1c, creatinine and lipid profiles, collected during the study.

After giving written informed consent, patients underwent a pre-screening visit where AER was measured from three consecutive timed overnight urine collections, with albumin measured in a unique laboratory, for selecting MA patients with AER of 30—300 μg/min in at least two out of three measurements. Patients underwent the baseline evaluation of GFR using the technique of the bolus injection of ^{51}Cr-EDTA for assessment of plasma clearance [15]. Patients with important renal failure (GFR <60 ml/min 1.73 m^2) were excluded from the study. After a 2 week pharmacological wash-out period as regards antihypertensive drug administration, patients were randomized for treatment either with enalapril ($N = 50$, 10 mg per day) or nifedipine GITS slow release ($N = 77$, 30 mg per day) with target diastolic blood pressure (DBP) value below 85 mmHg. Patients meeting the protocol eligibility criteria entered a 4 week run-in period. Enalapril and nifedipine GITS doses were increased if necessary to 20 mg/day or 60 mg/day, respectively, to meet the target blood pressure control. Hydroclorothizide (from 12.5 to 25 mg per day) was also superimposed to the treatments to accomplish the target blood pressure control. Atenolol was also used (50—100 mg/day) as 4th step treatment. Drug dosage was adjusted every month in order to achieve the defined target blood pressure levels. AER was measured every three months, while GFR was measured every 6 months. The study was approved by institutional review boards (Ethical Committee of the University of Padova and by the Italian National Ministry of Health).

Subjects

Adult caucasian T2DM (diagnosed according to the WHO criteria) with incipient diabetic nephropathy were enrolled in the study according to the following criteria: (1) treatment with diet and/or oral hypoglycemic drugs (sulphonilureas and metformin 500, 1500 mg per day,