The effect of metabolic control on development and progression of diabetic nephropathy

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Abstract. The progressively growing number of patients with end-stage renal failure (ESRF) associated with diabetes mellitus and requiring renal replacement therapy (RRT) stimulated both nephrologists and diabetologists to investigate the mechanisms linking hyperglycaemia to diabetic renal failure and to set up measures to prevent the onset and slow the progression of diabetic nephropathy. Over the last few decades, a large number of studies have investigated both the incidence of diabetic nephropathy and the relationship between metabolic control and the development of diabetic nephropathy.

Introduction

In spite of the increased attention assigned by both nephrologists and diabetologists to the many influences involving the onset and progression of diabetic nephropathy, such as genetic aspects, systemic hypertension, lipid and other associated metabolic abnormalities, haemostatic alterations and smoking habits [1,2], glycaemic control still remains a central issue. In the last decade, a large number of studies have investigated this issue, as well as the pathophysiological changes through which a persistent hyperglycaemia leads to the onset of overt diabetic nephropathy.

The central role of metabolic control is strongly supported by recent findings [3] demonstrating that isolated pancreas transplantation performed in patients prior to development of end-stage renal failure (ESRF) can reverse established lesions in diabetic nephropathy. In these patients, a functioning graft, which provides normoglycaemia, can be the only powerful variable influencing the course of both tubular and glomerular damage.

In this review, we focus first on the biochemical pathways involved in the pathogenesis of diabetic glomerulopathy, thereafter on the natural history of diabetic renal disease, and finally on studies that have evaluated the impact of metabolic control on development and progression of diabetic renal disease.

Biochemical pathways involved in the pathogenesis of diabetic nephropathy

As a preliminary consideration, there is a consistent agreement between studies on the similarity of the pathogenic mechanisms for development of morpholo-
ional alterations in type I and type II diabetes. In its early appearance, the first morphological alteration is hypertrophy of glomerular and tubular elements; subsequently, a thickening of glomerular and tubular basement membranes is evident, with enhanced glomerular permeability to albumin. This leads to progressive accumulation of extracellular matrix components in the glomerular mesangium and in tubulointerstitial structures [4].

The pathophysiological interpretations for understanding the biochemical mechanisms underlying these features are disparate and sometimes controversial. There is epidemiological evidence that the development of diabetic nephropathy is linked to hyperglycaemia [5]. Among the many mechanisms under study through which high glucose concentrations act on renal cells are the increased flux of glucose metabolism through the polyol pathway [6–8], the increased de novo synthesis of diacyl glycerol (DAG) and subsequent activation of protein kinase C (PKC) [9–11], the increased non-enzymatic glycation activity [12,13] and the aberrant synthesis or actions of cytokines and growth factors [14–17].

The first possibility involves intracellular formation of sorbitol from glucose, catalysed by aldose reductase [6]. Chronic hyperglycaemia leads to sorbitol accumulation in a variety of tissues, such as peripheral neurons, the lens of the eye, and renal tubuli. Treatment with inhibitors of aldose reductase may prevent some of the early features of diabetic nephropathy such as glomerular hyperfiltration [6]. However, there is no consistent evidence that these inhibitors may reduce late manifestation of nephropathy [7]. Organ dysfunction in diabetes caused by the increased flux of glucose through the polyol pathway has been linked to the hyperglycaemia-induced increase in the NADH/NAD⁺ ratio, which is associated with the de novo synthesis of DAG and the stimulation of PKC activity. Disordered cellular metabolism or depletion of myo-inositol may also ensue [6]. However, long-term supplementation of dietary myo-inositol in a rat model of type II diabetes had no effect on the development of diabetic glomerulosclerosis [8], although it was observed to reduce hyperfiltration in a rat model of type I diabetes [6].

The second possibility is linked to the activation of PKC through which hyperglycaemia stimulates extracellular matrix (ECM) production, presumably due to increased de novo synthesis of DAG. The increase in the NADH/NAD⁺ ratio resulted from the increased activity of the polyol pathway favouring this reaction. High ambient glucose promotes collagen IV gene transcription in murine mesangial cells, and this probably occurs through PKC activation [9,10]. Interestingly, a specific inhibitor of PKCβ reduced albuminuria and altered the retinal blood flow in diabetic rats [11].

A third mechanism is the non-enzymatic reaction (glycation) between glucose, progressively accumulated in the extracellular milieu, and amino groups of matrix proteins (Maillard reaction). Subsequently, the Schiff-base is converted into Amadori products which are more stable but still reversible sugar–protein adducts. Moreover, in the later stage of this reaction, the 3-deoxyglucosone (3-DG) reacts with the amino groups of various proteins and leads to formation of advanced glycation end-products (AGEs). AGEs are irreversibly attached to proteins and, consequently, the level of AGE in the diabetic tissue does not return to normal when hyperglycaemia is corrected, but instead these products continue to accumulate on the vessel wall. Increased AGE deposition is recognized as playing a central role in various degenerative processes [12,13] (Figure 1).

Transforming growth factor-β (TGF-β) is a central cytokine in cell growth and ECM production, and there is evidence implicating it in the pathogenesis of diabetic renal disease [14]. The development of renal hypertrophy is probably linked to the increased expression of TGF-β1 and the type II TGF-β receptor in the kidney because treatment of streptozotocin-induced diabetic mice with anti-TGF-β antibodies attenuates both the hypertrophy and the increase in mRNAs encoding z1-collagen and fibronectin [15]. In humans, glomeruli from kidneys of patients with diabetic nephropathy overexpress TGF-β protein, and the increase in TGF-β mRNA might be correlated with the degree of hyperglycaemia [16,17].

On the other hand, recent studies demonstrated that a high glucose concentration could, per se, cause a relevant influence on renal cell growth and ECM metabolism. These high glucose concentrations in tissue culture stimulate proximal tubule cell hypertrophy as well as mesangial cell production of types I and IV collagen and laminin. In animal models, no difference in the development of these effects is recognized between sustained hyperglycaemia and acute, repeated hyperglycaemia [18]. The latter, in fact, exerts in rat mesangial cells a more pronounced stimulatory effect on collagen production. In spite of this well-accepted biochemical model, many questions remain unanswered.

One argument under debate is the hypothesis that the raised intracellular concentration of glucose rather than its extracellular accumulation acts as a first step in the cascade of biochemical and morphological events leading to overt diabetic nephropathy. In cell culture, it was noticed that increased intracellular glucose concentration through enzymatic and non-enzymatic pathways causes pathological changes. Rat mesangial cells, transfected with the glucose transporter gene GLUT1, exhibit increased glucose uptake and metabolism with stimulation of ECM synthesis, even if these cells are grown at a normal extracellular glucose concentration [19].

Although the biophysical and structural bases for diabetic proteinuria remain unresolved, changes in charge- and in perm-selectivity of the glomerular basement membrane (GBM) are believed to contribute consistently to this phenomenon. Recently, a close correlation was noted between selective proteinuria and the heparan-sulphated proteoglycan content of GBM [20] in streptozotocin-induced diabetic rats. A similar effect was observed in vitro by incubation of
human mesangial and glomerular epithelial cells in high ambient glucose, which causes a decrease in heparan-sulphated proteoglycan synthesis and alters the sulphation patterns of epithelial cells [21,22].

The natural history of diabetic nephropathy

Type I diabetes

Much is known about the natural history of diabetic nephropathy in type I diabetes. The first clinical evidence of this disease is the presence of low but supranormal excretion of albumin. Microalbuminuria is defined as a urinary albumin excretion rate (AER) between 30 and 300 mg/24 h, corresponding to 20–200 μg/min in a timed specimen collection, or to 30–300 mg/g of creatinine in a randomly collected sample. Numerous studies have shown that without intervention, 50–80% of microalbuminuric patients progress from microalbuminuria to clinical albuminuria (>300 mg/24 h or >200 μg/min) and thereafter to overt nephropathy over the following 10–15 years, associated with the progressive decline of the glomerular filtration rate (GFR) and increase in serum creatinine [23–25]. During this period, the majority of patients develop frank hypertension. The relationship between hyperfiltration, microalbuminuria and the development of nephropathy is still under debate. The progression of renal disease in type I diabetes is, however, very different from patient to patient. Moreover, only a percentage of type I diabetic patients develop overt nephropathy. This fact suggests that other variables, in addition to metabolic control, may influence the course of diabetic disease. Among these, the most important are hypertension and/or genetic factors [1].

Many observations have demonstrated that in type I diabetes after 10–15 years of sustained microalbuminuria, a large percentage of patients, ranging from 30 to 50%, develop clinical albuminuria or overt nephropathy. Over a period of several years, depending on many factors, the GFR also declines. Krolewski et al. reported that ESRD occurred in 78% of patients with overt nephropathy within 18 years [26]. All in all, the cumulative incidence of diabetic nephropathy seems to have decreased over the years [26–28]. The Steno Hospital, Copenhagen, Denmark, reported long-term data which provided evidence of a substantial decrease in the cumulative incidence of proteinuria comparing patients diagnosed between 1933 and 1942 with those diagnosed between 1953 and 1962 [27,28]. In the retrospective analysis performed for a similar period in the Joslin Clinic, Boston, USA [26], the cumulative risk of overt nephropathy accounted for 35% after 40 years, but the cumulative risk of developing overt diabetic nephropathy progressively decreased in more recent years. In 1994, Bojestig et al. reported that the cumulative incidence of persistent albuminuria after 25 years of diabetes decreased from 30% among the patients diagnosed in 1961–1965, to 9% among the
patients diagnosed in 1966–1970 [29]. On the other hand, Rossing et al. reported similar insulin rates in patients diagnosed between 1970 and 1974 and from 1975 to 1979 [30]. In order to explain the decreased incidence of diabetic nephropathy or its absence, differences in control of high blood pressure and smoking habits have been suggested.

**Type II diabetes**

The majority of research in diabetes has been directed toward type I diabetes. However, the majority of diabetic patients have type II diabetes and, nowadays, we are witnessing an epidermic increase of older type II patients reaching ESRD and being proposed for renal replacement therapy (RRT) [2,31,32]. It has been reported that this phenomenon could be related to the striking increase in the prevalence of type II diabetes in the general population, related to ageing, and easier access to food and motorization leading to lower physical activity and obesity. Moreover, due to improved treatment of cardiovascular diseases and hypertension, type II patients live longer and are susceptible to progressing to ESRD.

The natural history and the exact percentage of type II diabetic subjects that develop nephropathy are still unknown. This is fundamentally because there is uncertainty about the denominator (total number of type II diabetics). Type II patients with renal disease are usually counted when they enter an RRT programme. However, this number is inaccurate since a number of patients will die before entering RRT because of selection or due to other causes. Moreover, since type II diabetes is often diagnosed many years after onset, it is possible that a subject with renal disease is found to be diabetic. A higher proportion of individuals with type II diabetes are found to have microalbuminuria and overt nephropathy shortly after the diagnosis of their diabetes because diabetes has actually been present for many years before the diagnosis is made. Finally, type II diabetes is a complex syndrome in which obesity, hypertension, dyslipidaemia and microalbuminuria often precede the onset of frank hyperglycaemia. Even if in type II diabetes microalbuminuria precedes overt proteinuria [33], in microalbuminuric type II patients only 20% develop overt nephropathy in a 10 year period [33], and by 20 years after onset of overt nephropathy, only 20% will have progressed to ESRD. Once the GFR begins to decline, the rate of decline varies considerably between individuals, but may not be substantially different between patients with type I or type II diabetes. Moreover, in type II diabetes, nephropathy has a different impact in different ethnic groups, with Caucasians having the least risk, Hispanics and African-Americans having a higher risk, and Asian Pacific Islanders having the highest risk [2,34]. Among Pima Indians, a group of native Americans living in Arizona, for whom accurate longitudinal data are available, the rate of nephropathy is 50% after 20 years of type II diabetes [35]. The GFR is often increased at the onset of the disease and remains elevated as long as normal urinary albumin excretion or microalbuminuria persists. After the onset of macroalbuminuria in Pima Indians, the GFR declines at least as rapidly as reported in type I diabetic subjects [36]. The disparities in prevalence of nephropathy in different ethnic groups suggest that, since the majority of studies has considered Caucasians, this may have given an underestimation of the true incidence of nephropathy in type II diabetes.

**Metabolic control, development and progression of diabetic nephropathy**

**Type I diabetes**

**Observational studies.** In 1978, Pirart reported a correlation between metabolic control and nephropathy in 4400 patients observed between 1947 and 1973 [37]. Hasslacher et al. demonstrated a significant association between the incidence of proteinuria and the degree of hyperglycaemia in The Netherlands, Germany and Sweden [26,38,39]. On the other hand, Andersen et al. [18] did not find such an association in a follow-up study of 1475 clearly defined type I diabetic patients of whom 531 developed nephropathy [27]. A similar lack of association was found in 1888 patients sequentially followed-up by the European Microalbuminuria Study Group, where only a non-significant trend (higher HbA1C levels) was found in microalbuminuric type I diabetic patients [40]. On the contrary, the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) found a correlation between microalbuminuria and higher HbA1C levels [41]. Similar results were also obtained in another population of type I diabetic patients in Israel in 1991 [42]. Some years later, longitudinal studies based on the evaluation of a defined time interval were performed and showed a clearer relationship between metabolic control and development or progression of nephropathy. One of these studies, conducted in the US over 2 years, showed a higher baseline glycohaemoglobin in type I diabetic patients who developed microalbuminuria compared with the lower levels detected in patients who remained normoalbuminuric [43]. Parallel results were found in a population of 210 patients followed-up for 6 years in Northern Ireland [44]. Moreover, the patients evaluated in the WESDR study were followed-up, and the risk of developing proteinuria was significantly greater in patients with more elevated HbA1C levels, compared with those with better metabolic control [45]. Chanteau and Wichmann observed that type I diabetic patients treated with more aggressive insulin infusion (CSII) or multiple dose insulin injections (MDI) showed a lower HbA1C level and a lower prevalence of overt nephropathy compared with patients treated conventionally [46]. Chase et al. previously have shown in a prospective evaluation of 230 type I patients that no patient developed microalbuminuria if HbA1C was
maintained within 10% greater than the upper limit of normal [47]. Krolewski et al. demonstrated that the relative risk of developing overt nephropathy increased abruptly in type I diabetic patients whose HbA1C value was >8.1% [48]. In a recent study, Bojessig et al. have shown that in a 10 year follow-up, regression, persistence or evolution of microalbuminuria was associated with increasing HbA1C levels [49].

**Interventional studies.** These studies generally are based on a longitudinal prospective design, aimed at assessing the efficacy of a more intensive metabolic control on the development of the major complications occurring in type I diabetes. In most of these studies, cardiovascular complications, neuropathy and retinopathy feature predominantly and receive the attention of the investigators, while nephropathy features only as a collateral complication or a secondary end-point. Although these studies usually have been carried out on smaller cohorts, they carry the advantage of being longitudinal and randomized.

In 1983, Homan et al. [50] published data on 74 type I diabetic patients who were followed-up for 2 years and randomly assigned to intensive insulin treatment (MDI) or conventional insulin therapy (CT). A striking difference was observed in the creatinine clearance, which declined significantly from 99.9 ± 23.5 to 82.9 ± 26.0 ml/min in patients on CT and, surprisingly, increased in the MDI group. Unfortunately, urinary AER was not measured whilst no effect was observed on retinopathy. The effect on AER was reported 1 year later by a multicentre collaborative trial comparing CSII vs CT. This longitudinal study, albeit lasting only 8 months and enrolling only 59 patients, showed a significant reduction of AER in 10 patients with microalbuminuria on CSII, whereas no change was observed in patients treated conventionally [51]. In the Steno 2 study, all patients with microalbuminuria were allocated randomly to CSII or CT for 2 years. A significant modification of the mean AER per year was noticed between the two groups, accounting for +7% in CT patients and -9% in those on CSII [52]. In a 4 year follow-up study performed in Oslo on 45 patients, AER decreased substantially in patients treated by CSII (mean HbA1C 9%), whilst remaining unchanged in subjects treated conventionally (mean HbA1C 10.5%) or by MDI (mean HbA1C 9.4%) [53]. When the data were reviewed after a 7 year follow-up according to HbA1C, AER significantly increased only in 14 patients with mean HbA1C >10.0% [54]. Beck-Nielsen et al. reported a 5 year follow-up study, comparing insulin infusion against conventional treatment in 24 normoalbuminuric patients, showing no significant change in the mean urinary AER in either group [55]. Three years later, Reichard et al. reported a 7.5 year intervention study comparing 48 intensively treated patients with 54 conventionally treated patients. HbA1C was 7.1% in the first group and 8.5% in the second. Overt nephropathy (albuminuria >200 mg/min) developed in one patient in the group receiving intensified treatment as compared with nine patients in the group receiving standard treatment. However, six patients in the standard treatment group developed subnormal GFRs [56]. The Diabetes Control and Complications Trial (DCCT) has now proved definitely that improved metabolic control that achieves near normoglycaemia can decrease the development and progression of early nephropathy as well as other long-term complications of diabetes. The DCCT was a randomized prospective 9 year multicentre trial in which the two main series of type I patients were enrolled in order to compare intensive and conventional treatment on the development of microalbuminuria and overt nephropathy (primary prevention trial) or on slowing down the aforementioned complications in subjects with background retinopathy. At baseline, mean HbA1C was similar in the two treatment groups but, after 3 months, mean HbA1C was 2% less in the intensive treatment group, and this difference was maintained throughout the study [57]. In the Primary Prevention Trial, the estimated cumulative incidence of microalbuminuria was 16% after 9 years, significantly less (P=0.04) than the 27% estimated after 9 years in patients on conventional therapy. In the secondary intervention trial, the 9 year estimated incidence of clinical albuminuria (>208 μg/min) was 5.2% in those on intensive treatment vs the 11.3% calculated in those on conventional therapy (P<0.01). Nevertheless, examining the progression of albuminuria in a small (n=73) subgroup of patients with AER >28 μg/min, no significant difference in development of clinical albuminuria was found between intensively treated and conventionally treated patients [57]. This result can suggest that a more intensive treatment could be more advantageous in the early phase of diabetic nephropathy rather than in later phases. However, the microalbuminuric patients represented a very small subgroup since this important trial originally was designed to assess the impact of metabolic control on retinopathy; thus, nephropathy was regarded only as a secondary end-point [57]. The 10 year follow-up data of the Stockholm Diabetes Intervention Study were published in 1996 [58]. After the first 7.5 years, intensively treated patients were left to control their own treatment, while treatment was intensified in the control group. On average, HbA1C between 6 and 120 months was 7.2 ± 0.6% in the intensified treatment group against 8.3% in the standard treatment group. At 10 years, the proportion of overt nephropathy was 7% in the intensified treatment and 26% in the conventional treatment group. On the other hand, GFRs were not different in the two groups either at baseline or at 10 year follow-up [58]. Finally, two recent studies have suggested that even in subjects with overt nephropathy and impaired renal function, an aggressive approach aimed at both blood pressure and metabolic control is effective in preserving the GFR [59,60]. In both these studies, an independent effect of metabolic control was demonstrated.

**Type II diabetes**

If we assume that the risk of developing proteinuria and renal failure is not different between type I and
type II diabetes, since the incidence of type II diabetes is generally greater, it would be logical to assume that the total number of uraemic type II diabetic patients should outnumber those of type I [34]. This is the case in most if not all Western countries. Although there is increasing evidence linking metabolic control to the risk of developing nephropathy in type II diabetic patients due to the difficulties in diagnosis definition and the heterogeneity of the disease, in many cases this relationship is not evident. It is possible that different risk factors play a different role in different age groups, i.e. that hyperglycaemia plays a major role in younger type II patients and hypertension plays a major role in older type II patients. Savage et al. [61] reported in the Appropriate Blood Pressure Control in Diabetes Trial (ABCD trial) a mean fasting glycaemia and HbA1C lower in patients with normoalbuminuria compared with those with microalbuminuria or overt nephropathy (186 vs 204 mg/ml and 11.1% vs 12.1 and 12.6%), respectively. On the other hand, in his German study, Hasslacher did not find any significant association between post-prandial blood glucose and development of proteinuria, even though the glycated haemoglobin was somewhat higher (P < 0.06) in the patients with nephropathy [62,63]. Two studies on type II African-American patients found no correlation between metabolic control and the presence of diabetic nephropathy [64,65]. On the other hand, two long-term prospective trials conducted on Indian-Americans showed that the risk of developing diabetic nephropathy was greater in patients with higher fasting blood glucose or higher HbA1C [35,66]. Two studies from Japan have reported an association between poor metabolic control and the likelihood of developing diabetic nephropathy. Yokoyama et al. studied 1065 type II diabetic patients with early onset (diabetes diagnosed before 30 years of age) who were divided according to the development of proliferative retinopathy before the age of 35. The subgroup that developed proliferative retinopathy before 35 was characterized by poor metabolic control, increased prevalence of familial diabetes and greater prevalence of female gender [67]. In 1998, Takanaka et al. reported a retrospective study of 123 type II elderly Japanese patients divided into normo- and microalbuminuric. The group that developed microalbuminuria showed a greater 6 year mean HbA1C than the group that remained normoalbuminuric (9.0 vs 8.1%, P < 0.01) despite no significant difference in 6 year mean blood pressure. The cut-off level of HbA1C separating normo- from microalbuminuric was 8.5% [68]. Very recently, Ravid et al. reported the results of a long-term prospective follow-up study performed on 574 patients with recent onset of type II diabetes [69]. Patients initially were normotensive and normoalbuminuric and had a normal renal function. After a follow-up ranging from 2 to 9 years, 111 patients (19%) had microalbuminuria and 90 (16%) overt albuminuria. A logistic regression model demonstrated that the correlation between HbA1C levels and the risk of albuminuria is exponential. Multiple logistic regression analysis showed that levels of total cholesterol, mean blood pressure and HbA1C were the main factors associated with the decrease in renal function and the increase in albuminuria [69]. Finally, here we want to report a study performed in type II diabetic patients on regular dialysis where survival after 5 years of dialysis was 78% in subjects with good glycaemic control (HbA1C 6.9%) before starting dialysis compared with only 47% in subjects whose mean HbA1C before starting dialysis was 10.5% [70]. More significant data are expected from a multicentre prospective interventional study on type II patients (UKPDS), that should represent for type II diabetes what DCCT is for type I, and whose results are not yet available.

**Conclusions**

A number of important studies culminating with the DCCT have now proven definitely that achievement of near normal glycaemia in type I diabetes can significantly reduce the risk of developing microalbuminuria and overt nephropathy. Although such a large amount of evidence is still lacking for type II diabetes, it is likely that improved glycaemic control will be of benefit in reducing the risk of developing nephropathy and slowing its progression. Such an effect is reliable even if we can expect that genetic heterogeneity, the potential presence of other underlying nephropathies,

**Table 1. The role of hyperglycaemia in diabetic nephropathy: observational studies in type I diabetes**

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<th>Studies demonstrating a favourable role of better metabolic control</th>
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<td>Pirart et al. (1978), 37</td>
<td>Andersen et al. (1995), 18</td>
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<td>Hasslacher et al. (1985), 38</td>
<td>Microalbuminuria Collaborative Study Group (1992), 40</td>
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<td>Chase et al. (1989), 47</td>
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patients' ages, difficulty in making a prompt diagnosis, more pronounced interference with other risk factors, and more uncertain therapeutic and dietetic compliance, together with other confounding factors, might make it difficult to demonstrate in a conclusive way the impact of metabolic control on the development of nephropathy in type II diabetes. In any case, nowadays it seems difficult to contest the fact that all physicians treating diabetic patients should try to achieve glycaemia as near as possible to that in normal subjects. On the other hand, there is no question that the major adverse effect of trying to achieve near-normoglycaemia is the increase in hypoglycaemic reactions. In the DCCT, subjects treated intensively presented a 3-fold increase in the number of hypoglycaemic reactions [57]. For this reason, scientists have investigated whether there is a threshold of metabolic control beyond which there is no further improvement whilst the hypoglycaemic risk increases. Since the relationship between glycosylated haemoglobin and the risk of developing nephropathy is exponential, it seems that at lower HbA1c levels the risk of nephropathy is less whilst the risk of hypoglycaemic attacks increases. For this reason, a practical goal should be a glycated haemoglobin of 7–7.5%. If we achieve this goal, we will diminish substantially the incidence of microvascular complications including nephropathy.

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