

A Perspective of Aldose Reductase Inhibitors and Diabetic Complications*

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The clarity of findings in the recent trials of intensive insulin treatment has proven that improved glycemic control delays the onset and retards the progression of diabetic retinopathy, nephropathy, and neuropathy. The results have revealed, however, that – even with intensive insulin therapy – normalization of blood glucose values was not achieved: a significant burden of complications was thus left on the diabetic population. This amplifies the necessity of pharmacotherapy aimed at controlling the consequences of elevated glucose levels that persist due to inadequate glycemic control. Such pharmacotherapy is currently available through aldose reductase (AR) inhibitor treatment. The concept of AR inhibition rests on the evidence – obtained with preventive AR inhibitor treatment – that any surplus of glucose occurring in a diabetic tissue is metabolized by AR, thus triggering a cascade of pathophysiological changes that progress to the advanced lesions characterizing the triad of diabetic complications. Since, axiomatically, AR inhibitors cannot be more effective than normoglycemia, the benefit *vs.* risk evaluation and duration of AR inhibitor therapy should be considered relative to that of intensive insulin treatment. The use of AR inhibitors is deemed to be justified, therefore, in patients threatened by diabetic complications – particularly with early peripheral neuropathy – and who cannot achieve adequate glycemic control.

* Dedicated to Professor Vladimir Prelog, my mentor, on the occasion of his 90th birthday.

DIABETIC COMPLICATIONS AND HYPERGLYCEMIA

It is generally accepted that an association exists between hyperglycemia and the development of complications of long-term *diabetes mellitus*^{1,2} such as neuropathy,³⁻⁷ nephropathy,⁸⁻¹² and retinopathy.¹³⁻¹⁷ Suppression of hyperglycemia should, therefore, halt their development, albeit in a tissue-specific fashion.^{18,19} Practically, the hyperglycemia-derived complications in insulin-dependent (IDDM) and non-insulin-dependent *diabetes mellitus* (NIDDM) could be prevented, arrested, or delayed by normalizing systemic glucose levels with strict control or pharmacotherapy (in NIDDM), or, by pharmacotherapy aimed at avoiding the pathophysiological consequences of the excessive glucose levels arising in tissues of diabetic subjects. The postulate that strict glycemic control should abate the development and progression of diabetic complications²⁰ was conclusively confirmed by the results obtained by intensified insulin treatment in patients with IDDM, *i.e.* by the *meta*-analysis of 16 randomized clinical trials,^{21,22} in the Oslo Study,^{23,24,6} in the Stockholm Diabetes Intervention Study (SDIS),²⁵ and, in the Diabetes Control and Complications Trial (DCCT).²⁶

In the DCCT, reduction of hyperglycemia to near-normoglycemia [mean hemoglobin (Hb)A_{1c}, 7.2%), maintained for up to 9 years, reduced both the risk and the progression of retinopathy,²⁷ neuropathy,²⁸ and nephropathy,²⁹ by 34 to 76%.²⁶ Near-normoglycemia was achieved by multiple daily insulin injections combined with frequent glucose monitoring, and close supervision by a multidisciplinary team of diabetes professionals.³⁰ The announcement of the DCCT results in 1993 was followed by a plethora of editorials, commentaries, and reviews, virtually all addressing the practical consequences of this mega-study. Two points of relevance to this discussion are the extrapolation of DCCT results to NIDDM, and their translation into medical care practice.

Extrapolation of DCCT Results to NIDDM

The issue has enormous public health implications since around 3% of the Western world has NIDDM: in subjects 60 years and older the prevalence is as high as 10 to 20%, and in certain ethnic populations approaches 40%.³¹ A virtual epidemic of NIDDM is now seen in Third World countries,³² *e.g.* in modernizing Pacific island populations³³ and in Western Australia.³⁴ While extrapolation of the findings in IDDM to subjects with NIDDM appears to be justified because of the common input of chronic hyperglycemia to the pathogenesis of diabetic microvascular complications,^{35,36} many qualifications preclude a blanket endorsement, particularly when one considers intensive insulin treatment in the large NIDDM population that appears most eligible: those who have chronic hyperglycemia despite therapy with diet, exercise, sulfonylureas, and/or insulin.³⁵ Indeed, the benefits of altering

microvascular events in this population may not outweigh the risks of an increase in macrovascular events.^{35,36} Consensus regarding relevancy of the findings in the DCCT to NIDDM is essential, therefore, before broad-based extrapolation efforts are begun.^{37,38,30}

Of note, although the currently available drugs for the treatment of hyperglycemia in NIDDM »have been effective in many patients, the difficulty in achieving near-normal glycemia in the majority of patients emphasizes the need for additional therapeutic options«.³⁹

Translation of DCCT Results into Medical Care Practice

Since the DCCT was not designed to determine how intensive management of glycemic control could be provided in a practical sense, or, to whom it should be provided,³⁸ it is of interest to scrutinize the DCCT based on data reflecting the medical care for diabetes as currently practiced in the USA: whereas the DCCT participants received care from a team of diabetes professionals, 98% of diabetic patients are treated by primary-care physicians whose specialty is *not* diabetes or endocrinology;³⁸ only 15% of patients use multiple daily insulin injections; only 40% self-monitor their blood glucose at least once daily,³⁷ while in the DCCT, most of the intensively treated patients measured their blood glucose at least 4 times daily. While the intensively treated group in the DCCT had their HbA_{1c} measured every month, in the USA, only 13 to 17% of all diabetic patients have ever heard of glycosylated hemoglobin.³⁷ It thus appears that medical care for diabetes, as currently practiced in the USA, neither meets ADA guidelines nor approaches the levels of either conventional or intensive treatment groups of the DCCT.⁴⁰

While the DCCT has generated data of profound scientific importance for our understanding of diabetic complications, the translation of the findings into daily clinical and public health practice faces numerous barriers.³⁸ This underscores the need for adjunctive pharmacotherapy. In fact, by conclusively incriminating hyperglycemia as *conditio sine qua non* for the development of diabetic complications, the clinical trials of intensive insulin treatment^{21,23-25,6,26-29} have also amplified the necessity of pharmacotherapy aimed at controlling the pathophysiological consequences of hyperglycemia remaining after imperfect glycemic control.

THE SORBITOL PATHWAY THEORY

Since the target organs of diabetic complications do not depend on insulin for the regulation of either glucose absorption, or of glucose metabolism, they are exposed to the wide diurnal fluctuations in systemic glucose concentrations occurring in diabetic subjects with inadequate glycemic control:

glucose levels in such tissues parallel the glucose levels in the blood (Figure 1).⁴¹ Whereas there is no shortage of plausible mechanisms proposed to explain the transformation of excess glucose in the diabetic nerve, retina, and kidney into tissue-specific damage, to date only the sorbitol-pathway mechanism has provided the basis for a pharmacological approach which has resulted in the marketing of two aldose reductase inhibitors,⁴²⁻⁴⁸ tolrestat, and epalrestat (in Japan).

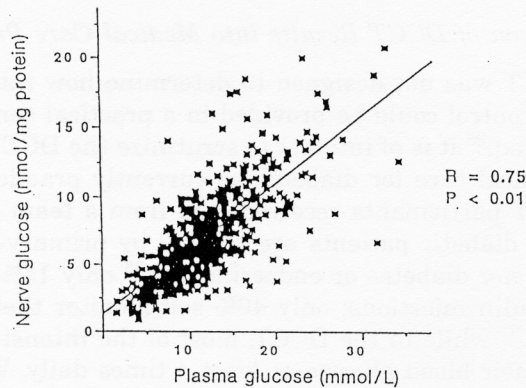


Figure 1. Glucose concentrations in plasma and sural nerve specimens from 336 patients with diabetic neuropathy.⁴¹

* Duration of diabetes, 11.8 ± 8.6 years (\pm SD).

The sorbitol pathway comprises two enzymatic reactions: in tandem, glucose is reduced to sorbitol by aldose reductase (AR; E.C.1.1.1.21) with NADPH as cofactor, and sorbitol is oxidized to fructose by sorbitol dehydrogenase (E.C.1.1.1.14) with NAD^+ as cofactor (Figure 2). Since the structural environment of the active site of AR does not favor glucose as substrate,⁴⁹ AR gains access to glucose only at concentrations that are above the glucose-binding capacity of hexokinase.⁵⁰ The metabolism of the glucose surplus by AR occurring in a diabetic tissue results in a correspondingly high rate

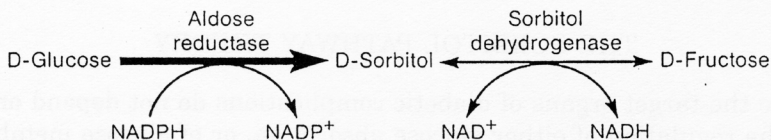


Figure 2. The sorbitol pathway.

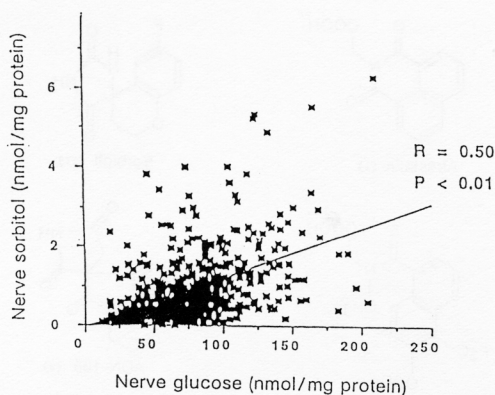


Figure 3. Glucose and sorbitol levels in sural nerve biopsy specimens from 336 patients with diabetic neuropathy.⁴¹

* Duration of diabetes, 11.8 ± 8.6 years (\pm SD).

of sorbitol formation: since sorbitol is produced faster than it is oxidized by sorbitol dehydrogenase, sorbitol accumulates (Figure 3).⁴¹

The disposal of surplus glucose *via* the sorbitol pathway entails increased consumption of the pyridine nucleotide cofactors, NADPH and NAD⁺, and their resulting deficit may amplify the metabolic perturbations arising from excessive sorbitol pathway activity.⁵¹ Variations in sorbitol pathway activity and their metabolic and functional ramifications may contribute to the wide range of susceptibility to complications of long-standing diabetes.^{52-56,2}

ALDOSE REDUCTASE INHIBITION

The presence of AR in tissues susceptible to diabetic complications has led to the hypothesis that the flow of excess glucose through the sorbitol pathway initiates a continuum of metabolic, functional, and early structural abnormalities that can progress to advanced lesions which we recognize as clinical disease. That increased AR activity acts as trigger of this cascade of pathophysiological changes rests on the experimental evidence that, in animal models of diabetic hyperglycemia, such abnormalities can be completely prevented by inhibiting AR⁴²⁻⁴⁶ – without reducing the highly elevated glucose concentrations. The results obtained with alrestatin (I, Figure 4), the first orally effective AR inhibitor,^{57,58} inspired the formulation of a pharmacological rationale for the development of AR inhibitors as drugs to prevent, arrest, or delay the development of diabetic complications initiated by the metabolism of surplus tissular glucose by AR.⁵⁹

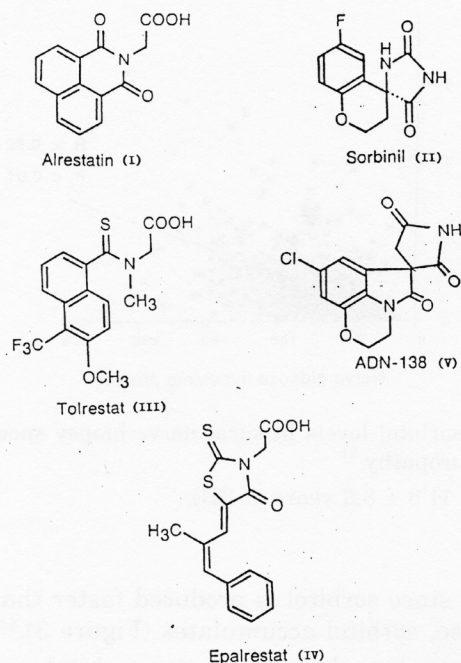


Figure 4. Chemical structures of some aldose reductase inhibitors.

- I:** 1,3-Dioxo-1*H*-benz[de]isoquinoline-2(3*H*)acetic acid (AY-22,284)
II: (*S*)-6-Fluoro-2,3-dihydrospiro[4*H*-1-benzopyran-4,4'-imidazolidine]-2'5'-dione (CP-45,634)
III: *N*-[[6-Methoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-*N*-methylglycine (AY-27,773)
IV: (*Z*)-3-carboxymethyl-[(2*E*)-2-methyl-3-phenylpropenylidene]-rhodanine (ONO-2235)
V: 8'-Chloro-2',3'-dihydrospiro[pyrrolidine-3,6'(5'*H*)-pyrrolo[1,2,3-de][1,4]benzoxazine]-2,5,5'-trione (ADN-138)

The AR-inhibitor concept has attracted many investigators, and over the past 25 years, scores of different substances have been found to inhibit AR.^{43,45} The search of AR inhibitors revealed the criticalness of their chemical structure:⁴⁵ by establishing the physico-chemical properties of a compound, the chemical structure is determining three characteristics that are critical for the usage of AR inhibitors in the pharmacotherapy of diabetic complications, *i.e.* the ability to inhibit AR; the potential for other pharmacological activity; and, the compound's pharmacokinetics. In conjunction with the intrinsic AR-inhibitory activity, the pharmacokinetics predestines the pharmacotherapeutic efficacy of an AR inhibitor, while combined with non-specific pharmacological activity, it may give rise to side-effects.

PAST CLINICAL TRIALS OF AR INHIBITORS

Only a handful of AR inhibitors has been tested in diabetic subjects, mainly for efficacy in symptomatic diabetic neuropathy,^{44,45,46,47,48} a common,⁶¹ complex ramification of chronic *diabetes mellitus*.^{62,63} Retrospectively, it is not surprising that, in patients with overt diabetic peripheral neuropathy, trials aimed primarily at clinical improvement have failed to produce unequivocal evidence of benefit from AR inhibitor treatment. Above all, the deficient understanding of the natural history of diabetic neuropathy has made it difficult to design proper clinical trials^{64-66,45,47,48,67} in the early eighties.^{68-70,62,63} For example, the very slow and variable progression of neuropathy and its dependence on glycemic control; the extent of tissular damage at the time of intervention and, the duration of treatment have not been considered;⁶⁷ the expectations on the type and magnitude of desired clinical benefit were ill-defined,⁶⁵ and there was no consensus on the best way to measure the benefit; and, the inherent deficiencies of the available methods, such as high variability,^{65,70-72,66,67} have not been taken into consideration to estimate the number of subjects needed to detect a statistically significant treatment effect.⁶⁵ The outcome of many trials of AR inhibitors was thus predestined by the selection of patients with too advanced neuropathy; by the small numbers of patients and, by the short study-duration.⁶⁷ Indeed, results from 6 to 12 month trials of systemically bioavailable AR inhibitors,^{60,45} such as sorbinil (**II**, Figure 4)^{43,73} and tolrestat (**III**, Figure 4),⁷⁴⁻⁸² indicated benefits, notably in patients with mild neuropathy^{77,80} and poor glycemic control.⁸³ Supporting evidence was provided by the finding that withdrawal of tolrestat after 4 years of treatment (and replacement with a placebo) revealed a clear worsening of conduction velocity, sensation and, possibly, pain, which were not seen in the patients who remained on the AR inhibitor.⁸⁴ Like long-term intensive insulin therapy,^{6,28,67} AR inhibitor treatment can be reasonably expected to delay rather than reverse the development of diabetic complications.

An important insight gained from AR inhibitor-trials in diabetic neuropathy was that the inherent limitations in sensitivity, reliability, and reproducibility restrict the role of clinical findings as primary measures of response to any treatment:⁷⁰ symptoms, *e.g.* neuropathic pain, paresthesia, and dysesthesia, do not appear to correspond to the degree of nerve fiber damage but may correlate with the extent of compensatory regeneration.⁸⁵ As a corollary, a new definition of diabetic neuropathy has emerged,⁷⁰ based on the concept that it represents a slow, progressive loss of nerve fibers with distinct, characteristic histomorphometric features.⁶³ Another contribution derived from AR inhibitor-trials was the use of morphometry⁸⁶⁻⁹⁰ to establish the bioavailability of an AR inhibitor at the site(s) of AR in the peripheral nerve, and to evaluate its pharmacological effects on diabetic neuropathy.

AR inhibitors have also been tested for their effect on retinopathy^{91–93} and incipient nephropathy.^{94–99,82} Three years of treatment with sorbinil produced no clinically important effect on the course of retinopathy, except a slight reduction in the rate of microaneurysm increase.⁹¹ Since in the primary prevention cohort of the DCCT, a decrease in the cumulative incidence of retinopathy became apparent only after approximately 4 years of intensive insulin treatment,²⁷ the duration of the Sorbinil Retinopathy Trial⁹¹ was thus too short to detect any significant differences between the progression of retinopathy in sorbinil-treated and non-treated subjects.¹⁰⁰ In patients with incipient diabetic nephropathy, treatment with AR inhibitors arrested^{93,82} or decreased^{95,97,98} the rate of urinary albumin excretion. A consistent affect on the glomerular filtration rate was observed only upon prolonged treatment.^{97,98}

At present, both tolrestat and epalrestat (**IV**, Figure 4) are approved for the treatment of diabetic sensorimotor neuropathy; however, once administered, an AR inhibitor will inhibit the AR-catalyzed disposal of surplus glucose arising in any diabetic tissue, such as retina and kidney, in which the inhibitor attains therapeutic concentrations.

FUTURE PERSPECTIVE OF AR INHIBITORS IN DIABETIC COMPLICATIONS

Initiation of AR Inhibitor Therapy

Ideally, treatment by intensive insulin therapy or AR inhibition should be initiated before a diabetic complication has reached a stage of »no return«. Based on DCCT data, this refers to IDDM patients with very mild to moderate non-proliferative retinopathy;²⁷ with microalbuminuria;²⁹ or, with mild-to-moderate diabetic neuropathy.^{28,67} A plethora of epidemiological data links the presence of detectable complications with the magnitude of hyperglycemia; poor glycemic control thus identifies the primary candidates both for intensive insulin treatment^{4–6,21,24,25,101,102,10,103,9,2,104} and/or for supplemental AR inhibitor therapy.^{58,43,75,76,47} The question is thus »what is poor glycemic control«, *i.e.* when to switch from conventional to intensive insulin administration, or – to AR inhibitor treatment.

Above all, epidemiological evidence suggests that end-organ response to exposure to diabetes – defined as the duration of hyperglycemia multiplied by its magnitude – differs in different vascular beds.^{105,102} Therefore, different degrees of hyperglycemia may be required to damage different vascular beds, or, certain degrees of hyperglycemia may be associated with other risk factors for vascular disease.¹⁰⁵ According to Reichard,¹⁰² »every patient must have an HbA_{1c} below 9% to prevent nephropathy, and most of them should

strive for HbA_{1c} below 7% – if this is possible without an unacceptable risk of hypoglycemia«. According to the DCCT results, »it is possible that, over a lifetime of IDDM, the risks of proliferative retinopathy, blindness, renal insufficiency, neuropathic amputations, and other macrovascular complications are all increased substantially with any increment in glycemia above the normal range, even at a lifetime mean HbA_{1c} of 7 or 8%«. ¹⁰⁴ Many patients feel, however, that »achieving good blood glucose levels is too high a price to pay to lose a good quality of life which is more important than a long life«, and »many patients still give priority to the good life over optimal blood glucose control where intensified treatment is introduced«. ¹⁰¹ Thus, »in the real world, great effort will be required to reproduce the results of the DCCT«. ¹⁰⁶ Combined, the data suggest that, in IDDM, the »poor-control entrance criterion« for AR inhibitor treatment should be similar to that recommended for switching from conventional to intensive insulin administration, *i.e.* a mean HbA_{1c} of 9%. For peripheral neuropathy, in post-pubertal IDDM patients, this may occur 5 to 8 years after diagnosis, ^{3,101} but soon after diagnosis in NIDDM patients. ¹⁰⁸

Duration of AR Inhibitor Treatment

The DCCT has ascertained that, after reducing hyperglycemia to near-normal levels, it takes several years to demonstrate a therapeutic effect. ¹⁰⁴ Clearly, AR inhibitor-treatment cannot be expected to surpass the effects of near-normoglycemia (*e.g.* Refs. 27–29) on the progression of diabetic complications. ⁴⁷ Therefore, like intensive insulin therapy, ¹⁰⁶ AR inhibitor-treatment should be continuous, probably over the life-time of an inadequately-controlled patient.

Extent of Aldose Reductase Inhibition (Dosage of AR Inhibitor)

Before the current, DCCT-derived understanding of the natural history of the triad of diabetic complications, and, particularly, of their slow progression during conventional insulin treatment and their slow regression despite tight glycemic control, ^{27–29,47} it was tempting to attribute the inconclusive results obtained in some early clinical trials of AR inhibitors to their »low potency«. ⁴⁸ Some animal studies had suggested, in fact, that complete inhibition of AR activity is needed for correction of peripheral nerve ^{109,110} and vascular defects; ¹¹¹ generally, however, functional improvement following AR inhibitor treatment was associated with incomplete sorbitol pathway inhibition, ⁴⁸ such as a 64% decrease in kidney sorbitol levels resulting in complete prevention of albuminuria in diabetic rats. ¹¹² Of clinical importance are the findings that, in patients with overt diabetic peripheral neuropathy and treated with either sorbinil ⁸⁸ or tolrestat, ⁹⁰ the morphometrically established improvement in nerve fiber pathology was associated with a 42% ⁸⁸ and 62% ⁹⁰ decrease in sural nerve sorbitol levels.

The view that complete inhibition of the flow of excess tissular glucose through the sorbitol pathway may not be required for clinical efficacy¹¹³ is supported by the results from the trials of intensive insulin treatment, *i.e.* that effective delay in the onset and slowing of the progression of diabetic retinopathy, nephropathy, and neuropathy in IDDM patients was achieved by reducing hyperglycemia to near-normal glucose levels. The findings suggest the existence of a certain »tolerance« for the consequences of »near-normal« glycemia which may vary between susceptible tissues within a diabetic patient, as well as between diabetic patients. Ideally, therefore, AR inhibitor-pharmacotherapy should supplement the endeavors to control blood glucose levels, *i.e.* it should decrease the metabolism of the remaining surplus glucose *via* the sorbitol pathway to within the limits of individual tissular »tolerance«.¹¹³

RISK/BENEFIT ASSESSMENT OF TREATMENTS

At present, only two practicable non-invasive methods are available to control the rate of development of diabetic complications: either to decrease the magnitude of hyperglycemia by intensive insulin treatment in IDDM³⁷ or by pharmacotherapy in NIDDM,³⁹ or, to decrease the metabolism of surplus tissular glucose *via* the sorbitol pathway by inhibiting the activity of AR. A risk/benefit assessment of each treatment can be summarized as follows.

Strict Glycemic Control

The results obtained in the DCCT (in patients with IDDM) have revealed that intensive insulin treatment is not without adverse effects and potential damage.¹¹⁴ The primary danger, and, indeed, a major limiting factor, is the increased, and, in some cases unacceptable, rate of severe hypoglycemia which was 3 times higher during intensive than during conventional treatment. The SDIS showed similar results.²⁵ In particular, intensive insulin treatment accentuated the risk of multiple episodes of hypoglycemia that required assistance with treatment and that caused coma, or seizure.¹¹⁴ While our understanding of iatrogenic hypoglycemia during insulin therapy is rapidly changing,¹¹⁵ both further insight into the basic mechanisms of its pathophysiology and pragmatic approaches to its prevention in IDDM are urgently needed.^{116,117} Of note, severe hypoglycemia is common and associated with significant morbidity even in a conventionally treated, insulin-requiring population.¹¹⁸ Therefore, »the risk to benefit ratio of prescribed levels of glycemic control for individual patients should be continually reappraised, particularly in those with long duration of diabetes who have vascular complications in whom the avoidance of severe hypoglycemia should become the paramount consideration«.^{118,106} Furthermore, the risk-to-benefit ratio de-

rived from the DCCT results may not be as favorable if intensive glycemic control is attempted by poorly supervised patients, or by inexperienced physicians.¹¹⁹ Another problem evidenced by the DCCT was the weight gain: at 5 years, patients receiving intensive insulin treatment had gained an average of 4.6 kg more than patients receiving conventional treatment.¹²⁰ Weight gain was also reported in the SDIS.¹²¹

Benefits and risks of intensive insulin treatment necessary to achieve normoglycemia in patients with NIDDM are not known at present.^{35,36}

AR Inhibitor Treatment

Risk of pharmacotherapy based on inhibition of enhanced AR activity in poorly controlled diabetic patients can arise, theoretically, from two sources. First, from inhibition of AR, *i.e.* based on the possibility that the sorbitol pathway provides a vital homeostatic mechanism, and, second, from unspecific pharmacological effects caused by the AR inhibitor's chemical structure. To date, despite ingenious speculations (*e.g.* Refs. 42, 45, 122–131), an essential physiological role for AR (or, the sorbitol pathway) has not been found.^{45,48,132} Supporting evidence that AR does not have a vital role in non-diabetic tissues was provided by the absence of any common, unusual toxic effects across all the animal species treated chronically with various, structurally distinct AR inhibitors.¹³³ AR thus appears to assume a role only in poorly controlled *diabetes mellitus*, *i.e.* when the surplus of tissular glucose can flow into the sorbitol pathway. The conclusion is upheld by a large body of experimental (*e.g.* Refs. 43, 45, 46, 48) and clinical data (*e.g.* Refs. 134, 43, 45–48) which demonstrate that blocking, or reducing the entry of excess tissular glucose into the sorbitol pathway prevents the development, or delays the progression of diabetic complications.

Like any drug, potentially, AR inhibitors could cause side-effects arising from pharmacological responses to some geometric features of their chemical structure, *i.e.* to a pharmacophoric pattern¹³⁵ other than that required for AR inhibition. This is exemplified by the phenytoin-like hypersensitivity reactions induced in some subjects by AR inhibitors characterized by a phenytoin-like spirohydantoin or spirosuccinimide structure, such as sorbinil^{136,137} and compound ADN-138 (V, Figure 4).¹³⁸ The only significant side-effect reported to occur in some patients treated with tolrestat is an occasional elevation of hepatic transaminases occurring in up to 5% of the treated diabetic patients.^{139,140,75,76,141} The elevations seemed to occur soon after the initiation of tolrestat treatment and reversed after treatment was discontinued. Of note, various liver-enzyme abnormalities are known to occur in diabetic patients, and, for the majority, the elevations seem to have little or no clinical significance.¹⁴²

CONCLUSION

In diabetic patients susceptible to the development of complications arising from inadequate glycemic control, similar benefits can be expected from intensive insulin treatment or pharmacotherapy with AR inhibitors.⁴⁷ Provided, first, that treatment is initiated before the development of a complication has advanced beyond a »point of a return«, *i.e.* a stage at which further progression of a complication becomes independent of hyperglycemia, such as in proliferative retinopathy, overt proteinuria, or end-stage neuropathy. Second, that treatment is protracted with modifications of therapy as required because of old age or other changes in clinical circumstances.¹⁰⁶ Albeit different, risks are known to occur with each treatment. Intensive insulin treatment endeavored to obtain tight glycemic control in IDDM can be accompanied by increased frequency of potentially harmful hypoglycemia and by weight gain. On the other hand, based on data obtained with the AR inhibitor, tolrestat, occasional hepatic enzyme elevations can occur, apparently with wide variations within different geographic regions.

Both protracted treatments, *i.e.* tight glycemic control and pharmacotherapy with AR inhibitors, are aimed at providing the diabetic patient with a longer period of healthy life and/or a shorter duration and reduced morbidity and disability arising from diabetic neuropathy, retinopathy, and, possibly, nephropathy. Since »it is sobering to realize how little of what is recommended for the treatment of individuals with diabetes is actually made available in the general population«,¹⁴³ »diabetic patients need pharmacological help over and above insulin and blood glucose monitoring«. ¹⁴⁴ Theoretically, therefore, at present, the optimal practicable approach to the control of diabetic complications would be a patient-acceptable glycemic control regimen supplemented with AR inhibitor treatment aimed at preventing the metabolism of the remaining surplus of tissular glucose by AR.

The future perspective of AR inhibitors can now be prognosticated with much greater confidence than some 15 years ago when most of their clinical trials have been initiated. This is due mainly to our improved general understanding of the natural history of neuropathy, retinopathy, and nephropathy, and, in particular, of the critical role of the total tissular exposure to hyperglycemia.

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SAŽETAK**Perspektiva inhibitora aldozne reduktaze i dijabetičkih komplikacija***Dušan Dvornik*

Nedvojbena nalazi novijih studija intenzivne terapije insulinom dokazali su da poboljšana kontrola glikemije odgađa začetak i usporava razvoj dijabetičke retinopatije, nefropatije i neuropatije. Rezultati su pokazali, međutim, da ni intenzivna terapija insulinom ne normalizira količinu šećera u krvi tako da dijabetičari ostaju izloženi bremenu komplikacija. To podvlači potrebu za farmakoterapijom koja je usmjerena sprečavanju posljedica suviška šećera koji preostaje zbog nepotpune kontrole glikemije. Postojeća odgovarajuća farmakoterapija osniva se na primjeni inhibitora aldozne reduktaze (AR). Konceptija inhibicije AR temelji se na spoznajama (stečenima preventivnom upotrebom inhibitora AR): prvo, da suvišak šećera u tkivu dijabetičara biva metaboliziran katalizom AR; drugo, da taj proces izaziva kaskadu patofizioloških promjena koje postupno dovode do oštećenja koja karakteriziraju trijadu dijabetičkih komplikacija. Teorijski, terapija inhibicijom AR ne može biti djelotvornija od normalizirane glikemije; pri procjeni odnosa između koristi i rizika takve terapije i pri izboru roka njezina trajanja treba zato uzeti u obzir odgovarajuću procjenu i izbor pri intenzivnoj terapiji insulinom. Upotreba inhibitora AR stoga je opravdana u pacijenata koji su ugroženi dijabetičkim komplikacijama (osobito ranom perifernom neuropatijom) i u kojih se ne može postići primjerena kontrola šećera u krvi.