

Mistakes, misunderstandings and controversies in diabetes: A review and personal account

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ABSTRACT

A number of controversies in diabetes have had too little attention. I discuss the following issues: (i) drug therapy; (ii) genetics; (iii) antihypertensive treatment in patients with normoalbuminuria and with abnormal albuminuria; (iv) insulin analogs; (v) cancer in diabetes; (vi) hypophysectomy; (vii) renal biopsy; (viii) low protein diet; and (ix) glycated hemoglobin. A closer look at these items is required in order to have a more realistic picture of diabetes research. A scheme of other controversies is also provided. (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2010.00012.x, 2010)

KEY WORDS: Drug and dietary therapy, Glycated hemoglobin, Glycemic control

INTRODUCTION

Important scientific discoveries in medicine, often with a subsequent great impact on patient care, can rarely be planned but they arise unexpectedly and often create paradigm shifts. According to the world famous chemist, Max Perutz, discoveries pop up in unexpected corners, like the Shakespearian Puck. This is my experience in diabetes research, both as an observer and as an active worker in the field for over 40 years, starting as a medical student under the guidance of Professor Knud Lundbæk. Diabetes research covers a vast area, from understanding the basic pathogenesis of diabetes, both type 1 and type 2, to explaining early and late renal and vascular complications. Not to mention acute issues, such as ketotic and non-ketotic coma as well as hypoglycemic attacks.

Earlier, I have discussed the positive side of the coin¹, but what about all the mistakes and misunderstandings; the topic of this paper? They might in fact be more common than the successes. The first controversy I encountered had been created by Marvin Siperstein from Dallas, Texas, USA².

THE SIPERSTEIN CONTROVERSY

Siperstein observed that in patients with type 2 diabetes, the muscle basement thickness could be increased in newly diagnosed patients. His mistake was that newly diagnosed type 2 diabetes is not the same as newly established diabetes, because the disease might have been present for years before diagnosis, as a result of the often silent nature of the disease. In addition, there could be technical problems in his measurements. The muscle basement membrane is not very well defined in contrast to that of the kidney. His misunderstanding was the conclusion he made indicating that this observation would support the genetic idea related to complications. Patients are predestined to

vascular disease by their genes, but not, for example, by poor glycemic control. His concept would obviously have had alarming consequences to patient care. Patients would no longer be controlled very well.

Siperstein's concept was negated by Ruth Østerby³. She documented that basement membrane thickness is normal in the glomeruli of patients with newly diagnosed type 1 diabetes where there is no silent period before diagnosis.

Subsequently, the genetic concept has hardly been supported by any study, but it is important to note that blood pressure control and lipid levels are important for the development of vascular sequelae to diabetes.

THE SULPHONYLUREA BATTLE

In the late 1970s, I observed the heated discussions about the possible harmful effects of sulphonylurea (SU), based on the American UGDP observations⁴. In Europe, almost all doctors, including myself, were observers on the sideline. Like the doctors at the Joslin Center, we believed that there might be problems with this study, and indeed there were problems or rather mistakes in the study. Some patients were recruited from cardiology centers and these patients had the greatest mortality. However, it took almost two decades before the results were negated by the UKPDS⁴ and later by the ADVANCE study⁵. All the same, a few years ago some American doctors advocated the use of glitazones and warned against the use of SU.

Once again: mistakes and misunderstandings. The controversy now seems to have ended. Interestingly, the use of metformin was never in question although the beneficial effect was only observed in a substudy of UKPDS and only in obese patients.

BLOOD PRESSURE AND DIABETIC RENAL DISEASE: WRONG IDEAS SOON NEGATED

Many years ago, diabetologists observed that antihypertensive treatment in patients with diabetic renal disease resulted in a

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10–20% increase in S-creatinine. Therefore, it became common knowledge that such a treatment would be unsafe, resulting in reduced renal function. This was not so surprising, but it was indeed a serious misunderstanding. The reason for this rather acute increase is in fact a beneficial phenomenon. The treatment results in decreased pressure over the glomerular membrane, evidently beneficial in the long run. Actually, I observed a positive correlation between blood pressure (BP) and decline of renal function. Antihypertensive treatment over several years actually reduced the fall rate of glomerular filtration rate (GFR) by approximately 50%, so end-stage renal failure (ESRF) was considerably postponed¹. That is to say, that the mistake of not treating these patients was as a result of a lack of understanding of the pathophysiology of the condition.

After the publication of my observations, Parving published similar results¹. Today, there is no longer any controversy about the treatment of diabetic patients with renal disease starting with microalbuminuria. Also, patients with non-diabetic renal disease benefit from this treatment.

TO TREAT OR NOT TO TREAT: ANTIHYPERTENSIVE TREATMENT IN NORMOALBUMINURIC NON-HYPERTENSIVE TYPE 1 DIABETIC PATIENTS

Investigators in Europe have for a long time observed that normoalbuminuric non-hypertensive type 1 diabetic patients have an extremely good prognosis, even after 10–15 years of observation. According to Østerby, they also have a limited degree of lesions on renal biopsies. It was therefore surprising that Michael Mauer in Minneapolis planned a large biopsy study, the so called rennin angiotensin system (RAS) study, intervening with the drugs Enalapril and Losartan versus control⁶. There were about 100 patients in each arm, followed for approximately 2 years. The results were not surprising; no effect of enalapril versus control, whereas the losartan group had more progression to microalbuminuria, so far unexplained.

It can be concluded that intervention with agents that block RAS cannot be recommended in such patients. The explanation of Mauer's opinion is very likely the fact that his earlier studies seemingly documented considerable lesions in normoalbuminuric patients. Østerby, working in Minneapolis for a period, studied similar patients and found very few lesions, but this study was never published. Carrying out so many biopsies on patients with a good prognosis could therefore have been avoided. In contrast, there might be an indication for such a treatment in type 2 diabetes. A reappraisal of hypertension guidelines suggest that a systolic BP of 140 mmHg should be the goal in most type 2 diabetic patients not 130⁷.

HYPOPHYSECTOMY IN TYPE 1 DIABETIC PATIENTS WITH SEVERE RETINOPATHY: THE TREATMENT IS WORSE THAN THE DISEASE

Today, such a devastating attempt at therapy in these patients is difficult to understand. Actually, it was first practiced in Stockholm and later a controlled clinical trial was carried out

in Aarhus. There might have been some beneficial effect on retinopathy, but after hypophysectomy these patients were extremely insulin sensitive and insulin doses had to be reduced considerably. Nevertheless, hypoglycemia was a serious complication and partly responsible of the over-mortality observed. In addition to this, the patients suffered from not having the important hormonal regulation from the pituitary gland. This procedure was soon abandoned and laser-treatment radically improved prognosis in patients with retinopathy.

Hypophysectomy was indeed a mistake in medicine and a misunderstanding of the balance between beneficial and potentially harmful effects.

TO USE INSULIN ANALOGS OR NOT: POTENTIAL OR POSSIBLE RELATION TO CANCER? A CONTROVERSY

Some of the new insulin analogs are also acting as growth factors and it has been postulated that they might aggravate diabetic retinopathy and even increase the risk of cancer. Rosenstock, however, found a similar risk of cancer using insulin glargine versus NPH-insulin in a 5-year randomized open-label study⁸. The project was originally planned to consider a worsening of retinopathy (not found) but the study was also very well suited for considering the risk of malignancy. Cancer often develops slowly and it cannot be excluded that a longer follow-up could provide different results.

Today, we have a choice: either to gain a somewhat better glycemic control by the analog or to risk a long term increase in malignancy. This is an ongoing controversy.

DIGAMI 1 and 2: Why Not the Same Results?

The DIGAMI 1 and 2 studies are examples of trials (relating to the role of glucose control, also with insulin, after myocardial infarction) where positive results were obtained in a preliminary study. Mortality was reduced by approximately 40% in DIGAMI 1. In the multicenter DIGAMI 2, which included more patients, the earlier results could not be confirmed, rather the contrary⁹. The conclusion is that it might be problematic to publish preliminary results with insufficient power. In contrast, it is difficult to point to mistakes but other studies have in fact subsequently documented that treatment in patients with cardiovascular disease should not be too strict and should not be changed too quickly. This is the lesson from the VADT trial and the ACCORD trial¹. In fact the DIGAMI studies left us with more questions than answers.

In my opinion, the same is the case in patients admitted to acute medical units, diabetics or non-diabetics. The concept of implementing acute and strict glycemic control in high-risk patients have certainly not been confirmed.

RENAL BIOPSIES IN TYPE 2 DIABETES WITHOUT RETINOPATHY: ARE THEY RELEVANT?

It has been suggested that a renal biopsy would be needed in proteinuric type 2 diabetic patients without retinopathy. Actually, it was argued that they had 'minimal change disease'. The

point is, however, that it is common to find glomeruli without lesions in such patients. In general, it is very rarely indicated to carry out a biopsy in diabetic patients¹.

HbA_{1c}: A RELIABLE MEASURE IN PATIENT CARE AND IN CLINICAL TRIALS

A major determinant of the long-term fate of patients is the average level of blood glucose. HbA_{1c} is a very practical substitute for this measure, but is probably not as accurate as it is widely believed and laboratory techniques might also vary. However, it would have been difficult to carry out large clinical trials, such as the UKPDS and DCCT trials, with the objective of optimizing glycaemic control. A problem is that patients seem to respond differently as far as the level of HbA_{1c} is concerned, but with the identical level of blood glucose with a difference of up to 1% of HbA_{1c}¹⁰. This phenomenon might also result in adverse effects in intensified glycaemic control trials, with, for example, a goal of 6% or 6.5%. The actual level of HbA_{1c} might in some patients correspond to a much lower level of blood glucose. This might add to adverse effects of intensified glycaemic control trials, such as the ACCORD study and the VADT.

In individual patient care, taking into consideration only HbA_{1c} might lead to hypoglycaemic attacks that patients cannot accept. In conclusion, it is probably a mistake to consider using only HbA_{1c} as an unproblematic measure of average blood glucose.

LOW PROTEIN DIET IN DIABETIC NEPHROPATHY: DOES IT WORK, IS IT FEASIBLE?

The low protein diet was originally termed the 'Giovanetti diet' and was introduced to relieve symptoms related to uremia. Later, with the common use of dialysis, it was hardly used any more, except for a few centers where the belief was that it could reduce the rate of decline in GFR. With the widespread use of agents that block the RAS, the use of the 'Giovanetti diet' became even less relevant. A recent study from Japan documented that most diabetic patients were unable to follow this strict diet and, in addition, the diet could not reduce the rate of decline in GFR¹¹.

Nowadays, this diet is used very little in the Western world and elsewhere where the general diet is usually low in protein content. Again, the concept might not have been a mistake but it was a misunderstanding to believe that patients were able to adhere to a diet with a doubtful effect.

Some of the issues discussed here, such as the Siperstein controversy, are based on imprecise techniques. The important SU battle had its origin in poor and imprecise recruitment. In retrospect, the idea that antihypertensive treatment could be dangerous to the kidneys was based on incorrect interpretations of a simple laboratory measurement. The strong belief in one's own preliminary measurement was the background for the failure of the RAS study. The idea that insulin analogs are harmful was based on an incomplete evaluation put forward in some papers that were heavily criticized at the European Association for the Study of Diabetes (EASD) congress in Vienna 2009. Regarding

Table 1 | Some other incorrect or problematic ideas within diabetology¹²

Pancreas or islet cell transplantation is a realistic possibility
Human leukocyte antigen genotyping is relevant in clinical practice
Routine measurement of C-peptide in classification of diabetes
Growth hormone treatment relevant in type 2 diabetes (to improve muscle volume and strength)
Careful investigations in all patients for renal arterial stenosis (RAS) important before inhibiting the RAS system
Insulin pump treatment should be used in most patients with type 1 diabetes
Inhaled insulin a relevant alternative to subcutaneous treatment
Prophylactic nicotinamide or insulin to individuals at risk for type 1 diabetes
Cyclosporin treatment relevant in newly diagnosed type 1 diabetes
Low dose angiotensin-converting enzyme inhibition relevant in diabetic renal disease

hypophysectomy, it is evident that the treatment was worse than the disease and that the idea was hopeless. Premature ideas were behind the belief that renal biopsies were necessary in some type 2 diabetic patients and the same is the case regarding a postulated beneficial effect of a low protein diet on GFR-preservation. HbA_{1c} does not seem completely reliable as a measure of average blood glucose, although a very important parameter.

Could these mistakes and misunderstandings have been avoided? Yes, some of them could probably have been avoided by a more serious evaluation of the techniques, study design and ideas behind the studies. Other problematic issues are listed in Table 1¹². Problems could also be avoided if glycaemic control is not too strict in type 2 diabetes. The lowest mortality is found in patients with HbA_{1c} around 7.5%¹³.

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