

The mystery of good metabolic control in type I diabetes – non-evidence based lessons from a pediatric clinic

Abstract

Too few patients with ‘Type 1 diabetes have enough good metabolic control to prevent complications. Residual insulin secretion is important, but also other physiological differences between patients contribute to the degree of blood glucose balance. Still, the treatment plays an important role and the way how the diabetes team work with the patient is absolutely crucial. It is proven that HbA1c can be influenced by intensity of treatment, and also that patients at certain clinics have lower HbA1c than at other clinics. Psychological approach and treatment policy explains some of this difference. Although it is difficult to study such factors in randomized, controlled double-blind studies, we have performed studies giving evidence of the importance of attitudes, goals, how the diabetes team works and what message it conveys. Thus some parts of treatment which could be called “art of medicine”, based on skill, experience, empathy and similar “soft” values should not be neglected.

Keywords: type 1 diabetes, hba1c, metabolic control, insulin secretion, treatment policy, team-work, education, psycho-social support, art of medicine, residual insulin, hypoglycaemia, keto-acidosis, insulin secretion

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Introduction

Type 1 diabetes is a very serious disease which in spite of a very intensive and heavy treatment causes serious acute and late complications and even increased mortality. However, there is hope as good metabolic control can prevent such complications,^{1,2} and we have been able to get lower HbA1c for decades than many comparable clinics, even in Sweden, without increasing the risk of severe hypoglycaemia.³

The problem is that most Type 1 diabetes patients in the world do not have enough good blood glucose control. Without any residual insulin secretion it is in fact very difficult to get a near physiological blood glucose, and most of the classical Type 1 diabetes patients lose their residual insulin secretion within a few years from diagnosis.⁴ Even when beta cell function declines a small residual insulin secretion will be important. It contributes to lower HbA1c and less blood glucose fluctuations, and only slight residual insulin secretion is enough to diminish the risk of keto-acidosis.⁵ A quite modest residual insulin secretion, shown as a response to a beta cell stimulation with serum C-peptide >0.20pmol/ml, decreases the risk of both serious hypoglycaemia and late complications.⁶

In addition c-peptide per se may have a physiological function.⁷ Thus it has been reported that C-peptide influences vascular permeability, decreases leakage in retinal vessels, and has a positive effect on nerve function. Thus, one important step to reach the aim good metabolic control would be to preserve residual insulin secretion. Treatment with monoclonal CD3-antibodies has shown encouraging results⁸⁻¹¹ and with suitable dose in the right patient population the benefit might well justify adverse events and risks. Treatment with auto-antigen is another concept of creating tolerance and stop the autoimmune process.¹² In a Phase II trial GAD-alum-treatment was

promising with significant preservation of residual insulin secretion accomplished by a very easy, well tolerated treatment, so far without any adverse events,¹³ and the efficacy remind still after 4years.¹⁴ However, another Phase II trial with a slightly different design and other patient population failed to show effect,¹⁵ and a European Phase III trial did not reach the primary endpoint, even though there were positive results in several pre specified subgroups.¹⁶

Combination therapies may become a solution for several patients with recent-onset diagnosis of Type 1 diabetes¹⁷ but for those who have completely lost their beta cells and have nothing to preserve there is only to hope for islet cell transplantations¹⁸⁻²⁰ or perhaps artificial pancreas²¹ if these patients should get near physiological blood glucose balance without very heavy intense traditional treatment. In spite of progress in the field we have to count with more traditional treatment for the majority of T1D patients the coming years.

Physiological factors in addition to beta cell function

Patients, and lay people, often talk about more or less “severe” diabetes, as if diabetes not always were the same serious disease! They are certainly right! Even though the degree of own insulin secretion is most important, there are other physiological factors influencing the blood glucose balance, factors which are difficult for the patient to do anything about. Puberty is such an example of a factor which is difficult for the patient to manage, very clearly influencing both insulin resistances by fluctuating hormones and insulin demand by the rapid growth in addition to the decreased insulin sensitivity. Furthermore, as well as genetic traits contribute to Type 2 diabetes, with its increased insulin resistance, these genetic traits can of course also add to the burden of Type 1 diabetes. Thus, it has been suggested that some patients seem to have both Type 1 and Type 2 diabetes, so called “double diabetes” or 1.5 diabetes.^{22,23} As a third example it is

worth mentioning the variation in glycation at similar blood glucose concentrations. Degree of blood glucose control is usually estimated by measuring HbA1c, which certainly seems well correlated to glycation of other tissues and development of vascular complications. However, the correlation between blood glucose measured by glucose sensors and HbA1c is not perfect, with a rather wide inter-individual variation.²⁴ This suggests that there may very well be patients with reasonably good blood glucose balance, but too high HbA1c, while there are others with surprisingly good HbA1c in spite of common and pronounced hyper-glycaemia. There is really no justice!

Does the diabetes team play any role for the degree of metabolic control?

It seems self-evident that the treatment recommendations play an important role for the degree of metabolic control of the patients. Patients may get prescriptions of insulin doses which are inadequate, and dietary recommendations which make it more instead of less difficult to get good blood glucose balance. Still there was for many years an ongoing, sometimes rather emotional, discussion among dialectologists who meant that we are all as good as everybody else. All types of treatment were said to be as good as any other type, one daily dose of insulin was as good as two or more doses, no diet was as good as any other diet etc. The DCCT study did effectively show that intensity of treatment does play a role¹ and later the Hvidore study showed that different clinics do have very different results (mean HbA1c in their patients).²⁵ However, it has been very difficult to point out any clear reason for this difference in degree of metabolic control²⁶ and the difference has persisted in spite of making the different clinics aware of that some clinics seem to be more successful than others.²⁷ One part of the explanation might have been different or selection of patient populations, but on the other hand it has been found that also in Sweden the pediatric diabetes clinics have very different mean HbA1c among their patients,²⁸ in spite of very similar patient populations at the different pediatric clinics, and without any possible selection bias as all patients within a catchment area of a clinic by necessity is taken care of by that clinic. One might suspect differences in use of e.g. insulin pumps, but clinics with high proportion of pumps among their patients have not lower HbA1c among their patients, but if anything in Sweden rather the opposite tendency. This is in accordance with difficulties to show that use of pumps have any heavy impact on degree of metabolic control²⁹ although pumps may be very useful in some patients and certainly may have other advantages in suitable patients. Neither are there any strong evidence that use of insulin analogues have improved degree of metabolic control in general, but of course in single individuals.³⁰ Better means of monitoring blood glucose with use of continuous glucose monitoring may certainly be of great help, and this technique will probably make a change for the patients and families, but because of costs one cannot expect such techniques to be used by a majority of patients in many countries still for some years. And not even continuous use of glucose sensors (CGM) has been proven to mean any difference in HbA1c for teenagers with diabetes, and very limited benefit for children.³¹ So what is the mysterious explanation to why some patients at some clinics do better than others?

Education and motivation crucial

Knowledge how to treat diabetes is crucial, if that knowledge is adequate and relevant! But knowledge is only of practical value if the individual is willing and able to use that knowledge! There are probably very few adults who do not know that smoking damages health, but many people still smoke, because they are not motivated

enough to stop smoking, or they are not able to stop smoking even if they would wish. Similar mechanisms are true regarding treatment of diabetes. But what is the evidence?

Evidence-based medicine should be the basis for treatment of diseases. But we have to admit that certain factors cannot be studied in the perfect randomized, controlled, prospective, double-blind fashion! There are some studies that support the lessons from own clinical experience presented below^{32,33} but much is just based on more than four decades of practical work with diabetic children and adolescents and their parents. In addition we have analysed what factors may explain the differences in HbA1c between different clinics in Sweden³⁴ and the results were rather clear: The explanation was not insulin dose, pumps or types of blood glucose monitoring, but much more attitudes among the diabetes teams, what goals they agreed upon, message they conveyed to the patients and parents, and how they worked together. These results together with clinical experience are presented below, which may give knowledge of value at least for a certain time, a certain culture, even though it may not fit all parts of the world or certain cultures, a fact which is true also for many other forms of the art of medicine.

Lesson 1: We rarely treat robinson cruseoe

For a pediatrician it is self-evident that a patient is not alone, an isolated individual living without a social context. It is important that information, education, motivation, support has to be given not only to the child but to the whole family, to other important people in the surrounding like teachers, sports leaders, grandparents, fellows and their parents. It would be impossible to expect a child or a teenager to live in a very special manner without support and understanding from the people around. What about adults?

Lesson 2: We communicate not only with words

Very young children understand rather few words and use even less. Still in preschool age a child may use and correctly understand less than a tenth of all words a verbal physician may have in her/his vocabulary. But still children understand when somebody is happy, sorry, hopeful, angry, afraid, enthusiastic...when something is important or not important, when something is a lie or truth. Already young children have learnt how to interpret the body language: eyes, body position, gestures, mimic, colour of the skin, sweating, odour, breath, and they know what tone of the voice means when it is hard, soft, friendly, aggressive, threatening, bored. Thus we may say with words what we theoretically want or expect, even though we may not even believe in the message ourselves, but the child will interpret the true message, and perhaps follow that message. Teenagers still have this competence, and they also understand and listen to the non-verbal message. This is probably true also for adults?

Lesson 3: A team is good when it functions as a team

A diabetes team may perhaps, if it is a good team, agree theoretically on certain rules and policies, but if those are not integrated deeply into the belief of the team members, they will send completely different messages. Thus the doctor may have some ideas about the importance of blood glucose monitoring, while the nurse may not have the same experience and opinion. Yes, they are good, but. And the dietitian may try to educate the patient about certain dietary rules, but the doctor has experienced different dietitians have different ideas. Nothing seems to be true, or evidence-based, so it is probably not so important. That message is sent via the eyes or just a change of the face...The nurse may underline the importance of injection sites, but the doctor

never cares etc. A team which sends different messages is probably sometimes deleterious! In addition the parents will send other messages, and other adults, and the teacher and the fellows. And not least others who have diabetes for 20 years who once learnt something else, or never did as the doctor recommended but still have survived. To keep the team aware of its policy it is necessary to meet regularly, discuss the patients, go through the results (e.g. HbA1c, incidence of hypoglycaemia) of the patients at the clinic, agree upon guidelines and views on all parts of the treatment.

Lesson 4: A teenager has a child inside

A teenager wants to be independent, sometimes even hate authorities, which may lead to a behaviour that is just the opposite of what authorities prescribe, if they prescribe. The stronger the bounds to the parents, the more dramatic the separation, the stronger force is needed for liberation. But simultaneously the teenager may need the love and care from the parents, may need to be helpless, dependent, needs comfort. There is both a child and an adult in the teenager. Even in adults there is often still a teenager!

Lesson 5: Listen!

Diabetes! The diagnosis is a disaster! Never cured, never the same life again, injections, blood tests, rules regarding food... In addition threatening complications, acute with unconsciousness, convulsions... late with risk of blindness, impotence, early death... For us, working with diabetes, the diagnosis is nothing remarkable. But for this single patient this is the first time, it is a dramatic change of her/his own life, a change of her/his own body, a threat to her/his own life! A shocking experience. Difficult to think clearly, difficult to understand what is told. There are so many questions circling around in the head, but no time to find them, to formulate them, to get answers. Because the doctor, or the nurse, or the dietician... they have all so much to tell, to inform about, that they have never time to be quiet, completely quiet for 10 seconds! To get a chance to listen to what the patient wants to ask, her/his fear, sorrow, questions, anxiety. Listen! Empathy! We have to listen to the patients, and to have empathy.

Lesson 6: The message at diagnosis is crucial

Many physicians and nurses want to be so kind and they tell: You do not have to be afraid. This is not dangerous. Diabetes can be treated well. You can have a normal life! You can eat as everybody else. You can eat anything! You can eat whenever you want. You just have to adapt your insulin dose. No, you do not have to stay at hospital. If you had had such a serious disease as a pneumonia or a severe gastroenteritis than you might have needed to stay at hospital, but not for diabetes! No, diabetes is nothing special!

Such a message is a lie, a false encouragement as we all want to be so kind. The patients will have to live with this for the rest of their lives, so therefore many mean that we should just encourage, be optimistic. – No wonder that patients do not care, do not take the treatment seriously, do not remember to take their injections, do not see the necessity of testing blood glucose, do not follow any dietary rules... And after some years, when there is no residual insulin secretion any longer and the blood glucose control is poor, then they are told to take the disease more seriously, then they are threatened by complications, told what they have to expect unless they improve their behaviour. Then it is too late!

No, we should be honest from the very beginning, at the same time as we are optimistic! You have reasons to be sorry, disappointed,

and angry. Your life will NOT be normal any longer., It is not normal to take injections, to test blood glucose, to follow dietary rules or count carbohydrates, to eat at regular times... it is not normal to get hypoglycaemia... What would we say to somebody who should start driving a car? You can drive as you like? There are no accidents any longer, no risks, nobody will be killed in a traffic accident!? No, we would tell the truth. You do not have to be worried all the time, but you have to learn how to drive, learn the rules, and follow the rules, even if there is no policeman close to you.- Similar with diabetes. You have got diabetes! Your life will NOT be normal, but it may be happy, exciting, fantastic and even long if you accept that you now have got diabetes, that you HAVE to follow certain rules, from the very beginning and for the rest of your life unless research finds a cure. And if that cure is found in 15 years from now, then you should have a healthy body to get use of this cure!

Lesson 7: High HbA1c is not only your fault!

To have diabetes means not only injections (sometimes hated), regular meals with certain content (very helpful, as it is too difficult for many patients to adapt their insulin doses!), rules, reminders, a lot of “You should not” and a lot of “Do not forget”. To have diabetes also means that you have to come for inspection and estimation by some “authority” at regular intervals! Somebody tells you that the HbA1c is too high, that you may have taken the wrong insulin doses, that you may have forgotten the doses now and then, that you may have eaten the wrong things in the wrong amounts at the wrong times, and that you have been too inactive, looked too much at TV or computer, that you have to change your habits, and that you do not test your blood glucose enough often, or that you do not draw the right conclusions! You do not seem to understand!? You are just bad, not very successful!

How can the patients stand this? How can they accept to come time after time to be condemned, threatened, not believed upon, and not listened to? How can they stand to show the truth when they are just criticized if they show poor blood glucose values?

No, remember that high HbA1c is primarily not YOUR fault. For the first it is probably the fault of your doctor! You have been recommended wrong insulin doses and regimen, inadequate methods to adapt your insulin doses, wrong message regarding food and eating habits, wrong advice how to treat hypoglycaemia etc. For the second it is the fault of your doctor, again, representing the inadequate treatment we can offer, with insulin that vary in absorption, injected subcutaneous instead of in the portal vein. The third reason for your high HbA1c is probably your body, perhaps with pubertal fluctuations of hormones, genetic traits of poor insulin sensitivity, ongoing inflammation, stress, infections etc. In the fourth place it is time to go through your own contribution. Could you change anything in your behaviour or in any way improve the treatment? Knowing that it is not only your fault that blood glucose fluctuates and HbA1c is too high makes it much easier to look objectively on your blood glucose values, look for patterns, see if there are any changes you could do to improve the balance. Diabetes is not YOU, but diabetes is something that you together with your collaborators have to control as well as possible, your diabetes can be criticized without you being criticized! I like YOU but not your diabetes, and not you're high HbA1c.

Lesson 8: What is your problem?

For the diabetes team a high HbA1c may be the problem, but the patient feels rather well! For her/him the hypoglycaemia is the problem, not being able to control herself, her feelings, her behaviour,

her sweating, her colour of the face. Or she feels too fat, or is ashamed of the lipomas at the injections sites. Or for the teenage boy the problem may be the risk of losing the place in the soccer team, or not being enough safe when he meets a girl. Can we help or support you with YOUR problem? HbA1c can wait for a while, or maybe that is part of the same problem? You will be better in soccer if you have a good energy supply, a better glucose balance! This can motivate to more careful treatment, not do omit any insulin injections. Furthermore, diabetes becomes more interesting. Before we have taught you repeatedly what to do but you have never learnt! Now you learn, because this is YOUR problem, chosen by yourself. What do you need to learn to solve the problem? Problem-based learning is nowadays used in education, and it is both natural and effective in clinical care.³⁵

Lesson 9: Short-term goals

Your problem is identified. To solve that problem it will help to get better blood glucose balance. Should we reduce your HbA1c from 8.5% to 8% in the next two months? You register your insulin doses, write down evident deviations in your way of living, and show me these data when we meet in month from now, and then I give you my best advice. And after two months we can agree whether we are satisfied for the moment, or whether we should aim at reducing your HbA1c further down.

Too often the aim is to have a normal HbA1c, which seems impossible to reach. The reason for this normal HbA1c is said to be avoidance of late complications, in 20years from now! Who cares about that very far future? Anything can happen before that! For a child or a teenager 20years in the future is impossible to grasp, and even for somebody aged 60years it may seem less relevant. Although we should know as much as possible about late complications, it is easier and more satisfying to have short-term goals.

What HbA1c makes us satisfied? What do we do when HbA1c increases? At our clinic the goal is a HbA1c between 45-55mmol/mol as we then know that there will most probably never develop any microvascular complications but for the individual patient there may be other goals related to the actual situation.

Lesson 10: Collaboration

Education, modern devices, threats, prescriptions nothing will have a good effect unless the patient will comply. Compliance sounds negative. Shouldn't you be friend with your diabetes? Some may be, others not. Why should I like injections, like blood tests, like regular meals, like visits to the doctor, like eye bottom photos? There is no choice. I have to accept my diabetes, but I decide myself. The diabetes team can only support, collaborate. If you test your blood glucose for three days in a row, before and after each meal, and in the evening and night, right down your insulin doses, your main meals, any special event and then we look together on the results and try to draw conclusions. This is a contract, an agreement.

The patient knows her/his diabetes best, but the diabetes team has experience for many years from other patients and their diabetes and how they managed. Together we may improve the glucose balance, even though it might not become perfect!

Non-evidence based but experience-based knowledge!

We are taught to be critical. . Certain ideas may fit somebody but not me, fit some patients but not all, fit some culture but not ours. Medicine is full of non-evidence-based knowledge, which is

experience-based and gradually becomes the truth, at least for some time. How many double-blind randomized placebo-controlled studies on coronary vessel operations are there? Perhaps not even on coronary vessel dilatation? In diabetes we have to base much of our treatment on experience. Most types of treatment design takes decades to evaluate when late vascular complications and survival is the end-point. The DCCT study showed that two different treatment regimens lead to different incidence of complications, but we do not know for sure what role HbA1c, blood glucose fluctuations, insulin concentrations, concentrations of other hormones etc played, and we do not know whether the number of insulin injections were more important than the number of visits to the diabetes team.

Sophisticated statistical analyses can give hints. But much said is just non-evidenced based experience. In this case we did studies which lead to a PhD Thesis^{36,37} on quality of care and these results have become the basis for a national project where education of diabetes teams at pediatric clinics in Sweden seems to have contributed to decreasing HbA1c in many clinics.³⁸ We may also learn to understand our patients, by listening to our patients, learning from their experience, and by trying to understand how it may be to live with diabetes. Insulin, love and care³⁹ is not only a slogan but has given both patients and diabetes teams some insight. Evidence, experience, empathy and policy may perhaps explain why our clinic could present a dramatic reduction of nephropathy in an unselected patient population earlier than most others,² and a clear reduction of development of severe retinopathy,⁴⁰ and lower mean HbA1c than many other Swedish paediatric clinics²⁸ but still without more hypoglycaemia than reported from other clinics.⁴¹

Conclusion

It is easier to get good blood glucose balance and lower HbA1c if the residual insulin secretion can be preserved. Until total cure can be offered, we have to work on methods to save beta cells and their function. It is reasonable to believe that as long as nobody has proven that diabetic patients need non-physiological insulin profiles and concentrations, they should try to mimic the normal situation. Sometimes that is best done with insulin pumps, in other patient's best with multiple insulin therapy. Modern devices such as glucose sensors may certainly be of great help, but until an automatic closed loop system takes over no device will help per se unless the patient can accept to use them in a correct and useful way. Scientific studies support that education, psychological support, how diabetes teams work play an important role. Empathy, honest but optimistic information, conscious team-work with a common message, clear treatment policy, education, support, motivation, short-term realistic goals, confidence, collaboration make the basis for long-term good results.

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Conflict of interest

Author declares that there is no conflict of interest.

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