To what extent should we lower HbA$_{1c}$ in diabetic subjects?

S. Hadjadj$^{a,*}$, P.-J. Saulnier$^{b}$, F. Torremocha$^{a}$, L. Labbé$^{a}$, R. Maréchaud$^{a}$

$^{a}$CHU de Poitiers, Department of Endocrinology Diabetology, 2, rue de la Milètrie, BP 577, 86021 Poitiers cedex, France
$^{b}$CHU de Poitiers, Clinical Research Center, 2, rue de la Milètrie, BP 577, 86021 Poitiers cedex, France

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Abstract

Current recommendations regarding glycemic control suggest that HbA$_{1c}$ should be lower than 6.5%. This is supported by data regarding microvascular disease, namely retinopathy rather than nephropathy. The question is not completely solved regarding cardiovascular diseases, where a strategy of very low HbA$_{1c}$ (“the lower the better”) is expected to be effective. Some ongoing studies will help to answer these unsolved questions.

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Résumé

Jusqu’où faut-il baisser l’hémoglobine glyquée des sujets diabétiques ?
Les recommandations concernant le contrôle de la glycémie suggèrent que l’hémoglobine glyquée doit être inférieure à 6,5%. Ces recommandations s’appuient sur les études sur la microangiopathie notamment la rétinopathie plutôt que sur la néphropathie. La question n’est pas entièrement résolue pour les maladies cardiovasculaires, où une stratégie visant un niveau très bas d’HbA$_{1c}$ (« plus c’est bas, meilleur c’est ») pourrait s’avérer efficace. Des études en cours permettront de répondre à ces questions non résolues.

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Type 2 diabetic patients are characterized by a chronic Hyperglycemia that contributes to the development and progression of micro- and macrovascular complications. In a large population-based cohort of French type 2 diabetic patients, there was a proportion of patients with cardiovascular diseases, such as myocardial infarction and peripheral arterial disease, in 10% and 19% respectively [1]. The proportion of diabetic patients with retinopathy or kidney disease was 33% and 30% respectively, with a vast majority of patients yielding complications such as non proliferative retinal disease and microalbuminuria [1]. Many prospective studies suggest a link between glycemic control and chronic complications in diabetes [2,3]. Interestingly the data on type 1 diabetes are of great importance. Type 1 diabetic complications are more directly related to glycemic control than in type 2 diabetes, as hypertension, lipid abnormalities, obesity and insulin resistance could be involved in the development and/or progression of diabetic complications. The data from the WESDR study support the use of conclusion drawn from type 1 diabetic patients in type 2 diabetic subjects [4].

The question is currently asked to which extent we should lower HbA$_{1c}$ in diabetic patients, particularly in type 2 diabetes. Two different strategies can be considered: - one

* Corresponding author.  
E-mail Address: s.hadjadj@chu-poitiers.fr (S. Hadjadj).

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could be summarized as “the lower the better”- the other one could be summarized as “a specific target, a specific threshold”.

Is a “threshold for HbA1c” recommendable? Many recommendations suggest to reach some specific threshold for HbA1c to lower the incidence of chronic complications. Some very recent American publications recommended to consider a threshold for HbA1c as low as feasible, at least targeting a threshold at 7% [5]. French recommendations released by the HAS consider several HbA1c thresholds according to the time to diagnosis of type 2 diabetes and to the use of medications, ranging from 6 to 7% [6]. However, the use of a threshold is particularly relevant if the relationship between a disease and a variable is not linear. The data on the relationship between blood glucose and diabetes, focusing on retinopathy support such a non linear relationship [7,8]. However, the relationship between cardiovascular events and blood glucose seems roughly linear [9]. In this case the use of a specific threshold is debatable as it has less scientific relevance since no “real” threshold exists. Nonetheless it may be very useful for clinicians in a real-life approach as it allows to avoid some glycomic control leeway keeping in mind that a lower value than the targeted threshold is not deleterious if safely obtained.

1. Microvascular complications

The epidemiological data linking background diabetic retinopathy according to glyemic threshold are available for several populations [8]. There is a general agreement showing that the split in deciles according to the distribution of fasting plasma glucose or of post oral glucose challenge plasma glucose or HbA1c leads to rather homogenous results regarding the risk of microaneurysms. They show that HbA1c threshold near 6.0% is associated with the development of diabetic retinopathy[8]. These data were further replicated in a Japanese population also showing a glycomic threshold at approximately 5.7% [7].

These data suggest that the strategy “a specific target, a specific threshold” can be applied here with a threshold for HbA1c to lower the incidence of chronic complications. Some very recent American publications recommended to consider a threshold for HbA1c as low as feasible, at least targeting a threshold at 7% [5]. French recommendations released by the HAS consider several HbA1c thresholds according to the time to diagnosis of type 2 diabetes and to the use of medications, ranging from 6 to 7% [6]. However, the use of a threshold is particularly relevant if the relationship between a disease and a variable is not linear. The data on the relationship between blood glucose and diabetes, focusing on retinopathy support such a non linear relationship [7,8]. However, the relationship between cardiovascular events and blood glucose seems roughly linear [9]. In this case the use of a specific threshold is debatable as it has less scientific relevance since no “real” threshold exists. Nonetheless it may be very useful for clinicians in a real-life approach as it allows to avoid some glycomic control leeway keeping in mind that a lower value than the targeted threshold is not deleterious if safely obtained.

Interestingly, some results suggest a linear relationship between glycemic exposure and micro-vascular disease [12,13].

Considering more advanced renal involvement, the paper by Fiorretto et al showing that a long term (10 years) normal glycemia – obtained by pancreas graft - was associated with a correction of renal histological parameters, is very important. This paper indeed shows that some fibrous lesions in the kidney are reversible at the price of a long-term strict normal glucose value, obtained with pancreas graft [14].

Altogether these data suggest that a threshold of 6.0% might be adequate to prevent the development of diabetic micro-vascular events. Interventional studies showed that an improved HbA1c leads to fewer micro-vascular events, in large-scale studies on type 1 diabetes, such as in the DCCT-EDIC [15], or in British [16], or Japanese [17] type 2 diabetic patients. However, the question is not solved for renal involvement, as conflicting results on microalbuminuria are available. Glyemic control at a threshold lower than 6.0% seems reasonable. Whether it is sufficient to reverse severe kidney lesions is difficult to assess. However, some studies suggest that a very low Hb1Ac should be targeted.

2. Macrovascular disease

Conversely to micro-vascular risk, many epidemiological data from non-diabetic populations suggest that there is a continuous relationship between glycemic control and cardiovascular risk. Coutinho et al have used a meta-regression analysis to assess the risk of macrovascular disease according to fasting or postprandial blood glucose. They found that the risk for coronary artery disease was present at very low glucose concentration, probably beginning at 72 mg/dl, even after exclusion of diabetic people [9]. In the EPIC Norfolk study, using a non diabetic large-scale cohort, HbA1c at non diabetic levels, was associated with a regular increase in the risk for cardiovascular events or cardiovascular mortality [18].

Data are convergent in type 2 diabetic patients showing a beneficial effect of improving HbA1c without clearly identified threshold, in observational studies: in a Danish cohort of type 2 diabetic patients, a change in 1% in HbA1c was associated with a 20% increased risk for all-cause mortality [19]. Accordingly, HbA1c was a strong risk factor for lower limb amputation (which is a composite of neuropathy, reflecting microvascular disease, and atherosclerosis) in a Finnish cohort [20]. Accordingly the use of the whole cohort of the UKPDS as an epidemiological study also supported the concept of a linear effect of HbA1c on cardiovascular risk, beginning below HbA1c 6.5% [21].

The data from interventional studies also support the improvement of HbA1c without any clear threshold. In the UKPDS, comparing two treatment strategies (intensive vs conventional blood glucose control), the 0.9% difference...
during the long-term period was not sufficient to be associated with a decreased risk in cardiovascular events [16]. There was no effect of “intensive glycemic control” compared to “standard care” regarding stroke and a borderline non-significant effect on myocardial infarction was noticed [16].

At variance, in the DCCT EDIC study, there was a significant reduction of approximately 40% in pre-specified macrovascular endpoints in those patients submitted to an intensified glycemic control (reaching a HbA1c level at approximately 7% for 6.5 years) versus those people in the conventional group (remaining at approximately 9% for 6.5 years), even if both groups merged to a HbA1c concentration at 8% during the epidemiological follow-up period (approximately 13 years) [22].

These data suggest that there is probably no specific threshold for macrovascular disease. Altogether these data suggest that for macrovascular endpoints “the lower the better” strategy could be used.

3. Ongoing clinical trials

What is expected from clinical trials targeting blood glucose control? Mainly a strong evidence that improving HbA1c decreases cardiovascular events, which is not supported by any clinical trial. Indeed improving HbA1c did not significantly impact the macrovascular endpoints during the DCCT trial [23], or the PROACTIVE study [24], and the multifactorial intervention in the STENO 2 trial was not specific enough to draw conclusions on glycemic control [25]. Several studies are currently examining this question and are going to deliver their results soon. The ongoing CREATE-ECLA studies [30] failed to show an association between glycemic intervention and cardiovascular endpoints.

4. Conclusion

It must be mentioned that the glucose-centered point of view is important for physicians involved in diabetes care, as it helps to recommend targets of blood glucose control. However, the PROACTIVE or the STENO 2 are good examples of intervention targeting blood glucose that proved to be beneficial on macrovascular endpoints when a conjunction of a beneficial effects was encountered on several risk factors such as HbA1c, lipids, blood pressure. Any effort should thus be made to improve glycemic control in conjunction of improvement of other cardiovascular risk factors.

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Conflicts of interest:

S. Hadjadj: Dr. Samy Hadjadj is participating as a member of scientific committees and speaker at the Servier laboratory satellite symposium ALFEDIAM Advance. He took part in the Advance study supported and promoted by Servier laboratory and is member of a national or international scientific council or committee of MSD laboratories.
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Reference


