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Near normal HbA1c with stable glucose homeostasis: The ultimate target/aim of diabetes therapy

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Dear Editor,

Please find the review article entitled “New normal HbA1c with stable glucose homeostasis: The ultimate target/aim of diabetes therapy”, which has been solicited consecutively to my contribution as speaker at the Hanefeld symposium to be held in Dresden.

Hoping that this review article is in agreement with your expectation.

Looking forward to hearing from you,

With best regards,

Louis Monnier

Near normal HbA1c with stable glucose homeostasis:

The ultimate target/aim of diabetes therapy

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Abstract,

Achieving near normal glucose homeostasis implies that all components of dysglycemia that are present in diabetes states be eliminated. Reducing ambient/overall hyperglycaemia is a pre-requisite to eliminate the risk of development and progression of diabetes complications. More controversially however, are the relative and related contributions of postprandial glucose excursions, glucose variability, hypoglycaemia and the dawn phenomenon across the spectrum of dysglycemia. For instance, it is likely that the dawn phenomenon contributes to ambient hyperglycaemia and that postprandial glucose excursions are at the cross road of ambient hyperglycaemia and glucose variability with glucose fluctuations as causative risk factors for hypoglycaemia. Proof-of-concept trials such as the ongoing FLAT-SUGAR study are necessary for gaining further insight into the possible harmful effects of some of these features such as excessive glycaemic variability and glucose excursions, still considered to be of minor relevance by several diabetologists. Whether their role will be more thoroughly proven through further intervention trials with "hard" endpoints, remains to be seen. In the meantime more consideration should be given to medications aimed at concomitantly reducing ambient/overall hyperglycaemia and those additional abnormal glycaemic features of dysglycemia.

Keywords: glucose homeostasis; quality of diabetes therapy.

1 Introduction

The role of any antidiabetic treatment should be to achieve a near to normal glycaemic control based on the fact that most observational, epidemiologic and several interventional studies [1,2,3,4] have shown that the incidence of cardiovascular events, premature death and microvascular diabetic complications are associated with the overall glycaemic exposure over time. The degree of sustained chronic (ambient) hyperglycaemia is quantified by the determination of circulating HbA1c levels representing glycaemic control over a 2-to 3-month period of time [3,4]. It has also been established that even in persons with a HbA1c level of 6.5% (diagnostic threshold for diabetes), the risk of coronary heart disease and ischaemic stroke is 2- to -3 fold higher compared to those with a value of 5.5% [7]. There is incontrovertible evidence that ambient hyperglycaemia is a key player in the pathogenesis of diabetic complications at least of microvascular diseases, both in type 1 and type 2 diabetes. Such an evidence has been provided by two landmark interventional trials: The Diabetes Control and Complications Trial (DCCT) in type 1 diabetes [3] and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes [4]. Both these studies have demonstrated a consistent benefit of intensive therapies on the incidence of microvascular complications (DCCT) and of all related-diabetes complications (UKPDS). The evidence is less clear for macrovascular complications because the ACCORD (Action to Control Cardiovascular Risk in Diabetes) [8], the ADVANCE (Action in Diabetes and Vascular Disease: preterax and diamicron modified release Controlled Evaluation) [9] and the VADT (Veterans Affairs Diabetes Trial) [10], i.e. the three major randomised control interventional trials to compare intensive treatment with standard strategies, have shown a modest benefit in terms of macrovascular outcomes or have even failed to demonstrate any significant improvement in the short term [11]. In the ACCORD study [8] the risk of death, and especially as a result of cardiovascular disease, was found to be greater on intensive than standard therapy bringing the study to an early termination. The disappointing cardiovascular outcomes with intensive intervention led several authors to challenge the then current therapeutic strategies employed in an attempt to achieve near normal glucose control [12, 13]. However, these authors failed to acknowledge that the studies included in their meta-regression analysis were of a relatively short duration up from 1 to 5.6 years. Since, it has been recognised that lowering-glucose treatment requires a much longer period to demonstrate the cardiovascular benefit of improvement in glucose control [14,15,16,17]. The pivotal role of hyperglycaemia as a causative factor of macro-vascular complications was confirmed at least by five studies: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study in type 1 diabetes [14,15] and the analyses of the extended follow-up of such studies as the UKPDS [16], ACCORD [17], VADT [18] and the Steno-2 study [19] in type 2 diabetes. Figure 1 represents the time course of the benefit of lowering-glucose strategies (intensive vs standard) on the relative risk of major cardiovascular outcomes in the different interventional trials mentioned above. The observations indicate that a significant reduction in the relative risk of cardiovascular disease becomes evident only when the duration of follow-up was beyond 10 years as seen in the extended follow-up of the UKPDS [16] and the VADT [18] studies. Recently however, surprising results were observed by the EMPA-REG OUTCOME Investigators [20] after a median observation time of 3.1 years. It is highly likely that the improvements on cardiovascular outcomes in empagliflozin- treated subjects with type 2 diabetes are not simply due to the glucose-lowering effect of the drug but possibly due to improvements in blood pressure, cardiac function and body weight.

Reverting to the results of the UKPDS [4], it has been demonstrated that the incidence of clinical complications was positively and significantly associated with HbA1c and that there is no definitive threshold of HbA1c for any type of diabetes complication. When setting the baseline risk of complications at 1 when the HbA1c level is 5.5%, the analysis of the UKPDS data indicates that this risk increases 1.5 and 2 fold higher when the mean HbA1c level reaches 7 and 8%, respectively. There is also a remnant risk for adverse cardiovascular events even when HbA1c levels range between 5.5 and 7%, i.e. below the current ADA [21] and IDF [22] recommended target of <7% and even below 6.5% which is currently used for defining the presence of diabetes [23].

2. Features of dysglycaemia involved in the evolution of type 2 diabetes

The features of dysglycaemia in persons with type 2 diabetes can be roughly divided into the following components (figure 2):

- Normal glucose exposure, which corresponds to the area between 0 and 100 mg/dL (0-5.6 mmol/L) in the fasting state increasing to a postprandial peak <140 mg/dL (<7.8 mmol/L) before return to baseline values within 2-3 hours

- Additional excessive glucose exposure, which is only observed in patients with diabetes, in other words in those with HbA1c levels ≥ 6.5% according to American Diabetes Association (ADA) standards [23]. This additional glucose exposure observed in persons with type 2 diabetes can be separated into three further subcomponents: (a) the dawn phenomenon [24-26], (b) post-prandial hyperglycaemia [27-29] and (c) basal hyperglycaemia. These aforementioned dysglycaemic states do not necessary occur simultaneously in the evolution of type 2 diabetes and can vary in their contribution throughout the natural history of the disease (figure 3) [30].

2.1 The dawn phenomenon

This phenomenon corresponds to a rise in plasma glucose and/or insulin requirement towards the end of the nocturnal period, in the absence of any dietary (carbohydrate) intake. The dawn phenomenon is mainly due to the circadian variation in hepatic glucose production, which starts to increase in the evening and reaching a peak towards the end of an overnight fast and then declining during daytime until its late afternoon nadir [31]. The two main consequences of this rise of circulating blood glucose overnight includes elevation of the early morning fasting blood glucose and secondly abnormally high and delayed post-breakfast glucose excursions referred to as the "extended dawn phenomenon" [27]. This latter phenomenon is postulated to be due to the combined influence of an overproduction of glucose by the liver complemented by the intestinal hydrolysis of breakfast carbohydrate. Both phenomena, and more specifically the dawn phenomenon is not observed in non-diabetic subjects [32] since the hepatic glucose output in the early morning is counteracted by an increase in the endogenous insulin secretion [33].

We have recently demonstrated [34], in a group of 50 well-controlled persons with type 2 diabetes with a HbA1c ranging from 5.7 to 6.5% and predominantly treated with dietary measures alone (34 out of 50), that the "dawn phenomenon" is evident whilst the mean postprandial glucose (131 mg/dL, 7.3 mmol/L) and overall 24-hour glucose levels (115 mg/dl, 6.4 mmol/L) remained within the normal range in most of them (figure 4). This

suggests that the dawn phenomenon is likely to be the earliest expression of dysglycaemia in the natural history of type 2 diabetes (figure 3). Furthermore, we have demonstrated that its contribution to the overall glucose exposure cannot be neglected since 0.4% (expressed as percentage point) of the HbA1c in type 2 diabetes can be explained by the dawn phenomenon [26].

2.2 Postprandial hyperglycaemia

This glycaemic state is defined as the increment (the AUCs of the glycaemic profiles) above the horizontal lines set for each meal at pre-meal glucose values (figure 2).

In 2003 [28], we demonstrated that postprandial hyperglycaemia made the greatest contribution to the overall hyperglycaemia (70%) in persons with type 2 diabetes treated with oral anti-diabetic agents. In 2007 this finding was confirmed by analysing the 24-hour continuous glucose profiles of non-insulin-treated type 2 diabetic subjects presenting at different levels of HbA1c [27]. As soon as HbA1c levels exceeded 6.5% we observed an abnormal elevation of post-meal glucose levels. This phase of dysglycaemia has been recently confirmed (figure 4) in a study of 100 persons with type 2 diabetes (HbA1c < 7%), treated either with dietary measures alone or in combination with oral anti-diabetic agents [34]. The difference between those exhibiting mild dysglycaemia (HbA1c 6.5-6.9%, n = 50) compared with those with even better glycaemic control (HbA1c < 6.5%, n = 50) was due to the greater post-meal excursions in the former group. In those with a HbA1c < 6.5%, the proportion of individuals with an average two-hour post-meal glucose (mean of post-breakfast, post-lunch and post-dinner values) above the upper limit of normal of 140 mg/dL (7.8 mmol/L) was less than a quarter. In contrast, more than one half of those with an HbA1c level between 6.5% and 6.9% exceeded this threshold value [34]. Therefore, persons with a HbA1c ≥ 6.5% but < 7%, i.e. "residual dysglycaemia" differ pathophysiologically from those with a HbA1c < 6.5% by virtue of the greater frequency and magnitude of the post-meal glucose excursions. In both groups, the "dawn phenomenon" was present whilst basal hyperglycaemia was absent. Therefore, one can conclude that excess postprandial hyperglycaemia is the second abnormality in the dysglycaemic continuum/spectrum of type 2 diabetes provided that the HbA1c levels remain below 7% (figure 3). The calculated absolute contribution of postprandial glucose excursions to the HbA1c level is usually of 0.6% when the HbA1c is below 6.8%, which increases to a constant 1% beyond this level and remaining stable despite ever increasing HbA1c [29] (figure 5).

According to these observations, one can hypothesize that eradication of both the dawn phenomenon and postprandial hyperglycaemia would permit to decrease the HbA1c level by a total of 1%, i.e. 0.4% for the dawn phenomenon [26] and 0.6% for the post-meal glucose increments. Consequently, such a reduction in those individuals with HbA1c level below 6.8% should result in a near normal level of HbA1c (<5.8%). It should be noted that the reduction can be even more pronounced in certain individuals with a fall of 1.4% (0.4% for the dawn phenomenon and 1% for the post-meal glucose increments). Consequently, those with an HbA1c a high as 7.5% can achieve a near normal HbA1c level provided that both the dawn phenomenon and abnormal postprandial glucose excursions are eradicated. Consequently the risk for the development and progression of micro or macro-vascular complications could be either eradicated or at least strongly delayed according to the data from the United Kingdom Prospective Study (UKPDS) [16] and as has been suggested by Zoungas et al [35].

2.3 Basal hyperglycaemia

When the HbA1c is between 7.5 and 8%, the relative contribution of the postprandial and basal hyperglycaemia to the overall hyperglycaemia becomes equivalent, whereas beyond 8% basal hyperglycaemia becomes increasingly the predominant defect [28, 36]. This observation is simply due to the fact that the absolute contribution of the postprandial hyperglycaemia across the increasing HbA1c spectrum beyond 7% remains stable at approximately of 1% of HbA1c as mentioned above [29]. Therefore, any increase in glucose exposure beyond this HbA1c threshold of 7% is due to a linear increase in absolute basal hyperglycaemia [28] evident beyond 8% of HbA1c [28,29]. This therefore represents the final stage in the worsening of glycaemic control in persons with type 2 diabetes, corresponding predominantly to a progressive deterioration of basal hyperglycaemia during both the diurnal and nocturnal periods.

In summary, this stepwise deterioration of glycaemic control is illustrated schematically in figure 3 representing the initial stage of an isolated dawn phenomenon (HbA1c below 6.5%), followed by the combination of a dawn phenomenon with postprandial hyperglycaemia (HbA1c between 6.5 and 6.9%), i.e. when subjects are in the so-called of "intermediate" stage of dysglycaemia. The final phase is reached with the addition of progressive basal hyperglycaemia, when the HbA1c is ≥ 7%, being the last member of the "triumvirate" of abnormalities seen in type 2 diabetes.

3. Relationship between postprandial glucose excursions and glycaemic variability

Glycaemic variability refers to glucose fluctuations from peaks to nadirs [37-40]. Peaks, especially in type 2 diabetes, usually correspond to postmeal glucose excursions while nadirs can indicate risk of hypoglycaemia during the inter-prandial and nocturnal periods. The glycaemic variability has been extensively described and investigated during the last decade mainly by using the newly developed technology of ambulatory continuous glucose monitoring (CGM). At present, several methods are employed to quantifying the magnitude of glucose variability [39-42] including: the standard deviation (SD) around the mean glucose value, MAGE (Mean Amplitude of Glycaemic Excursions) and the MODD (Mean Of Daily Differences), the CONGA (Continuous Overlapping Net Glycaemic Action), the M-index of Schlichtkrull [43] and the Lability Index [44]. These parameters investigate either the within-day or between-day glucose variability for which CGM is required available in a limited number of medical units. Therefore, one of the new challenges in the near future is to develop simplified methods for the assessment of glycaemic variability. Such methods should be able to be based on the measurement of capillary glucose concentrations by using the structured self-blood glucose monitoring at accurately selected time-points. One of the approaches for addressing this issue is to consider that, at least in type 2 diabetes, glycaemic variability and postprandial glucose excursions are inter-correlated. By using CGM in a population of 63 patients with type 2 diabetes, Suh et al [45] recently demonstrated that postprandial glucose excursions were strongly correlated with glycaemic variability, at least in a subset of subjects who were under reasonable glycaemic control (HbA1c < 7.5%). These findings are in general agreement with our own observations in a post hoc analysis of the results of a multicenter prospective randomized trial [46] that was conducted in a small number (n = 30) of persons with type 2 diabetes treated with metformin and secondarily allocated after randomization to one of two DPP-4 inhibitor preparations either vildagliptin (n= 14) or sitagliptin (n = 16) as add-on therapy for a period of 8 weeks. In a post hoc analysis of the results of this study, we observed that the changes in postprandial glucose increments from baseline to end point were strongly and positively correlated with those of glycaemic variability (MAGE) [30]. In addition, a few

years ago, we noted that in most persons with type 2 diabetes, the highest postprandial glucose peaks recorded were mid-morning or 1 or 2 hours after having breakfast [27]. These abnormally high glucose excursions after breakfast may be referred as an ”extended dawn phenomenon”.

We then went on to investigate in people with non-insulin-treated type 2 diabetes (n = 271) the relationship between the increment in blood glucose from the pre-breakfast value after an overnight fast to the 90-min post breakfast value (x value) and the glycaemic variability assessed from the SD around the 24-hour mean glucose value (y value). A highly significant positive relationship was observed between the two parameters: $r = 0.74$, $p < 0.0001$ (figure 6). These results not only confirm that glycaemic variability and postprandial glucose excursions are strongly linked but also provide a simpler method to CGM for quantifying the glycaemic variability based on only two determinations of capillary glucose at pre and post breakfast time points sufficient to allow a reliable assessment of within-day glucose fluctuations.

4. Glucose variability: is this glycaemic disorder an important matter?

At present, the role of glycaemic variability on the development and progression of cardiovascular diseases is a subject of debate. In a recent issue of Diabetes Care, Hirsch and Bergenstal had a Point-Counterpoint debate [47,48]. Hirsch provided arguments that glucose fluctuations are deleterious and that control of glycaemic variability should be a primary treatment target [47]. Bergenstal instead argued that we should give preferential consideration to other markers than glycaemic variability [48].

4.1 Glycaemic variability: worthy of consideration?

Ten years ago, Ceriello et al [49] epitomised postprandial excursions as “dangerous waves” for vascular endothelial cells of vascular walls through the activation of oxidative stress, one of the key pathophysiological mechanisms for the development of diabetic vascular complications [50,51]. Subsequently this hypothesis was confirmed by us when we demonstrated that in non-insulin-using type 2 diabetic patients, the 24-hour urinary excretion rate of 8-iso PGF2alpha a marker of the activation of oxidative stress, was strongly correlated with the Mean Amplitude of Glycaemic Excursions (MAGE) [52] which was later re-affirmed by Ceriello [53]. Using the glucose clamp technique in persons with type 2 diabetes, upward and downward swings of glucose concentrations are paralleled by oscillating plasma levels of nitrotyrosine, another marker of oxidative stress [53]. More recently, we reported that the 24-hour urinary excretion rate of 8-isoPGF2alpha depends equally on the ambient hyperglycaemia and the glycaemic variability, as estimated by HbA1c levels and MAGE respectively, in non-insulin-treated type 2 diabetes [54]. According to these and other observations, the pathogenesis of diabetic complications appear to be a consequence of both chronic hyperglycaemia and short-term excessive glucose variability resulting in enhanced glycation and activation of oxidative stress.

4.2 Glycaemic variability: significance in diabetic complications?

Key observations opposing the view that glycaemic variability is important in the development of diabetic complications were mainly provided by two retrospective analyses of the Diabetic Control and Complications Trial (DCCT) [55,56] and the HEART2D Study [57]. Analysis of the DCCT data set [55,56] concluded that glucose variability has only a minor contribution to vascular complications. However, it should be noted that the

conclusions were limited to microvascular complications in persons with type 1 diabetes on insulin treatment. The HEART2D study was initially designed to answer whether control of basal hyperglycaemia or postprandial hyperglycaemia is best for reducing cardiovascular outcomes in patients with poorly controlled type 2 diabetes who had a history of myocardial infarction [57]. Participants were further assigned to either a basal insulin strategy targeting fasting and inter-prandial glycaemia or an insulin regimen with three daily injections of a rapid-acting insulin analogue at premeal times in order to attenuate postprandial glucose excursions. A similar lowering effect of ambient hyperglycaemia represented by HbA1c was observed with the two insulin regimens. No difference in the incidence of cardiovascular events was detected between the two regimens despite the lower postprandial glycaemia with the prandial insulins compared with the basal group at interim analysis, when the study was halted after a mean follow-up of 2.7 years. It was therefore concluded that better control of postprandial excursions and probably reduced glucose variability does not provide any benefit in terms of macrovascular outcomes.

4.3 Pros and cons of glycaemic variability as a risk factor of macrovascular diseases

From the aforementioned studies, there arises the question as to why glycaemic variability as an activator of oxidative stress in non-insulin-treated type 2 diabetes, did not appear to exert any significant influence on the cardiovascular outcome in those treated with insulin. We derived an answer to this question with a cross-sectional study that compared three groups of subjects including type 1 diabetes and type 2 diabetes treated either with oral hypoglycaemic agents or in combination with insulin [54]. The 24-hour urinary excretion rate of 8-isoPGF2 alpha was only elevated in those subjects treated with oral hypoglycaemic agents (OHAs) remaining within the normal range in the other two groups treated with insulin. These results were observed despite the fact that glycaemic variability (MAGE) was significantly higher in those on insulin versus those on oral therapy alone. In addition, in a subgroup of those with type 2 diabetes, the 24-hour urinary excretion rate of 8-isoPGF2alpha was evaluated at baseline whilst on treatment with OHAs and several months or years after initiation of insulin treatment. A drastic reduction in the 24-hour urinary excretion rates of 8-isoPGF2alpha was seen from a highly elevated level before initiation of insulin returning to within the normal range following the introduction of insulin treatment. These results strongly suggest that insulin *per se* exerts an inhibitory effect on the activation of oxidative stress [58].

From a clinical care point of view, these observations support the concept that treatments with insulin should be implemented as early as possible in the time course of type 2 diabetes [59], bearing in mind the clinical characteristics of the patient [13]. Therefore, randomized interventional control trials comparing 2 groups of subjects maintained at similar levels of HbA1c but submitted to therapeutic strategies aimed at reducing glycaemic variability in one group but not in the comparator, is needed to provide a clear answer as to whether glycaemic variability contributes to adverse cardiovascular outcomes in type 2 diabetes. The protocol of the ongoing FLAT-SUGAR Study has been designed to address this issue [60]. In this proof-of-concept study, participants will be randomized and enrolled into two groups according to whether they will be treated with a basal-bolus insulin regimen or a combination of basal insulin and a prandial GLP-1 receptor agonist. The primary end point will be the changes in glycaemic variability that should normally be lower in the latter group than in the former. The secondary end point will be changes in several biological markers of inflammation,

activation of the oxidative stress, renal and cardiac functions. Should the results of this preliminary study be consistent with the hypothesis, this would lead to a long-term study with "hard" cardiovascular outcomes in order to validate the potential role of glycaemic variability.

5. Relationship between glycaemic variability and hypoglycaemia

As hypoglycaemic episodes can contribute to the occurrence of adverse cardiovascular events [8, 61-66], it is important to know whether glycaemic variability contributes to hypoglycaemia. It is well accepted that hypoglycaemia is more frequent when mean glucose values are low, with recent data [67, 68] indicating that increased glucose fluctuations around the mean glucose value can play an additional role in precipitating hypoglycaemia. These results based on the DOVES trial [67] and the DCCT data set [68] have been confirmed by our own data [69]. Similar results were observed in an unpublished analysis by ourselves of 828 day-patient glycaemic profiles that were obtained from ambulatory CGM carried out in subjects with type 1 diabetes (331), type 2 diabetes treated with insulin (216) and non-insulin-treated type 2 diabetes (222). In each group, the frequency of hypoglycaemic episodes (defined as all interstitial glucose values < 56 mg/dL, 3.3 mmol/L) was calculated after the 3 groups had been divided into 3 further subgroups according to whether the 24-hour mean glucose value was < 150 mg/dL, (8.3 mmol/L), between 150 and 180 mg/dL (8.3-10.0 mmol/L) or > 180 mg/dL (10 mmol/L). Finally, in each subset, the frequency of hypoglycaemic episodes was compared according to whether the glycaemic variability (SD around the mean glucose value) was above or below the mean SD in each selected subgroup i.e. 60 mg/dL in type 1 diabetes, 50 mg/dL in insulin-treated type 2 diabetes and 30 mg/dL in non-insulin-treated subjects, values were rounded to the nearest ten. The results are illustrated in figure 7a for type 1 diabetes, 7b insulin-treated type 2 diabetes, and 7c non-insulin-treated type 2 diabetes. The frequency of hypoglycaemic episodes ranked according to decreasing ordinal scale were Type 1 diabetes > insulin-treated type 2 diabetes > non-insulin-treated type 2 diabetes. In each type of diabetes, as expected, the ranking frequency of hypoglycaemic episodes was as follows: study days with mean glucose values less than150 mg/dL (8.3 mmol/L) > study days with mean glucose values between 150 and 180 mg/dL (8.3-10.0 mmol/L) > study days with mean glucose values > 180mg/dL (10 mmol/L). More importantly in each subgroup of patients, the frequency of hypoglycaemic episodes increased substantially when the glycaemic variability was increased above the mean SD value. Glycaemic variability seems therefore to be strongly associated with hypoglycaemia, although it is not possible to know whether glycaemic variability is the chicken or the egg. Glycaemic variability being a causative risk factor for hypoglycaemia is a possibility as the majority of hypoglycaemic episodes recorded in the present study were asymptomatic and thus were not subject to a subsequent glucose rebound due to excess self-treatment with carbohydrate-containing drinks or snacks.

6. Concomitant reduction of ambient hyperglycaemia and glycaemic variability: Is this possible?

The benefits of attaining normal or near normal levels of HbA1c with its ensuing reduction in the risk of diabetic complications should not be counterbalanced by an increased risk of hypoglycaemic episodes [8-10, 66]. Therefore, during the stage of "intermediate" dysglycaemia where basal hyperglycaemia is absent and glucose values during nocturnal periods are within the normal range [34], therapeutic intervention should avoid the use of anti-diabetic agents or strategies that increase the risk of hypoglycaemia. Such agents include the sulfonylureas or glinides [70], basal insulin [71]. Instead insulin sensitizers [72] incretin-based therapies such as

the DPP-4 inhibitors or the GLP-1 receptor agonists should be employed at this stage of the natural history of type 2 diabetes [73-78]. Unfortunately glycaemic variability and chronic ambient hyperglycaemia were rarely studied in parallel in large interventional trials. For instance, in the 4-T study [79], HbA1c levels were improved when patients were switched from a basal insulin therapy to a basal-bolus insulin regimen although this resulted in an increased frequency of hypoglycaemic episodes. As the glycaemic variability was not assessed it is not possible to know whether this effect was due or not to an increase in the magnitude of glucose excursions. Another example is the 4B study [80] that was designed to compare the efficacy and safety of exenatide twice daily or thrice daily mealtime insulin lispro in those inadequately controlled by optimised insulin glargine and metformin therapy. Whilst similar improvements in ambient hyperglycaemia (HbA1c) were observed in both groups, exenatide resulted in fewer episodes of hypoglycaemia considered as a whole (30% vs 41% respectively) and more particularly during the day (15% vs 34% respectively). However, given the fact that exenatide is a GLP-1 receptor agonist mainly aimed at reducing postprandial glucose excursions, it is highly likely that this category of antidiabetic agents can be of value in reducing both ambient hyperglycaemia and glucose variability. In a post-hoc analysis of the OPTIMA study [30] using CGM it has been demonstrated that the DPP-4 inhibitors sitagliptin and vildagliptin, when prescribed as add-on therapy in persons with type 2 diabetes not sufficiently controlled on metformin alone, resulted in a significant reduction in ambient hyperglycaemia (HbA1c, AUC under glycaemic profiles). This reduction was concomitantly associated with significant decreases in postprandial glucose exposure and glycaemic variability (MAGE) with a positive relationship between these 2 parameters [30]. These results demonstrate that it is possible to reduce both the ambient hyperglycaemia and glucose variability in a concomitant manner. Therefore, the assessment of glycaemic variability should be more extensively and thoroughly evaluated in all forthcoming interventional trials. Such assessments will be crucial to define which drugs have the potential to reduce glucose fluctuations and to finally resolve the debate as to whether reduction in glycaemic variability has a positive impact or not on cardiovascular outcomes.

7. Conclusion

The current situation can be summarized by 3 terminologies: “consensus”, “disensus”, and “non sensus”. “Consensus” because, despite a small number of discordant opinions, it is now well accepted that chronic exposure to ambient hyperglycaemia is a key player in the pathogenesis of diabetic complications. The “disensus” is based on the fact that there exists a large spectrum of opinions on the role of both postprandial glucose excursions and glycaemic variability as risk factors for adverse cardiovascular outcomes. The “non sensus” would be to deny any impact of short-term excess postprandial glucose fluctuations on the development or progression of vascular complications.

Although at present, we lack the evidence, we hope that the ongoing or future randomised control interventional trials will be able to provide a clear answer to the question as to whether more consideration should be given to postprandial hyperglycaemia and glucose variability which are regarded as minor or ancillary components of dysglycaemia relative to overall hyperglycaemia.

Disclosure of interest

All authors declare that they have no conflict of interest with the content of this review

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Legends of figures

Fig. 1 Influence of duration of follow-up upon the relative risk of major cardiovascular outcomes in patients with type 2 diabetes submitted to intensive glucose lowering as compared with standard therapy. A significant reduction in the relative risk was only observed when the duration of follow-up was longer than 10 years: extensions of the UKPDS [16] and VADT [17] studies. In contrast the use of intensive therapy did not significantly reduce major cardiovascular events when the follow-up remained shorter than [8-10] or nearly 10 years [4]

Fig. 2 The respective contributions of the different components of glucose exposure in persons with type 2 diabetes are depicted on the left part of the figure (i) normal glucose exposure (grey shaded rectangle); (ii) exposure to basal hyperglycaemia (black area) and (iii) exposure to postprandial hyperglycaemia (white area). The dawn phenomenon corresponds to the spontaneous rise in basal hyperglycaemia observed before breakfast time. The aims of treatment are indicated on the right part of the figure

Fig. 3 Respective contributions of the 3 main glycaemic disorders (dawn phenomenon, basal and postprandial hyperglycaemia) to the dysglycaemia of type 2 diabetes mellitus across the HbA1c spectrum. The dawn phenomenon is a permanent feature of glycaemic disorders with worsening HbA1c

Fig. 4 Mean 24-hour glycaemic profile in persons with type 2 diabetes, who were divided into 2 groups. Group 1: HbA1c < 6.5% group 2: HbA1c between 6.5 and 6.9% (n = 50). Exposures to basal and postprandial hyerglycaemia are illustrated by black and white areas, respectively

Fig. 5 Absolute impact of postprandial hyperglycaemia on HbA1c (expressed as percent points) in persons with type 2 diabetes across the HbA1c continuum/spectrum [29]. Reprinted with the permission of Mary Ann Liebert, Inc., publishers

Fig. 6 Relationship between postprandial glucose excursions (x = increment from the breakfast glucose value to the 90-min postbreakfast glucose value (mg/dL) and the glycaemic variability (y = SD around the 24-h mean glucose value, mg/dL).

Fig. 7 Total hypoglycaemic episodes (interstitial glucose concentration < 56 mg/dL during continuous glucose monitoring) expressed as number/patient-day in 3 groups of persons with diabetes: type 1 (n = 313, figure 7a); type 2 treated with insulin (n = 216, figure 7b) and type 2 treated only with diet or oral antidiabetic agents (n = 222, figure 7c).

Figure 1

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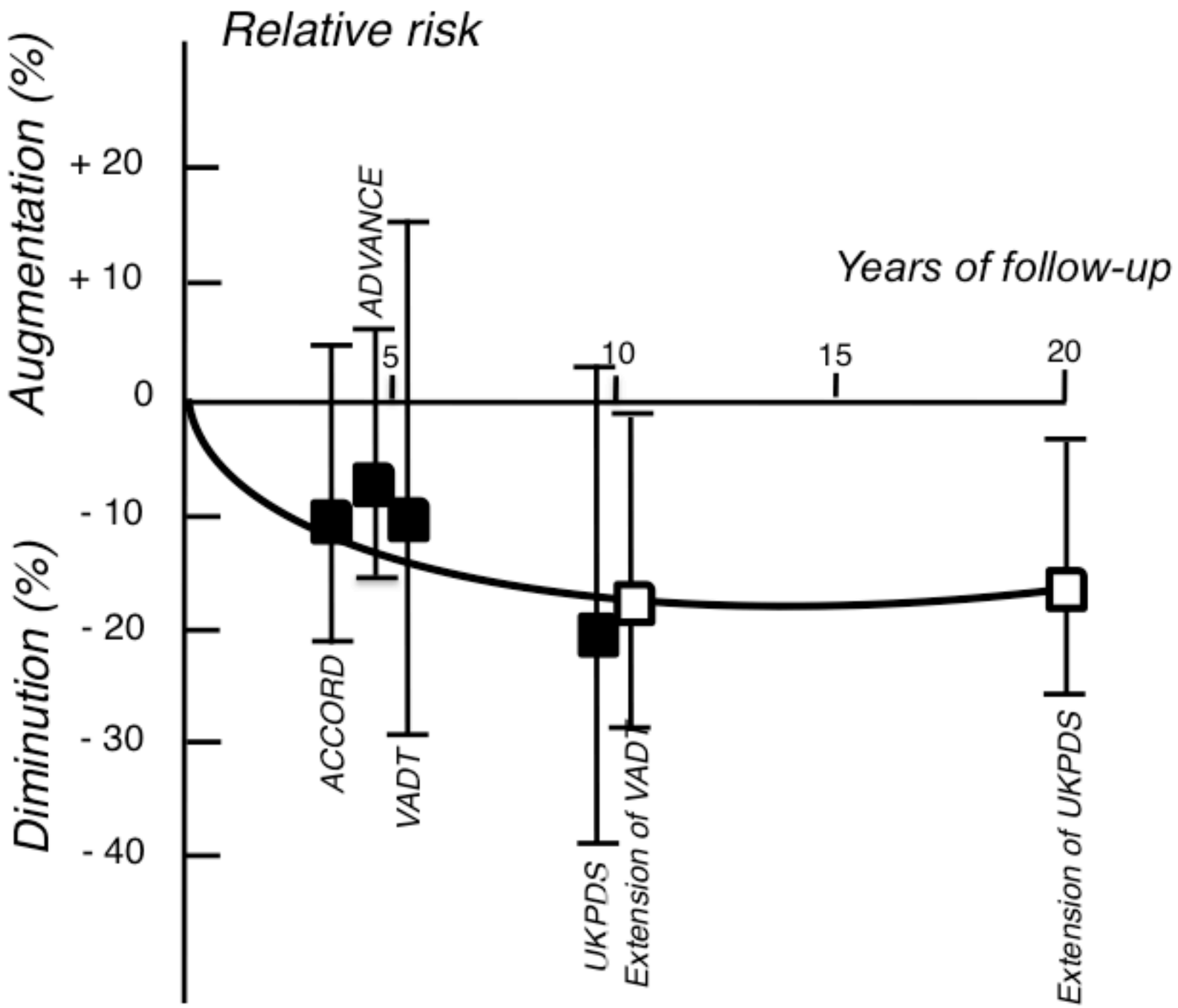

Figure 2

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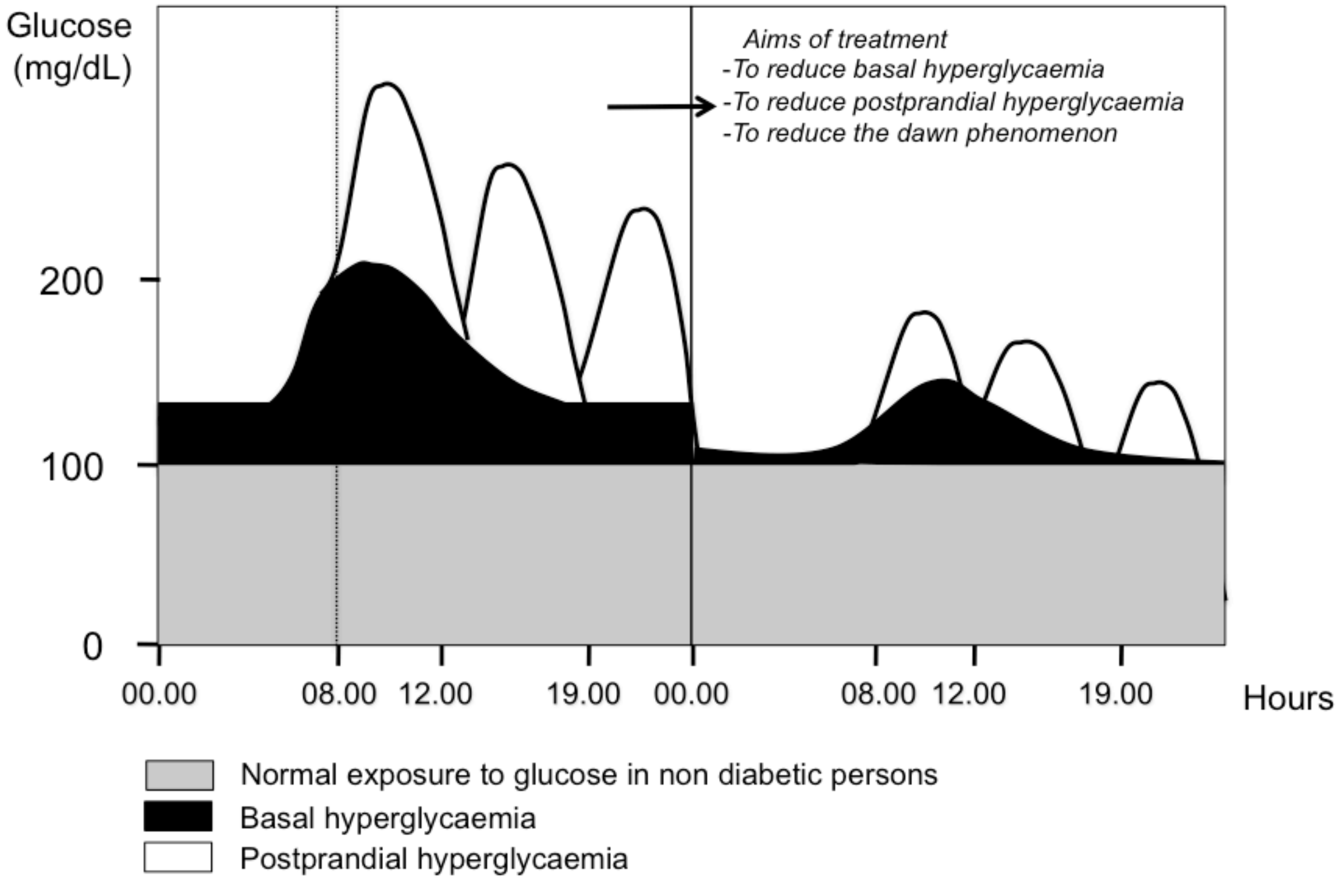

Figure 3

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	HbA_1c
Basal hyperglycaemia largely > Postprandial hyperglycaemia	8.0%
Basal hyperglycaemia approximately equivalent to Postprandial hyperglycaemia	7.5%
Postprandial hyperglycaemia > Basal hyperglycaemia	7.0%
Isolated postprandial hyperglycaemia	6.5%
Dawn phenomenon	5.7%

Figure 4

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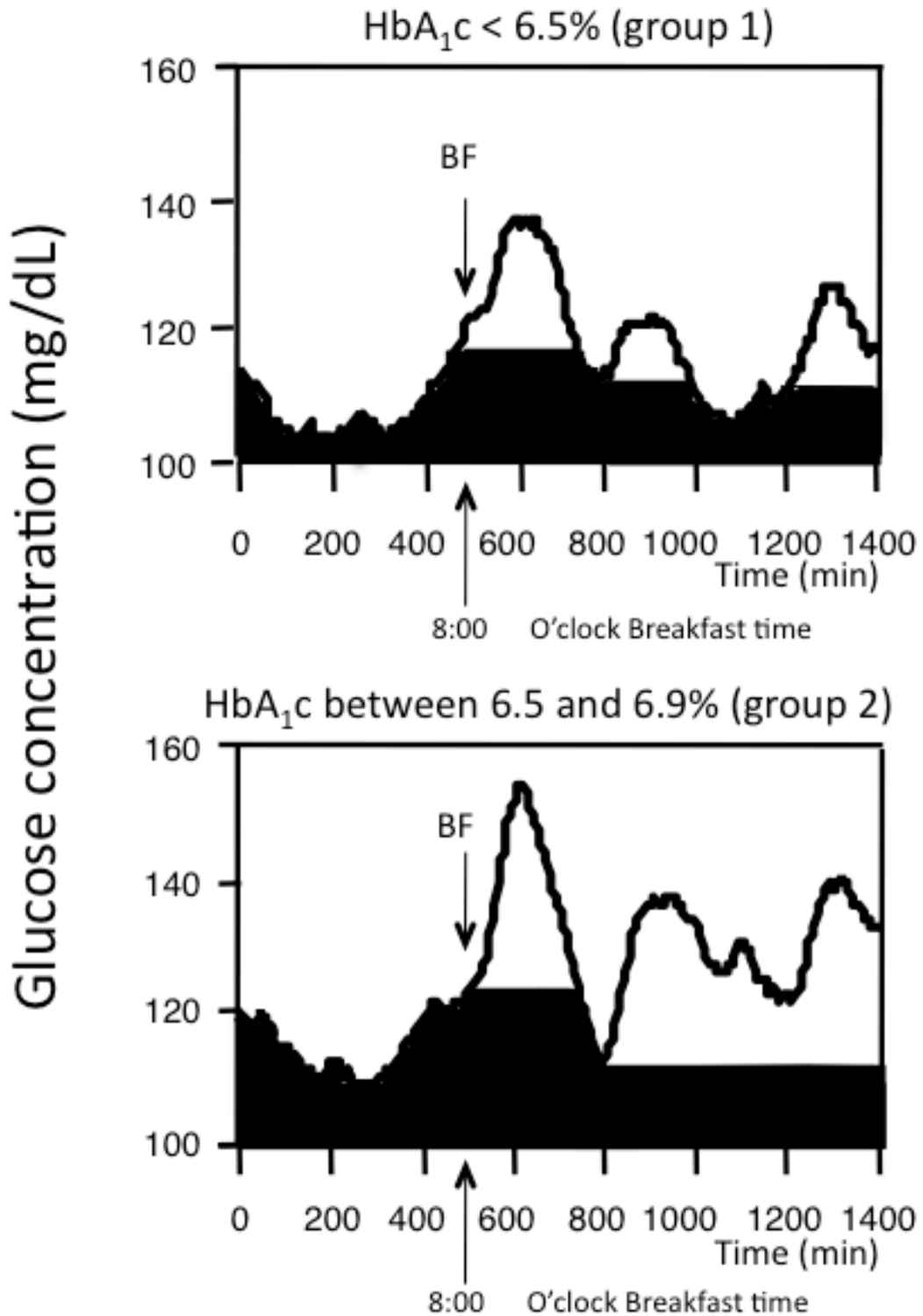

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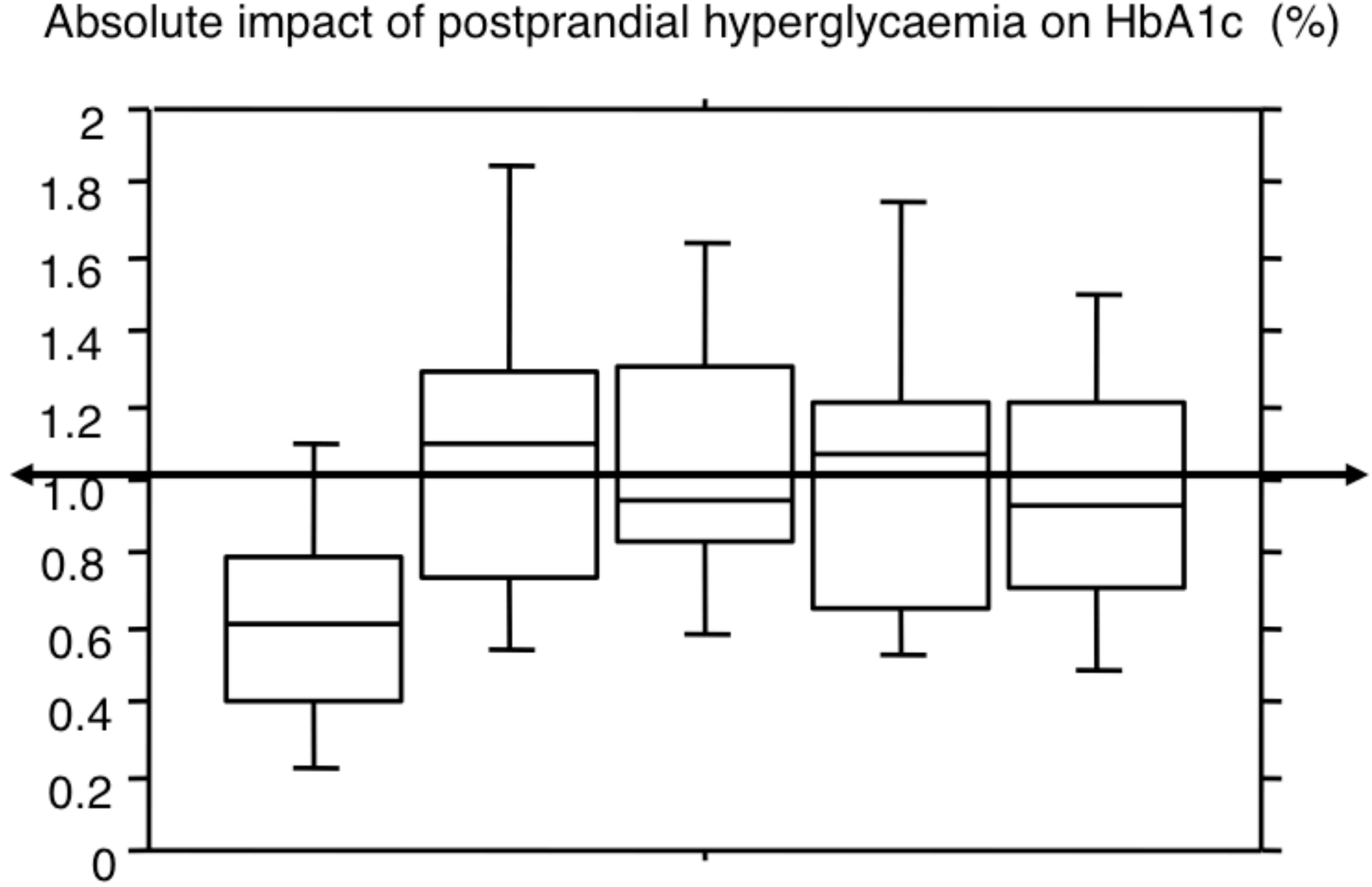

Figure 6

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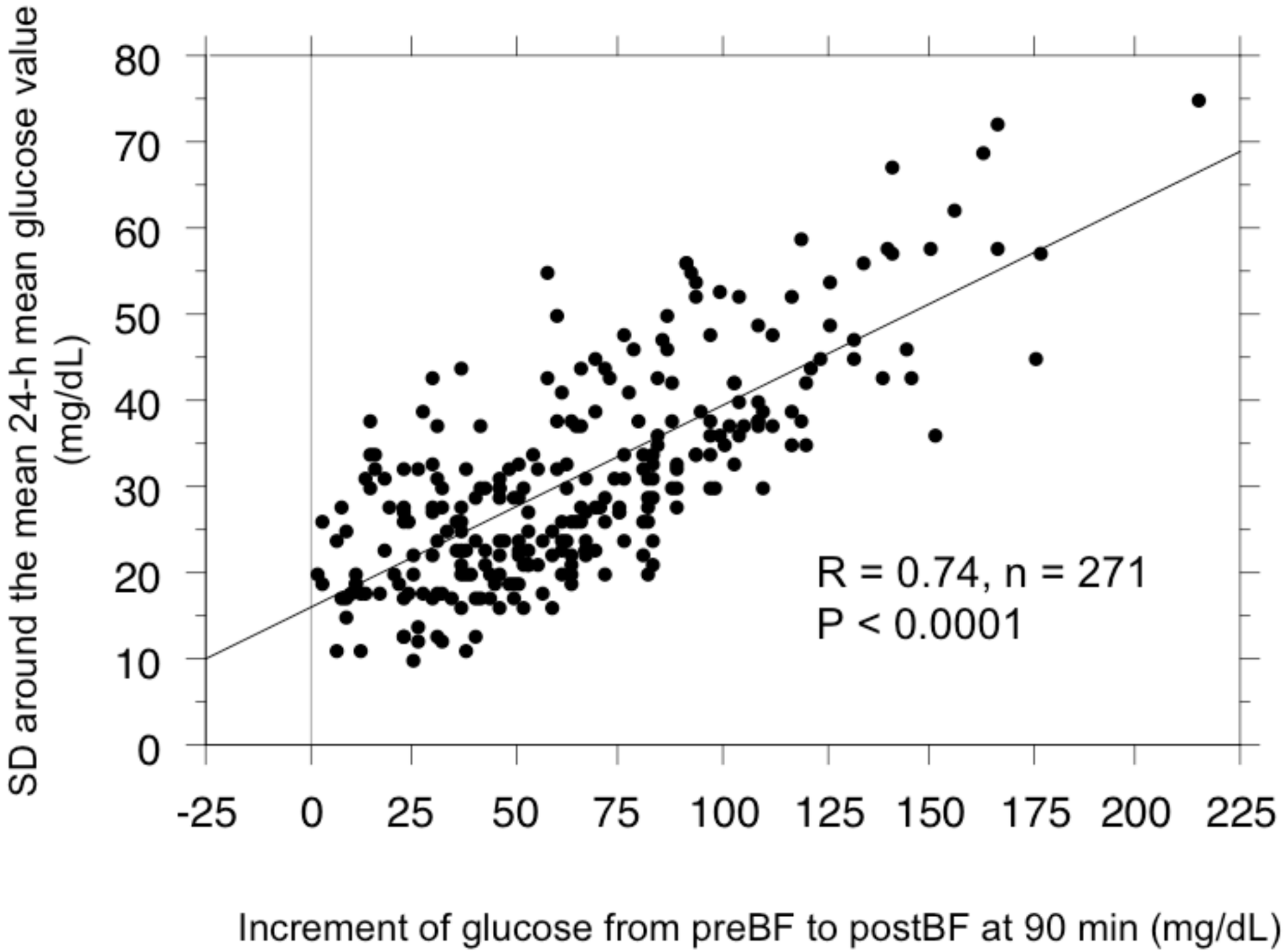

Figure 7

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