Type 2 diabetes: A well-characterised but suboptimally controlled disease. Can we bridge the divide?

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Abstract

From a pathophysiological point of view, type 2 diabetes is a well-characterised disease, since the glycaemic disorders result from three main mechanisms (the De Fronzo’s triumvirate): a defect of β-cell function, decreased disposal of glucose in peripheral tissues and overproduction of glucose by the liver. Each defect is subject to 24-h circadian variations and to inevitable worsening with time. As a consequence, therapeutic strategies should reflect whether patients retain sufficient insulin secretion or suffer from a more severe secretory defect that progresses from being responsive to oral diabetic agents to the insulin-requiring stage. Identifying the different pathophysiological stages is a prerequisite for successful therapeutic strategies. This assessment can be done by considering on the one hand the HbA1c and on the other the glycaemic profiles. For the latter, either discontinuous (self-monitoring of blood glucose) or continuous glucose monitoring can be used. However, many difficulties remain for bridging the divide between well-understood pathophysiological concepts and suboptimal glycaemic control achieved in clinical practice. The main drawback is the difficulty in providing therapies at recommended doses to stochastic phenomena such as either intestinal absorption of carbohydrates or fluctuations in both pharmacokinetics and pharmacodynamics of hypoglycaemic agents.

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Résumé

Le diabète de type 2 : une maladie bien caractérisée mais insuffisamment contrôlée. Peut-on combler le fossé ?

Le diabète de type 2 est une maladie bien documentée, puisque les désordres glycémiques sont expliqués par trois mécanismes principaux (le triumvirat de De Fronzo) : un défaut de la fonction β cellulaire, une diminution de l’utilisation du glucose au niveau des tissus périphériques et un excès de production du glucose par le foie. L’un des problèmes majeurs réside dans le fait que toutes ces altérations ne sont pas stables, mais sont l’objet de variations circadiennes et d’une détérioration progressive sur le long terme. De ce fait, les stratégies thérapeutiques devraient être ajustées périodiquement. Le choix entre médicaments devrait normalement être fait à partir de l’évaluation de l’insulinosécrétion résiduelle selon que son altération est modérée ou plus ou moins sévère, la sévérité allant de l’état où le sujet répond encore correctement aux antidiabétiques oraux jusqu’à l’étape de l’insulinoréquérance. L’identification de ces étapes doit précéder l’utilisation de stratégies thérapeutiques personnalisées. Cette évaluation peut être réalisée grâce à un double regard, l’un étant fixé sur l’HbA1c et l’autre sur les profils glycémiques. Pour ces derniers, l’évaluation peut être réalisée en utilisant des enregistrements continus ou discontinus de la glycémie. Toutefois, il reste difficile de combler le fossé entre des concepts physiopathologiques bien expliqués et des résultats cliniques insuffisants en termes de contrôle glycémique. La lacune la plus importante est la difficulté de fournir des réponses déterministes comme le choix d’une thérapeutique donnée à dose recommandée, à des phénomènes probabilistes comme l’absorption intestinale des glucides ou les fluctuations pharmacocinétiques et pharmacodynamiques des agents hypoglycémiants.

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Striving to achieve tight glycaemic control is one of the main challenges in the treatment of patients with type 2 diabetes, since there is now an extensive evidence for the deleterious effects of excessive glycaemia on the development and pro-
In order to improve the clinical outcome for persons with type 2 diabetes, many structured education programs were initiated [6–8], guidelines were developed to provide more stringent recommendations [9–12], treat-to-target therapeutic strategies were implemented [13,14], and new antidiabetic drugs were developed expanding our therapeutic armamentarium [15]. Despite all these efforts, a large proportion of persons with type 2 diabetes remain poorly-controlled and exhibit HbA1c levels well above the recommended targets [8,16–18]. At first glance, this failure seems to be surprising, since the pathophysiology of the disease is now well-explained [19–22]. For instance, there is now cogent evidence that overt type 2 diabetes is a disease characterised by three main abnormalities:

- a defect of the β-cell function [23–26];
- a state of insulin resistance [20,27];
- an overproduction of glucose by the liver [28,29].

Despite the currently available oral hypoglycaemic agents (OHAs) are able to target deficiencies in either the endogenous insulin secretion or the insulin sensitivity at different target sites [30], the attainment of satisfactory diabetes control becomes more and more difficult the longer the duration of the disease [31]. Furthermore, current OHAs for persons with type 2 diabetes have several limitations, including inadequate HbA1c reductions [15], inability to control postprandial hyperglycaemia, increased risk of hypoglycaemic episodes, weight gain [32], gastrointestinal side effects and fluid retention with oedema. The purpose of the present review is firstly to identify the various factors that contribute to the inability to translate from the well-understood pathophysiological concepts into near normal blood glucose control utilising with the currently available therapies. The second question is to know whether certain new agents or strategies that have been more recently developed can be helpful for bridging the divide between pathophysiology and near normoglycaemia in clinical practice.

1. Why the pathophysiology of type 2 diabetes is more complex than a simple defect in both insulin secretion and sensitivity?

As mentioned above, type 2 diabetes is predominantly characterised by defects both in insulin action and secretion. However, it is now clear that both abnormalities over the time course of the disease vary considerably and also in relationship to each other [19,23,26]. Furthermore, it is now well-known that the expression of insulin resistance has different patterns in the three major target tissues concerned in insulin action:

- the liver;
- the muscle;
- the adipose tissue [22,23].

In addition, insulin resistance exhibits circadian fluctuations both in the liver and the peripheral tissues [28] that can explain some of the metabolic abnormalities that are observed in the glycemic profiles of type 2 diabetic patients including the “so-called” dawn phenomenon [34].

1.1. Multiple target sites of insulin resistance

Regulation of the whole-body glucose homeostasis is primarily controlled by insulin. Numerous studies, especially those using the hyperinsulinaemic euglycaemic clamp technique [35] combined or not with the use of stable or radioactive tracers such as glucose $^{13}$C and $^{14}$C [36,37], respectively, have demonstrated that insulin resistance is a fundamental component in the pathophysiology of diabetes [22]. The consequences are the following:

- an overproduction of glucose by the liver, since insulin has an inhibitory effect on the hepatic glucose output [30];
- a decreased disposal of glucose at the periphery, that is in the tissues responsible for insulin-mediated glucose uptake [20,27], namely the muscles and to a smaller extent the adipose tissue.

In the fat cells, insulin has also a suppressive effect on lipolysis which is the most insulin sensitive process followed first by hepatic glucose production and far behind by peripheral glucose uptake [33]. According to this observation, it is not surprising that all treatments or strategies which result in increased plasma insulin concentrations through either stimulation of the residual insulin secretion (sulfonylureas) or through insulin replacement [38,39] cause an increased fat cell mass and thus weight gain. The latter side effect does not seem to occur with the new class of antidiabetic medications that mimic the actions of the hormone glucagon-like-peptide-1 (GLP-1) [40,41]. At present the GLP-1 analogues result in slight but significant weight losses [42], while inhibitors of the dipeptidyl peptidase-4 (DPP-4) – GLP-1-enhancers – have globally no effect on the body weight [43].

1.2. Insulin sensitivity in peripheral target tissues and liver are subject to circadian variations

In patients with type 2 diabetes both hepatic and peripheral (muscle) insulin sensitivities are subject to circadian variations [28]. For example, hepatic glucose production starts to rise in the evening and reaches a peak towards the end of an overnight fast and then progressively declines during the daytime to reach a nadir by late afternoon, particularly in those patients who retain sufficient residual insulin secretion. Such observations provide a strong explanation for the “dawn phenomenon” and its consequences that can be listed as follows:

- in type 2 diabetes the glucose tolerance is worse in the early morning than at any other time with the postprandial excursions more marked after breakfast than after any other meal [44];
- in insulin-treated type 2 diabetic patients insulin requirements are highest at the end of the night and during the postbreakfast period corresponding to the dawn and “extended” dawn phenomena, respectively.
The latter phenomenon is due to the combined effects of hepatic glucose production and intestinal hydrolysis of breakfast carbohydrates. All these phenomena and more specifically the circadian rhythmicity of hepatic glucose output provide a rationale for the effectiveness of recent treat-to-target insulin therapies [13,14,45]. Injecting a long-acting insulin analogue or an intermediate-acting NPH insulin before dinner or at bedtime prevents the nocturnal rise in hepatic glucose production and as a consequence achieves better control of both pre- and postbreakfast glucose values. The progressive decrease in hepatic glucose production which occurs over the morning and postlunch periods provides an explanation for the occurrence of blood glucose nadirs in the late afternoon and therefore the highest risk for hypoglycaemia especially in those patients who are treated with such OHAs as sulfonylureas [46–49].

1.3. Time courses of insulin secretory dysfunction and insulin sensitivity in the long-term

At present there is cogent evidence that frank type 2 diabetes is a disease characterised by a steady decline over time in the quality of glucose homeostasis. By analysing continuous glucose patterns over 24 h (Fig. 1), we have recently demonstrated that the deterioration of glucose homeostasis can be approximated to a three-step process [44]. The first step corresponds to a loss in postprandial control that occurs in patients with HbA1c between 6.5 and 6.9% and with a mean diabetes duration of 4.2 years. As mentioned above, the second step is characterised by a deterioration of the glycaemic control during the pre- and postbreakfast periods in patients who exhibit HbA1c levels between 7 and 7.9% and who have a mean diabetes duration of 8.3 years. The final step in the deterioration of diabetic control occurs generally beyond the end of the first decade of diabetes duration and is represented by a chronic sustained basal hyperglycaemia over both nocturnal and interprandial periods and excess postprandial glycaemia. In conclusion, the natural history of the worsening of dysglycaemia in type 2 diabetes is marked by an early loss of prandial glycaemic control that precedes a deterioration of basal hyperglycaemia. This deterioration progresses from a period corresponding to a short time-interval limited to the end of the overnight fast up to an extended period that covers the nocturnal and interprandial periods considered as a whole [44]. Such a progression towards more severe stages of the disease results from an increasing alteration [19,20] of the three main mechanisms responsible for determining glycaemic control:

- the β-cell-function;
- the insulin sensitivity of peripheral tissues;
- the hepatic glucose production [21,22].

The data from the UK Prospective Diabetes Study indicates that the gradual increase in both HbA1c and fasting glucose concentration is mainly due to a relentless linear deterioration in β-cell function from the time of diagnosis [26,35]. Additional studies have demonstrated that the two other disorders, that is the insulin resistance of peripheral tissues and the hepatic glucose overproduction do not progress at the same rate throughout the time course of the disease. Both insulin resistance and hepatic glucose output increase early in the development of the disease and reach a quasi plateau once the diagnosis has been ascertained. However, it should be noted that even several years after diagnosis, the insulin sensitivity can be subject to a further deterioration due to two injurious consequences of the diabetic milieu, that is the so-called glucotoxicity and lipotoxicity. Both contribute to further aggravate the β-cell dysfunction and increase the insulin resistance and as a consequence, contribute

![Fig. 1. Twenty-four hour recordings from the CGMS in five groups of patients with type 2 diabetes. Curve 1: A1c < 6.5%, curve 2: ≥ 6.5–< 7%, curve 3: ≥ 7–< 8%, curve 4: ≥ 8–< 9%, curve 5: ≥ 9% [44].](image-url)
to the secondary failure of initially successful treatments. All these data collectively help to explain why type 2 diabetes is a relentless progressive disease that requires advances from monotherapy with oral antidiabetic agents to combination therapy using multiple oral agents [30] and finally insulin replacement without undue delay [38,39].

2. Can we implement more stringent strategies in order to achieve a better glycaemic control in type 2 diabetes?

At first glance, appropriate strategies aimed at reducing glycaemic disorders in type 2 diabetes need to consider on the one hand insulin resistance and on the other β-cell dysfunction. For achieving this objective, physicians can use old and new antidiabetic medications that can be classified into three main categories according to their mechanisms of action:

- insulin sensitizers, example metformin [50,51] and glitazones [52] that act directly on insulin sensitivity of peripheral tissues and liver;
- insulin secretagogues, example sulfonylureas [53] or glinides [54,55] and incretin mimetics [42,43] that stimulate the residual β-cell function during fasting and/or postprandial periods;
- old and new insulin preparations [56,57] that become necessary as replacement therapy when the endogenous insulin secretion is inadequate [11,14,39,58,59].

During the past years, several guidelines were published in an attempt to structure a therapeutic approach [10,11]. All indicate that in most patients the pharmacological treatment should be started by using the insulin sensitizer metformin which remains the safer and cheaper medication when initiating pharmacotherapy for type 2 diabetes [60]. This recommendation is also based on the fact that at the time of diagnosis the patients are predominantly insulin resistant. If metformin fails to achieve or sustain satisfactory glycaemic control, that is HbA1c < 6.5% [10,12] or insulin resistance, that is HbA1c < 7% [9,11], another medication should be added without delay. However, there is no clear consensus between the different organizations [10,11]. Considering that the choice should be based on the pathophysiology of the disease, the second medication should normally be selected on a clear rationale which is obviously the magnitude of the β-cell dysfunction [61]. However, there arises the question how to quantify the residual insulin secretion. It is well-known that the HOMA index as described several years ago by the Oxford Group is certainly a valuable marker of insulin secretion in longitudinal studies conducted in large populations of patients. However, it is also well-recognized that its reliability is not guaranteed at the individual level [62]. Furthermore, the HOMA calculation implies a measurement of plasma insulin concentration at fasting, a parameter which is rarely done in clinical practice. For that reason, it is important that the physicians have a simple mean for assessing the degree of the residual β-cell function. We have been using for several years a four-point diurnal glycaemic profile consisting of glucose determinations at 3-h intervals from 8:00 am to 5:00 pm [61]. The first blood sample was collected before breakfast, the second at 11:00 am and the third 2-h after the beginning of the lunch. The last sample was collected at 5:00 pm. The four values of the so-called diurnal profile are respectively reflecting fasting, postprandial (after breakfast and lunch) and postabsorptive states [63]. In stage I, patients retain a sufficiently high secretion but delayed-insulin response to a nutrient challenge and improvements in diurnal glycaemic profiles are usually observed as daytime progresses along (Fig. 2a) [64,65]. Such improvements are explained by:

- an over stimulation of insulin secretion after meals, especially after lunch;
- an improvement in sensitivity and reduction in hepatic glucose output throughout the course of the day [28].

Thus, at this stage of the disease, agents that stimulate insulin secretion in a non glucose-dependent manner such as sulfonylureas and glinides are inappropriate tools for therapy. In stage II patients where the disease has progressed to a more marked insulin deficiency, the diurnal glycaemic profile generally differs from that observed in stage I. Meals do not have a sufficient stimulatory effect on insulin secretion, thereby the postprandial blood glucose levels over the second part of the day that is after lunch and at extended postlunch times (at 5:00 pm) are generally higher than at prebreakfast time (Fig. 2b) [64,65]. In this case, the aim of treatment should be to reinforce insulin secretion and to compensate for the insulin secretory defect. Therefore, insulin secretagogues should be chosen, the target being to achieve postlunch glucose levels inferior than 7 mmol/l (126 mg/dl) and extended postlunch glucose levels superior than 4.4 mmol/l (80 mg/dl) [48,66,67]. The second target permits to reduce the risk for hypoglycaemic episodes, since the blood glucose value in the late afternoon corresponds to and is at the same level as the other glucose nadirs that are observed over a 24-h period [44]. Stage III which is synonymous of severe insulin secretory defect is usually suspected when insulin secretagogues at maximal doses fail to achieve the above mentioned objectives, that is 2-h postlunch glucose inferior than 7 mmol/l and HbA1c inferior than 7% (Fig. 2c). At this stage, insulin treatment should be initiated [10,11,39]. In conclusion, it appears that each stage is characterised by specific pathophysiological defects that need different choices of antidiabetic treatments, in order to achieve goals as close as possible to near normal glycaemia.

2.1. Choice between insulin sensitizers at initiation of monotherapy and more generally at early stages of the disease

Metformin is generally recommended as first line therapy at the time of diagnosis of type 2 diabetes [11]. However, an alternative choice is to prescribe a glitazone as initial monotherapy [32]. At present, the arguments for prescribing metformin rather than one of the glitazones are based on the low cost and the long-recognized safety of metformin. The efficacy of both drugs in terms of HbA1c reduction seems to be within the same range: −1.0 to −1.5% as initial monotherapy [15]. These observations raise the question whether the data of the ADOPT
study that was published one year ago [32] can be helpful for making therapeutic decisions. This study was designed to compare the responses to metformin and rosiglitazone given as first line monotherapies of recently diagnosed type 2 diabetes. One of the primary outcomes was to assess the respective efficacy of the two therapies by determining the time to monotherapy failure that was defined as a confirmed level of fasting plasma glucose greater than 180 mg/dl. The comparison between the two insulin sensitizers can be analysed by using several criteria.

2.1.1. The analysis of efficacy

The analysis of efficacy seems to indicate that rosiglitazone should be a better choice as initial therapy. This opinion is based on the observation that the proportion of patients who failed to maintain a fasting glucose below 180 mg/dl (< 10 mmol/l) was higher with metformin than with rosiglitazone.

2.1.2. The analysis of the efficacy:safety ratio

The analysis of the efficacy:safety ratio attenuates the preceding conclusion, since it appears that metformin and rosiglitazone were similar when the safety was taken into account. The study confirmed that metformin is associated with frequent gastrointestinal side effects, while rosiglitazone results in weight gain and in fluid retention.

2.1.3. The analysis of the cost:benefit ratio

The analysis of the cost:benefit ratio seems to indicate that metformin, a drug with a relatively low cost should be the logical choice when initiating pharmacotherapy for type 2 diabetes [11].

2.1.4. Additional scientific arguments for metformin as initial monotherapy

Even though the low cost of metformin is important, it would be equally important to strengthen the choice on the basis of scientific rationale rather than on economic considerations. One argument for gaining further insight into the debate can be given by the analysis of the HbA1c that shows no difference between the rosiglitazone and the metformin groups at three years of follow-up (Fig. 3). By contrast, the time that the fasting glucose remained below 10 mmol/l was shorter in the metformin group than in the rosiglitazone group. An intriguing question is why such a difference between the two therapies. Considering HbA1c as an integrator of both fasting (FPG) and postprandial (PPG) glucose [68–70], the results of the ADOPT study [32] suggest that the poorer control of FPG observed with metformin when compared with rosiglitazone should be associated with a better control of PPG on metformin, since the two treatments achieved similar HbA1c levels. As type 2 diabetes is characterised by an early loss of postprandial control [44], the ADOPT study seems to reinforce the recommendation for using metformin as initial treatment. Additional data concerning the antihyperglycaemic action of metformin and glitazone could provide help in choosing the most appropriate therapy. For instance it is well-recognized that metformin and glitazone enhance insulin sensitivity at both peripheral and hepatic tissues. However, metformin is a better suppressor of the hepatic glucose production, while glitazones act mainly on peripheral tissues to stimulate insulin-mediated glucose uptake [71]. Since the deterioration of fasting glucose depends mainly on the hepatic glucose overproduction and since both abnormalities coincide generally with the diagnosis of the disease, it seems logical to initiate the treatment.
with metformin rather than with glitazones at the time of diagnosis [10,11]. In conclusion, metformin appears as the best first line pharmacological therapy in patients with type 2 diabetes.

2.2. Choice between insulin secretagogues as second line therapy

When metformin alone or combined with glitazones fails to achieve the objectives, that is HbA1c < 6.5 or 7% [9,12] there arises the issue of adding one of the available insulin secretagogues. Until recently, the choice was limited to sulfonylureas [53] or glinides [54]. Both medications lower blood glucose but according to their mechanism of action, sulfonylureas are more efficient on the fasting and pre-prandial than on the prandial hyperglycaemia, while the reverse is usually observed with glinides. As a consequence, the physician should assess the relative contributions of basal and postprandial hyperglycaemia to the overall hyperglycaemia before implementing treatment with a secretagogue. Such an assessment can be made by using a four-point diurnal profile. However, according to our results, the postprandial glucose is a major contributor to the overall hyperglycaemia before implementing treatment with a secretagogue. Such an assessment can be made by using a four-point diurnal profile. However, according to our results, the postprandial glucose is a major contributor to the overall hyperglycaemia before implementing treatment with a secretagogue.

Fig. 3. Time-course of HbA1c and fasting glucose in the metformin (black circles) and rosiglitazone (open circles) groups. Adapted from the ADOPT study [32].

hyperglycaemia and since the absolute efficacy of these drugs (−0.6 to −0.9% of HbA1c) still permits the target to be reached (<6.5 or 7%). In those patients whose HbA1c levels ranged from 7.5 to 8%, the choice could be between repaglinide and sulfonylureas according to whether the patients are at low or high risk of hypoglycaemia.

2.3. Choice between insulin regimens in patients suffering from severe insulin deficiency

Insulin should be implemented as soon as OHAs at maximal doses do not achieve satisfactory diabetic control [10, 11]. At present, there is little doubt that patients with a sustained level of HbA1c > 8% should be treated with insulin (ADA recommendations). Since in these patients basal hyperglycaemia is preponderant over prandial hyperglycaemia, insulin regimens based on basal insulin should be preferred to prandial insulin at initiation of the insulin therapy. If the target cannot be achieved, premeal boluses of rapid insulin analogues should be added, especially before the meals that result in the more pronounced glycaemic excursions [39]. The problem is slightly more complex in those patients who exhibit HbA1c levels between 7 and 8%. In this situation, most patients are reluctant to being treated with insulin. Furthermore, despite recent publications of more stringent recommendations, many physicians delay insulin treatment until further deterioration in HbA1c occurs. Recently, we have estimated that the mean interval of time that separates the moment at which HbA1c levels reach 7 and 8% is approximately four years [44], a duration which is not negligible in terms of risk for development or progression of diabetic complications. The new recommendations [10, 11] indicate that an insulin treatment should be initiated as soon as HbA1c remains above 8% with maximal doses of OHAs combining insulin sensitizers (metformin + glitazone) with an insulin secretagogue. At present, it is recommended to start insulin with one injection of a long-acting insulin analogue before dinner or at bedtime [10]. With such a regimen, the insulin action reaches a maximum over a period corresponding to the dawn and extended dawn phenomena, that is over a period that covers the end of the overnight fast and the postbreakfast period [44]. In patients with HbA1c ranging between 7 and 8%, plasma glucose values over this time-interval are usually more elevated than at any other period of daytime (Fig. 1). However, one third of the patients who have HbA1c levels between 7 and 8% do not exhibit a progressive glucose rise at the end of the nocturnal period. As a consequence, the prebreakfast glucose remains below 126 mg/dl (<7 mmol/l). Nevertheless, these patients with near normal glycaemia before breakfast experience abnormal postbreakfast excursions which result in sustained hyperglycaemia over the entire morning period. In order to combat this glycaemic profile which is limited to the postbreakfast period, it is probably preferable to administer a small bolus of a rapid-acting insulin analogue at prebreakfast than a long-acting insulin analogue before dinner or at bedtime. The first option has the advantage of avoiding hypoglycaemia that usually occurs when long-acting insulin analogues are prescribed to patients who have near normal glucose concentrations during night-time (Fig. 1). Continuous glucose monitoring can be a useful tool for guiding the choice between these two insulin regimens. When this type of monitoring is not available, the clinician can use, as a surrogate, the glucose values at prebreakfast and at 2-h postbreakfast. The observation of concomitant elevation of both pre- and postbreak-
fast glucose suggests that the basal hyperglycaemia should be controlled first and as a consequence that the insulin regimen should be initiated with either an intermediate-acting insulin or a long-acting insulin analogue. By contrast, an elevated post-breakfast with a near normal fasting glucose indicates that a bolus of rapid insulin analogue be administered before breakfast in order to blunt the postbreakfast glucose excursions. Tailoring the insulin replacement rather than adopting standardised insulin strategies is a more logical approach to achieve a satisfactory metabolic control without the risk of hypoglycaemia.

As the management of type 2 diabetes remains unsatisfactory in many patients, it can be concluded that at each stage of the disease the choice between the different hypoglycaemic agents should be guided by the pathophysiology of the disease and by reviewing the glycaemic disorders from two perspectives. Firstly, survey the HbA1c, that is the classical “gold standard” parameter which is used to assess the glycaemic control over a period of up to three months [68,69]. Secondly, focus on the glucose profile during the daytime. Glycaemic profiles can either be obtained from continuous [49] or discontinuous (self) glucose monitoring [81–83] for deciding which class of oral antidiabetic agent or which type of insulin regimen is the most appropriate.

Returning to the purpose of this review: “Can we bridge the divide?”, the difficulty to bridge the divide is mainly based on the fact that all medical decisions, example determination of the amount of dietary carbohydrates at a given meal, the choice of type and dose of antidiabetic agents or insulin injections are purely deterministic, based on fixed doses for the given medication. These deterministic decisions are intended at providing appropriate answers to nondeterministic problems but to stochastic phenomena that are governed by probability. For instance, the intestinal absorption of carbohydrates [84,85], the pharmacokinetics and pharmacodynamics of OHAs [86,87] and of insulin preparations [88–90] are purely stochastic and depend on conjunctural factors. As mathematicians are still in the quest of deterministic solutions for stochastic problems, it seems highly unlikely that physicians might provide a complete and successful answer to the problem that has been raised in the title and introduction of this review. In conclusion, our therapeutic approach is probably condemned to remain approximate even though we have to strive for finding therapeutic strategies that should be as close as possible to the ideal.

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