An overview of the rationale for pharmacological strategies in type 2 diabetes: from the evidence to new perspectives

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SUMMARY
Therapeutic strategies in type 2 diabetic patients should not only integrate both the targets and indications of the different therapies but should be also a compromise between the patient’s and physician’s goals and willingnesses. The rationale for therapeutic targets is based on recommendations that differ from one country to another. Even though HbA1c remains the “gold standard”, monitoring of blood glucose at fasting and postprandial time-points is a complementary tool for estimating both the quality and safety of diabetic control. Despite the lack of available strong evidence-based data it seems that achieving glucose levels < 130 mg/dl at fasting and < 180 mg/dl or < 140 mg/dl over postbreakfast or postlunch periods, respectively, might be a reasonable goal in most countries. The choice of appropriate strategies for treating type 2 diabetic patients should ideally be based on pathophysiological considerations. However for practical reasons, decisions for initiating or completing antidiabetic treatments are usually made by using such simple parameters as HbA1c and plasma glucose levels. The bridge between pathophysiological and clinical rationales can be obtained from the analysis of the relative contributions of fasting and postprandial glucose to the overall hyperglycaemia. In patients with HbA1c < 7.3%, postprandial glucose makes the major contribution to the overall hyperglycaemia, whereas the contribution of fasting glucose becomes progressively predominant in patients with HbA1c > 7.3%. As a consequence of these observations, initiation of antidiabetic treatments or implementation of second-line therapies should be aimed at reducing either postprandial excursions or fasting hyperglycaemia according to whether HbA1c levels are found respectively below or above a cut-off value of 7.3%.

Key-words: Pharmacological strategies · Type 2 diabetes mellitus.

RéSUMÉ
Revue du rationnel des stratégies pharmacologiques dans le diabète de type 2 : des preuves aux nouvelles perspectives

Les stratégies thérapeutiques dans le diabète de type 2 doivent non seulement intégrer les objectifs et les indications des différents traitements, mais devraient également être un compromis entre les buts et les souhaits du patient et de son médecin. Le rationnel des cibles thérapeutiques est fondé sur des recommandations qui diffèrent d’un pays à l’autre. Même si l’HbA1c reste « l’étalon or », la mesure de la glycémie à jeun et en période prandiale est un outil complémentaire pour l’estimation de la qualité et de la sécurité de l’équilibre du diabète. Malgré l’absence de données fortes et fondées sur les preuves, il semble que l’obtention des cibles suivantes puisse être considérée comme raisonnable dans la plupart des pays : glycémie à jeun < 130 mg/dl et glycémies après le petit déjeuner ou le repas de midi respectivement inférieures à 180 mg/dl ou 140 mg/dl. Le choix des stratégies appropriées pour le diabète de type 2 devrait, idéalement, reposer sur des considérations physiopathologiques. Toutefois pour des raisons pratiques, les décisions pour débuter ou compléter un traitement antidiabétique sont généralement prises à partir de paramètres simples comme l’HbA1c ou les glycémies. La liaison entre les rationnels physiopathologique et clinique peut être obtenue à partir de l’analyse des contributions respectives des glycémies à jeun et postprandiale à l’hyperglycémie globale. Chez les patients qui ont une HbA1c < 7,3 %, la glycémie postprandiale contribue de manière majoritaire à l’hyperglycémie globale, tandis que la contribution de l’hyperglycémie de jeûne devient progressivement prépondérante chez les patients ayant une HbA1c > 7,3 %. Dans ces conditions la mise en route d’un traitement antidiabétique ou la prescription d’une thérapeutique additionnelle devrait avoir pour objectif de réduire soit les excursions glycémiques postprandiales, soit l’hyperglycémie de jeûne selon que l’HbA1c se trouve respectivement en dessous ou en dessus d’une valeur seuil de 7,3 %.

Mots-clés : Stratégies pharmacologiques · Diabète de type 2.
he rationale of therapies in such chronic diseases as type 2 diabetes is schematically based on two components. The first one is usually developed from the evidence-based medicine and is defined on different recommendations and guidelines that were published over the last years in several countries [1]. However treatments of chronic diseases are not limited to evidence-based objectives and should be adapted both to the individuals’ perception of the disease and to the patients’ willingness to face their own health problems [2]. Self-management of diabetes which includes compliance, adherence, persistence to following dietary measures and lifestyle recommendations and to taking medications [3, 4] is one of the main burden of health care providers in their search for “doing the right things right” [5, 6]. Such a goal can be integrated as the sum of efficacy + safety+ quality of life + treatment satisfaction [7]. The two first components are both defined by the evidence–based medicine and the different official recommendations, and are further delivered by medical practitioners during repeated medical visits. However efficacy and safety instructions are usually modulated by the patients who integrate in their own treatment the two remaining components, i.e. the quality of life and the treatment satisfaction. In other words, treatment effectiveness is always a compromise between the physician’s rationale which includes efficacy and safety and the patient’s rationale which can be identified as quality life and treatment satisfaction. Furthermore both physician’s and patient’s rationales can be divided into 2 parts: (i) a rationale of objectives in terms of metabolic control that can be defined by thresholds of glycated Hb, blood glucose concentrations and such other parameters as plasma lipid levels, blood pressure… (ii) a rationale for the indications of the different treatments including lifestyle interventions and pharmacological therapies. Therefore it appears that the rationale for therapeutic strategies in type 2 diabetic patients is much more complex than limiting the objectives to “doing the right things”, i.e. to recommendations of the evidence-based medicine. In order to fulfill both patients’ and physicians’ requirements and/or willingnesses, the previous sentence should be completed and stated as “doing the right things right” [6], and the debate should be to discuss how to integrate the rationales of both objectives and indications of the different therapies while taking into account the patient’s and physician’s rationales. The purpose of the present review is to gain further insight into this major problem which conditions the success or failure of diabetes management.

Rationale for therapeutic objectives

The recommendations for adults with diabetes differ from one country to another [1]. The last standards of Medical Care as edited every year by the American Diabetes Association (ADA) [8] indicate that HbA1c should be strictly maintained below 7% when referenced to a non-diabetic range of 4.0 - 6.0% using a DCCT-based assay. Recommended preprandial glycaemic goals are set within a 90 - 130 mg/dl (5.0 - 7.2 mmol/L) range. The statements for postprandial glucose goals remain much more elusive since the ADA recommendations indicate that consideration of postprandial glucose excursions should be limited to individuals who have preprandial values within targets, but who are not meeting HbA1c goals. In such individuals postprandial values 1-2 hours after the start of a meal should be controlled and managed in order to reduce average postprandial glucose values at levels < 180 mg/dl (10 mmol/L). As HbA1c is an integrated measure of glucose exposure over daytime [9] and since both interprandial [10] and postprandial glucose concentrations [11, 12] are highly correlated with HbA1c, the current position statements on glycaemic control have been revised in order to provide the correlation between HbA1c and mean plasma glucose levels [13], both being considered as reflections of the average exposure to hyperglycaemia. This relationship indicates that a mean plasma glucose concentration of 135 mg/L corresponds to an HbA1c level of 6%. From this baseline equivalence any 35 mg/dl increment in mean plasma glucose level corresponds to a 1% increment in HbA1c level. However this relationship has been established from data of the DCCT in type 1 diabetic patients [13]. Therefore it is questionable to know whether such results can be extrapolated to non-insulin-using type 2 diabetic patients. Even though measurements of HbA1c can be considered as an excellent indicator of metabolic control over stable periods of diabetic control in patients with type 2 diabetes, this marker is not necessarily sufficient in those who require rapid therapeutic adjustments. As mean plasma glucose levels exhibit faster changes than HbA1c levels when dietary measures are started or reinforced or when pharmacological modifications of the antidiabetic drug treatment are implemented, blood glucose monitoring at several time-points over daytime can be proposed as a complementary tool for estimating the diabetic control in such situations. However it is difficult to recommend intensive regimens of blood glucose self-monitoring in type 2 diabetic patients who are not familiar with this technique that can rebut many of them. In order to solve this problem we have tested whether one given glucose value of daytime might serve as a global indicator for estimating both the quality and the safety of the metabolic control [14]. For this purpose we have used a model based on a 4-point diurnal glycaemic profile with determinations of plasma glucose concentrations at 8:00h, 11:00h, 14:00h and 17:00h.

The rationale for the timing of the 4 plasma glucose (PG) determinations was initially determined by giving a priority choice to the 2 PG values which are usually considered to reflect a real fasting state (prebreakfast PG at 8:00h) and a non-questionable postprandial period (2-h postlunch PG at
predict a HbA1c < 7% was equal or slightly higher than 90%.

In order that specificity to be optimal, i.e. in order that specificity to predict a HbA1c < 7% was equal or slightly higher than 90%, treatment success was tested. Two cut-off plasma glucose values were calculated. The first one was the best cutpoint balancing between high sensitivity and specificity and the second was calculated in order that the clinical screening for treatment success be optimal, i.e. in order that specificity to predict a HbA1c < 7% was equal or slightly higher than 90%.

The data are shown in Table I. From the analysis of these results it appears that the upper limit of normal (130 mg/dl) as defined by the ADA for preprandial PG values [8] has certainly been correctly chosen since this value is comprised between the two optimal cut-off PG values at fasting i.e 109 and 145 mg/dl (Tab I). By contrast, setting peak postprandial glucose thresholds at 10 mmol/l (180 mg/dl) as suggested by the ADA [8] could be adequate for the postprandial period since this value is comprised between the two optimal PG cut-off values at 11:00h, (164 and 200 mg/dl) but is probably too high for the postlunch period at 14:00h, a time-point where the optimal cut-off values were 126 and 164 mg/dl, respectively (Tab I). These observations raise the question whether postmeal PG thresholds should be set at levels lower than 180 mg/dl. For instance other organizations have recommended that upper target limits for postmeal PG levels should be set at 140 mg/dl (American College of Endocrinology) or at 135 mg/dl (International Diabetes Federation) [17, 18]. Such recommendations appear to be too stringent for postbreakfast periods, but are certainly appropriate at postlunch times. Even though it would be helpful to have some uniformity in guidelines around the world, our results outline the difficulty for providing an average target of postprandial glucose. Despite the lack of available strong evidence-based data it seems that achieving peak glucose levels at <180 mg/dl and at <140 mg/dl over postbreakfast and postlunch periods, respectively, might be a reasonable goal for most patients in most countries.

However the patient’s approach is somewhat different since it has been largely established in different populations of diabetic patients that despite the development of recommendations, the objective of achieving a good or fair diabetic control still remains a difficult challenge in the medical care of diabetes. For instance, in a study conducted in French patients with type 2 diabetes and managed on an ambulatory basis, only a small proportion (12.8%) exhibited a satisfactory diabetic control (HbA1c ≤ 6.5%) [19]. Similar results were observed by GADEE et al. [20] since in patients submitted to an intensified therapy intervention including both lifestyle and pharmacological reinforcements, the authors found that only 15% of the subjects achieved the treatment goals, i.e. HbA1c < 6.5%. Such data indicate clearly that the patient’s objectives are different from those of their health care providers [4]. For instance one of the main patient’s concern is to avoid hypoglycaemic episodes. In this view we have demonstrated [14] that the extended postlunch time which corresponds usually to one of the nadir of daytime [21-23] could be used as a safety marker in the management of type 2 diabetic patients, especially of those who are treated with pharmacological agents that exhibit a stimulatory effect on the insulin secretion. Therefore self-monitoring of blood glucose in the late afternoon seems to constitute an excellent approach for assessing both the quality and safety of the glycaemic control in type 2 diabetic patients [14]. This extended postlunch glucose value should be normally maintained within a 80-109 mg/dl (4.4-6.0 mmol/l) range, the lower limit being a safety indicator of hypoglycaemic risk whereas the upper ensures the quality of the diabetic control [24].

### Rationale for therapeutic indications

Appropriate strategies for treating type 2 diabetes imply first to have in mind that type 2 diabetes is a disease characterized by a progressive loss of β-cell function [25, 26] (Fig 1). The diabetes continuum from impaired glucose tolerance to clinical diabetes and further to severe insulin defects is marked by a steadily decline in the quality of glucose homeostasis with a progressive increase in both plasma glucose and HbA1c levels [27], despite the reinforcement of treatments by progressively adding mono- or multi-oral drug therapies to lifestyle recommendations and then by shifting from oral drug treatments to insulin therapy combined or not with antidiabetic oral agents. For that reason, the rationale of therapeutic indications in type 2 diabetic patients needs to keep one eye on the pathophysiology of the disease and the other eye on the indicators of diabetic control, i.e on HbA1c and plasma glucose levels.

<table>
<thead>
<tr>
<th>Time-points</th>
<th>Optimal values (mmol/L) balancing between high sensitivity and specificity (1)</th>
<th>Optimal values (mmol/L) based on specificity ≥ 90% for treatment success (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 8:00 h</td>
<td>8 (145)</td>
<td>6 (109)</td>
</tr>
<tr>
<td>At 11:00 h</td>
<td>11 (200)</td>
<td>9 (164)</td>
</tr>
<tr>
<td>At 14:00 h</td>
<td>9 (164)</td>
<td>7 (126)</td>
</tr>
<tr>
<td>At 17:00 h</td>
<td>7 (126)</td>
<td>6 (109)</td>
</tr>
</tbody>
</table>

(1) Corresponding glucose values as expressed in mg/dl are indicated between parentheses.
Pathophysiological considerations can help the physician for choosing the appropriate strategy at initiation of the treatment. At present, it is well-recognized that the glycaemic disorders as observed in type 2 diabetic patients result from 3 main metabolic abnormalities: a state of insulin resistance, a reduction in the β-cell function and an increase in the hepatic glucose production [28, 29]. These abnormalities are not constant over the time-course of the disease and their relative contributions are dependent on the stage of the diabetic state [30, 31]. At the beginning, the insulin sensitivity decreases rapidly and progresses steadily towards more severe stages of insulin resistance especially in muscle and adipose tissue [31]; the β-cell function alteration is only characterized by a loss of the early insulin secretion [32], while the hepatic glucose output remains within the normal range [29, 33]. This stage is associated with either an impaired glucose tolerance state or an isolated postprandial hyperglycaemia [34]. In such situations, lifestyle interventions [35] or pharmacological treatments with either acarbose [36] or short-acting insulin secretagogues [26], that act preferentially on postprandial glucose excursions, should normally be used as first-line therapies (Fig 1). However, in the near future, insulin sensitizers might be perhaps indicated at this stage when there exist clinical reasons to think that insulin resistance is the preponderant factor of glycaemic disorders. This is the case in those patients who exhibit an excess of body weight. Derangements of plasma glucose above 126 mg/dl at fasting are usually due first to an additional insulin sensitivity reduction that results in an insulin resistant steady state and second result from the onset of an overproduction of glucose by the liver. The development of fasting hyperglycaemia leads generally to the diagnosis of the disease (Fig 1). At this stage (Phase I of overt type 2 diabetes) pharmacological treatments aimed at reducing both insulin resistance and hepatic glucose overproduction should be prescribed. Two classes of insulin sensitizers, represented by metformin and thiazolidinediones, are available. Metformin is certainly more active on the liver than on peripheral tissues [37], whereas thiazolidinediones are probably more efficient on the peripheral glucose uptake than on the hepatic glucose output [38, 39].

When further worsening in glucose homeostasis occurs, i.e when target glycaemic goals are not achieved with insu-
lin sensitizers, the residual β-cell function is sufficiently compromised such that the quantity of insulin that can be released is insufficient to adequately control glycemia (Fig 1). At that stage (phase II) such conventional insulin-secretagogues as sulfonylureas should be prescribed in addition to insulin sensitizers [26, 40] in order to re activate the insulin secretion. Finally, at the third phase of deterioration of the residual β-cell function, all oral antidiabetic drugs become ineffective for controlling glycaemic disorders (Fig 1). Therefore an insulin therapy alone [41] or in combination with oral antidiabetic agents [42] should be initiated when a patient exhibit the so-called “oral antidiabetic drug secondary failure”, a state which is usually characterized by HbA1c levels above 8%, even with maximal doses of oral antidiabetic agents.

However the use of a pathophysiology-based strategy remains difficult in clinical practice since its implementation requires to evaluate the residual insulin secretion. At present all indexes that have been described for such evaluations are adapted for epidemiological studies or interventional trials in large populations of patients, but are not sufficiently reliable to be used at individual levels [43-45]. For that reason, decisions for initiating or completing therapeutic strategies in type 2 diabetic patients need to be made from such simple parameters as HbA1c and plasma glucose levels.

In recent years, new data have provided broader information for the on-going debate on the respective roles of the 3 components of the glucose triad: HbA1c, fasting glucose and postprandial glucose [10-13]. While many clinicians continue to emphasize fasting glucose and HbA1c to guide management, observational studies have indicated that postprandial glucose may play an equivalent role, at least [46, 47]. By using the 4-point diurnal glycaemic model, as described above, we have demonstrated that the relative contributions of postprandial and fasting hyperglycaemia to the overall diurnal hyperglycaemia are dependent on the degree of diabetic control as estimated from HbA1c levels [47]. The results as indicated in Figure 2 show that whatever was the quality of diabetic control, postprandial glucose made a substantial contribution to the overall hyperglycaemia. However when patients were divided into five groups according to quintiles of HbA1c, we found that postprandial glucose levels made the highest contribution (70%) in the lower quintile (HbA1c < 7.3%), i.e. in patients with well-to-satisfactory-controlled diabetes [47]. By contrast, fasting hyperglycaemia appeared as the main contributor of the overall hyperglycaemia in patients with poorly-controlled disease, i.e. in the 2 upper quintiles (HbA1c ≥ 9.3%). For the patients who had HbA1c levels ranging between 7.3% and 9.2%, the contribution of postprandial and fasting hyperglycaemia were approximately equivalent.

Since the contribution of postprandial hyperglycaemia to the overall hyperglycaemia is predominant in patients with HbA1c < 7.3%, first-line antidiabetic treatments or any attempt to reinforce the antidiabetic treatments in this type of patients should mainly be focused on treatments acting on postprandial glucose (Fig 3), i.e. on such oral drugs as alpha-glucosidase inhibitors [48-50], short-term insulin secretagogues [51-57], rapid insulin analogs [58, 59] and such potential interesting candidates for diabetes therapy as incretin hormones [60-62]. By contrast, in patients with HbA1c higher than 7.3%, initiation of treatments or implementation of additional therapies in order to ensure a better diabetic control should be done by using oral antidiabetic drugs such as sulfonylureas, thiazolidinediones and metformin [26, 37, 63, 64] or by prescribing insulin regimen [65, 66] aimed at reducing fasting hyperglycaemia (Fig 3) since the contribution of the later becomes progressively predominant in patients who are not fairly-controlled.

This strategy can be illustrated by two cases of newly diagnosed diabetic patients whose HbA1c are 8% and 9%, respectively. Both are treated with diet and metformin as first-line therapies. In both patients a 1% drop in HbA1c is observed, leading to HbA1c levels at 7% in the first patient and at 8% in the second one after a few weeks of treatment. In order to achieve a target of less than 6.5% [17, 18], it is suggested to choose the second-line therapy among either alpha-glucosidase inhibitors or glinides in the first patient who has HbA1c level within the range where contributions of postprandial glucose are predominant. By contrast, addition of sulfonylureas or thiazolidinediones would be more adapted to the second patient who remains at HbA1c levels where fasting glucose is making the greater contribution.

When two- or three-drug oral treatments are not sufficient to reach the recommended targets [8, 17, 18], a wide panel [65-67] of insulin regimens has been proposed: (i) addition of premeal insulin boluses to oral agents [59, 68]; (ii) once-daily injections of intermediate-acting or long-acting insulin at bedtime or before breakfast in combination or not with oral antidiabetic agents [69-71]; (iii) twice-daily combinations of intermediate- and rapid-acting insulin [59]; and more complex protocols such as basal-bolus regimens [72]. At present, it is difficult to know which protocol provides the best results for achieving or approaching normoglycaemia since there is no study that has compared the various insulin regimens as a whole. There are many reasons to think that the discrepancies as observed between the different studies that have compared one given regimen with another are simply due to the fact that the comparative trials have been made in different types of patients at various stages of the disease [66].

Our data can be helpful for selecting the most physiological insulin regimen when type 2 diabetic patients exhibit secondary failure to oral antidiabetic drugs, i.e. when metabolic control remains insufficient even with maximal doses of oral agents. As above mentioned [47], we have demonstrated, first that postprandial glucose contributes more than
Figure 2
Relative contributions of postprandial (white columns) and fasting (black columns) hyperglycaemia (%) to the overall diurnal hyperglycaemia. Variations with quintiles of HbA1c (reference 47). Postprandial glucose makes the major contribution (70%) in the lower quintile (HbA1c < 7.3%). Fasting glucose is the main contributor in the 2 upper quintiles (HbA1c ≥ 9.3%). The contributions of postprandial and fasting glucose are approximately equivalent for the patients with HbA1c ranging between 7.3 and 9.2% (From Diabetes Care 2003, vol. 26: 881-5. Copyright © 2003 American Diabetes Association. Reprinted with permission from The American Diabetes Association).

Figure 3
Rationale for therapeutic strategies based on the results of the study cited as reference [47]. First or second line antidiabetic treatments should be aimed at reducing either postprandial glycaemic excursions or fasting hyperglycaemia according to whether HbA1c levels are found respectively below or above a cut-off value of 7.3%.
fasting glucose to the overall hyperglycaemia in patients with HbA1c < 7.3%, second that contribution of postprandial and fasting glucose are approximately equal in patients with HbA1c ranging between 7.3% and 9.2%, and third that fasting glucose becomes the major contributor when HbA1c levels are ≥ 9.3%. Furthermore in most patients treated with oral antidiabetic drugs, mid-morning, i.e. postbreakfast, glucose excursions are usually more pronounced than after the other meals [46].

As a consequence of these results, the following strategies can be suggested for initiating or reinforcing an insulin therapy in type 2 diabetic patients. In those who have HbA1c between 6.5% and 7.3% with maximal doses of oral antidiabetic drugs, a once-daily single injection of a rapid insulin analog before breakfast can be sufficient for reducing HbA1c levels below 6.5%. As postprandial and fasting glucose contribute equally to the overall hyperglycaemia in patients with HbA1c levels between 7.3% and 9.2%, several strategies can be chosen in such situations. The most classical is to use a twice-daily combination of intermediate- and rapid-acting insulins, the injections being made before breakfast and at bedtime [59, 73]. Another alternative is to start the treatments progressively with predinner or bedtime long-acting insulin analogs and to further increase the dose up to achieving HbA1c < 6.5%. However many patients with type 2 diabetes require large insulin doses (> 1 unit per kg) to achieve such targets. Therefore if a patient is not well-controlled with a once-daily reasonable dose (less than 1 unit per kg of ideal body weight) of long-acting insulin analog, it is likely better to add boluses of rapid insulin analogs to the basal insulin therapy rather than to pursue insulin adjustments by increasing indefinitely the basal dose. In this case, insulin boluses should be injected first before breakfast, i.e. before the meal that usually gives rise to the highest postprandial glucose excursions [73]. When HbA1c levels are ≥ 9.3% despite maximal doses of oral antidiabetic drugs, the residual insulin secretion is generally too deteriorated and the glycaemic disorders are usually so marked that it is difficult to expect an optimal glycaemic control by using long-acting insulin analogs once a day. In this case, the insulin treatment should be started by using twice-daily injections of premix insulin preparations and, preferentially, by using basal-bolus regimens.

In conclusion it appears that tailoring the therapeutic strategies rather than proposing “ready-to-wear” protocols remains the best method for managing type 2 diabetic patients. This observation can be applied to both treatments with oral antidiabetic agents and insulin regimens. The goals of such treatments is to achieve the targets as early as possible through the time-course of the disease, to implement more physiologic regimens and to increase the patient’s compliance. However it is important to outline that such goals are rarely achieved in clinical practice since the patient’s adherence to recommendations is a common barrier to effective diabetic control. For instance even when such ambitious insulin regimens as basal-bolus protocols are recommended for a given patient it is, in many situations, necessary for the physician to negotiate with the patient a less ambitious insulin regimen consisting of a once-daily insulin injection. Returning to the introduction of this article, balancing the patient’s and physician’s rationales remains in most cases the main basis for the management of type 2 diabetic patients.

References


69. Cusi K, Cunningham GR, Comstock JP. Safety and efficacy of normalizing fasting glucose with bedtime NPH insulin alone in NIDDM. Diabetes Care, 1995, 18, 843-51.


ERRATUM

An error occurred in the n° 6/2004 issue Diabetes & Metabolism on page 545 of the article by MP Matta et al. “What are capillary blood ketone levels in type 1 diabetic patients using CSII in normal conditions of insulin delivery?”. Figure 2 was printed twice (the first graph was an error). The correct figures with their appropriate captions are given below.

The editors apologize for the inconvenience this caused for the authors and readers.