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Simulating Glycosylated Hemoglobin (HbA_{1c}) Levels in Diabetes Using an Interactive Educational Virtual Diabetes Patient Simulator

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ABSTRACT

In 1996, an interactive educational diabetes simulator called AIDA was released without charge on the Internet as a noncommercial contribution to continuing diabetes education. Over the past 5 years, over 100,000 people have visited the AIDA Web pages at http://www.2aida.org and over 25,000 copies of the program have been downloaded free-of-charge. Previous Diabetes Information Technology & WebWatch columns have described various user feedback comments about the AIDA software. This current column overviews the method applied for modelling glycosylated hemoglobin (HbA_{1c}) levels within an updated version of the AIDA program (v4.3). The result seems to be a useful and novel addition to the diabetes simulations, providing a parameter with which most users will be familiar, and able to relate. It is expected that the HbA_{1c} indicator may prove useful in enhancing the educational value of the diabetes simulations.

INTRODUCTION

THE AIDA program is a freeware piece of computer software that permits the simulation of plasma insulin and blood glucose profiles for demonstration, teaching, and self-learning purposes. It has been made freely available, without charge, on the World Wide Web as a noncommercial contribution to continuing diabetes education. In the 5 years since its Internet launch over 100,000 people have visited the AIDA website—http://www.2aida.org—and over 25,000 copies of the program have been downloaded, *gratis*.

The AIDA software has been overviewed previously elsewhere in this journal.[1–3] Briefly it incorporates a compartmental model that describes glucose–insulin interaction in patients completely lacking endogenous insulin secretion (i.e., type 1 diabetic patients). The model contains a single extracellular glucose compartment into which glucose enters via both intestinal absorption and hepatic glucose production. The model also contains separate compartments for plasma and "active" insulin,[4,5] the latter being responsible for glycemic control while insulin is removed from the former by hepatic degradation.

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The AIDA software comes with 40 educational case scenarios as standard, each of which represents a snapshot of the metabolic status of a typical patient with respect to type 1 diabetes. It is easy for users to add or create further case scenarios, as required.

EXAMPLE SIMULATION WITH AIDA v4.0

Figure 1a shows a baseline simulation for one of these 40 example case scenarios using AIDA v4.0. The only information that the user is provided about this patient is what follows: "This woman is on a four times daily insulin regimen, taking three 'shots' of a short-acting preparation before each of the main meals, with an intermediate-acting preparation before going to bed. She injects using an insulin pen—but has not yet managed to stabilise her glycemic control. She tends to eat a lot more towards the end of the day and so finds herself going markedly hyperglycemic overnight. How might you control these extremely raised blood sugar levels during the night, without sending her 'hypo' as a result?"[6]

The upper graph shows the simulated blood glucose data for this case, while the lower graph provides a composite display of information regarding insulin and carbohydrate intake. The distribution of the meals eaten can also be seen in this panel along with the four times daily regular (short-acting; Velosulin) and intermediate-acting (Insulatard) insulin regimen. Superimposed on these graphs are predicted steady-state blood glucose and plasma insulin profiles as calculated by the AIDA model.

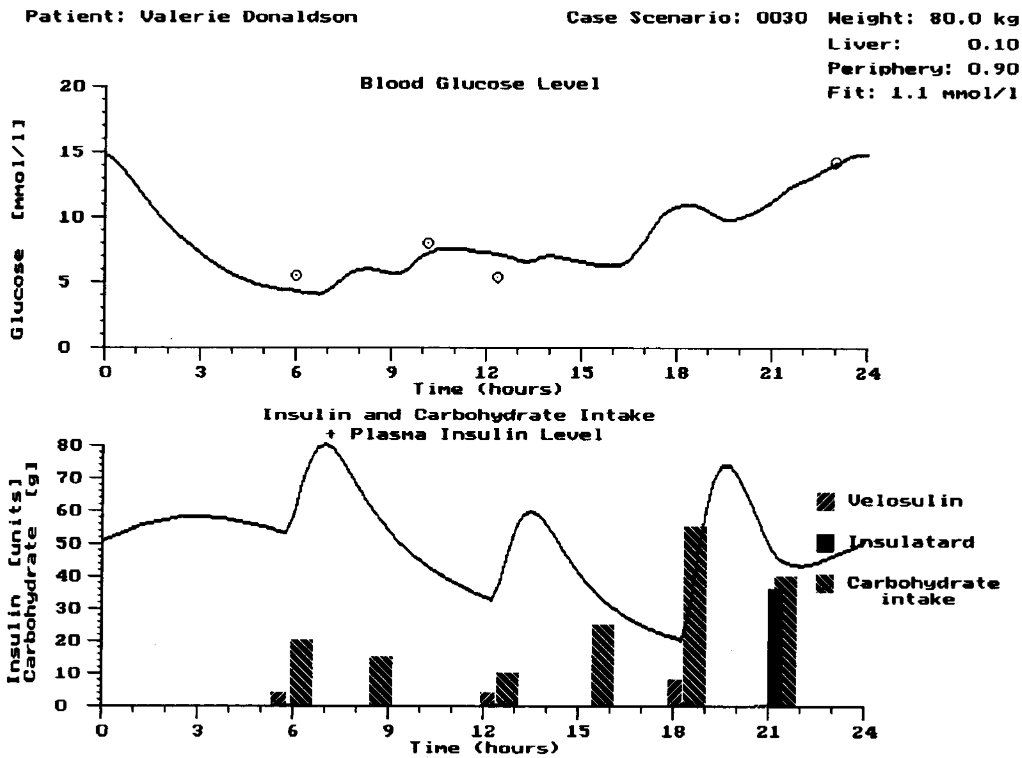
Having performed such a baseline simulation users can then alter any of the input variables to simulate the glycemic effects of such changes. For example, a user could simulate what would happen to a hypothetical patient's blood glucose profile if the bedtime Insulatard dose was increased by two units, or the injection time moved earlier, or the bedtime snack shifted later, or the carbohydrate content of supper decreased by 10 g. A user could transfer the patient to Humulin M3 in place of the previous short- and intermediate-acting preparations, or perhaps try the case scenario with a different "pen regimen" taking a longer-acting insulin preparation at night. The list of possibilities is endless—a near infinite number of simulations can be performed with AIDA.

As can be seen in Figure 1A, the "virtual diabetic patient" in this example tends to have quite high blood glucose levels overnight. Figure 1B shows a simulation of one possible way of reducing this hyperglycemia; the effect of moving the intermediate-acting (Insulatard) injection from bedtime to before supper and decreasing the bedtime snack from 40 g of carbohydrate to 20 g being shown. While these adjustments do not bring the overnight blood glucose levels fully under control—they do substantially reduce the night time hyperglycemia that was previously occurring.[6]

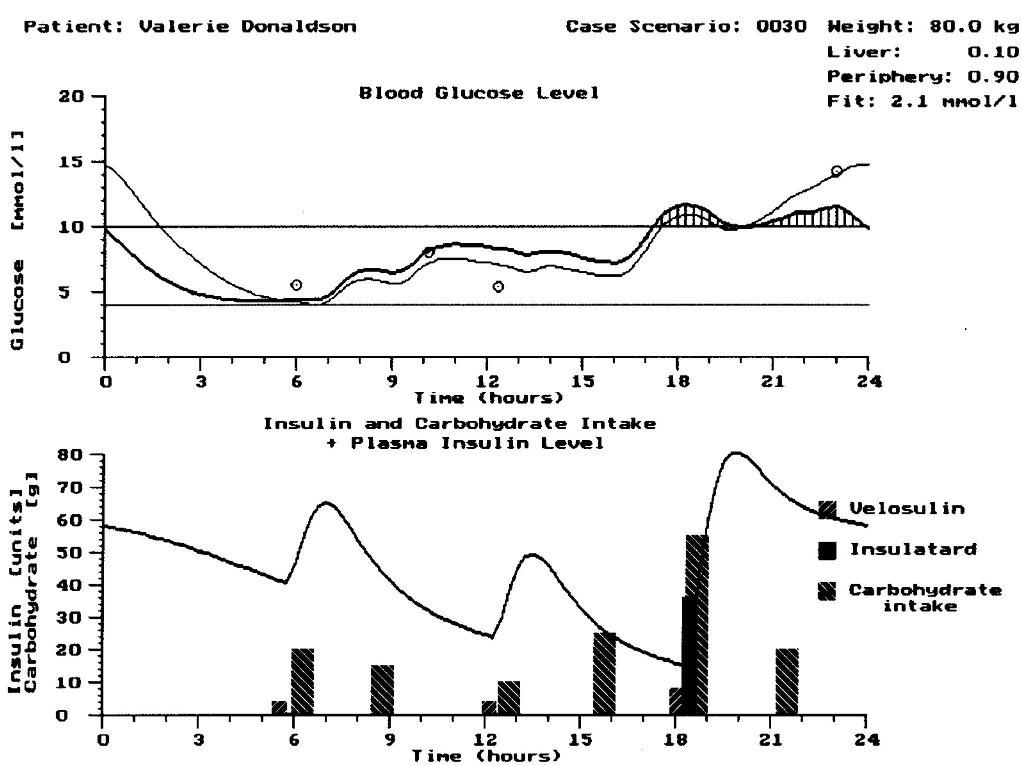
The AIDA software can simulate a wide variety of other insulin dosage and dietary adjustments. However it should be stressed that the purpose of AIDA is to create a learning environment for communicating and training intuitive thinking when dealing with insulin dosage, dietary and lifestyle adjustments. The software is not meant for individual patient glycemic prediction or therapy planning.[1] In this respect, AIDA appears most of use for

FIG. 1. (A) Baseline simulation for "Valerie Donaldson" using the AIDA v4.0 diabetes simulation software. This virtual diabetic patient is on a four times daily insulin regimen, taking three shots of a short-acting preparation (Velosulin) before each of the main meals, with an intermediate-acting preparation (Insulatard) before going to bed. She injects using an insulin pen—but has not yet managed to stabilize her glycemic control. She tends to eat a lot more towards the end of the day and so finds herself going markedly hyperglycemic overnight. (Modified from Tatti and Lehmann[6]). **(B)** Shows a simulation using AIDA v4.0 in which the bedtime intermediate-acting (Insulatard) insulin injection has been moved to before supper and the bedtime snack has been decreased from 40 g of carbohydrate to 20 g. The current simulation is given by the bold (dark) curve while the previous simulation is represented by the less dark line. While the adjustments do not bring the overnight blood glucose level fully under control, they do substantially reduce the nighttime hyperglycemia. A user-definable normoglycemic range (set at 4–10 mmol/L [72–180 mg/dL]) is shown superimposed. Further practical examples of the use of the AIDA software can be found elsewhere in the literature,[1,7,8] and on the Web at http://www.2aida.org (Modified from Tatti and Lehmann[6].)

A


Patient: Valerie Donaldson
Case Scenario: 0030
Weight: 80.0 kg
Liver: 0.10
Periphery: 0.90
Fit: 1.1 mmol/l
Blood Glucose Level
Glucose [mmol/l]
Time (hours)
Insulin and Carbohydrate Intake
+ Plasma Insulin Level
Insulin [units]
Carbohydrate [g]
Velosulin
Insulatard
Carbohydrate intake

B


Patient: Valerie Donaldson
Case Scenario: 0030
Weight: 80.0 kg
Liver: 0.10
Periphery: 0.90
Fit: 2.1 mmol/l
Blood Glucose Level
Glucose [mmol/l]
Time (hours)
Insulin and Carbohydrate Intake
+ Plasma Insulin Level
Insulin [units]
Carbohydrate [g]
Velosulin
Insulatard
Carbohydrate intake

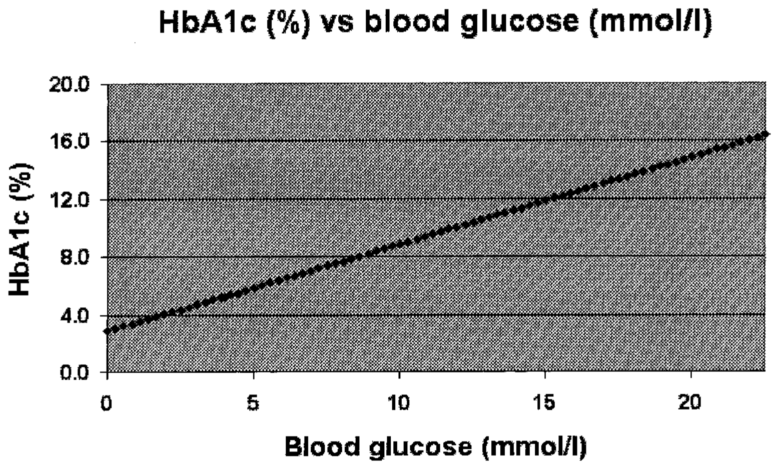


FIG. 2. Relationship between HbA_{1c} and mean blood glucose levels based on the formula given in Equation 1.

recreating clinical situations—rather than trying to predict best outcome.[6] Further examples of the application of AIDA as an educational tool can be found elsewhere in the literature,[1,7,8] and a full demonstration can be viewed on-line at, or downloaded without charge from, the AIDA website (http://www.2aida.org). User comments about the AIDA software (from a wide range of end users—e.g. patients, their relatives, health-care professionals and students) can also be found elsewhere in the literature,[2,3,7,9,10] as well as on the Internet at http://www.2aida.org/reviews

This current Diabetes Information Technology & WebWatch column overviews the method applied for modelling glycosylated hemoglobin (HbA_{1c}) levels within an updated version of AIDA (v4.3).

HbA_{1c} BACKGROUND

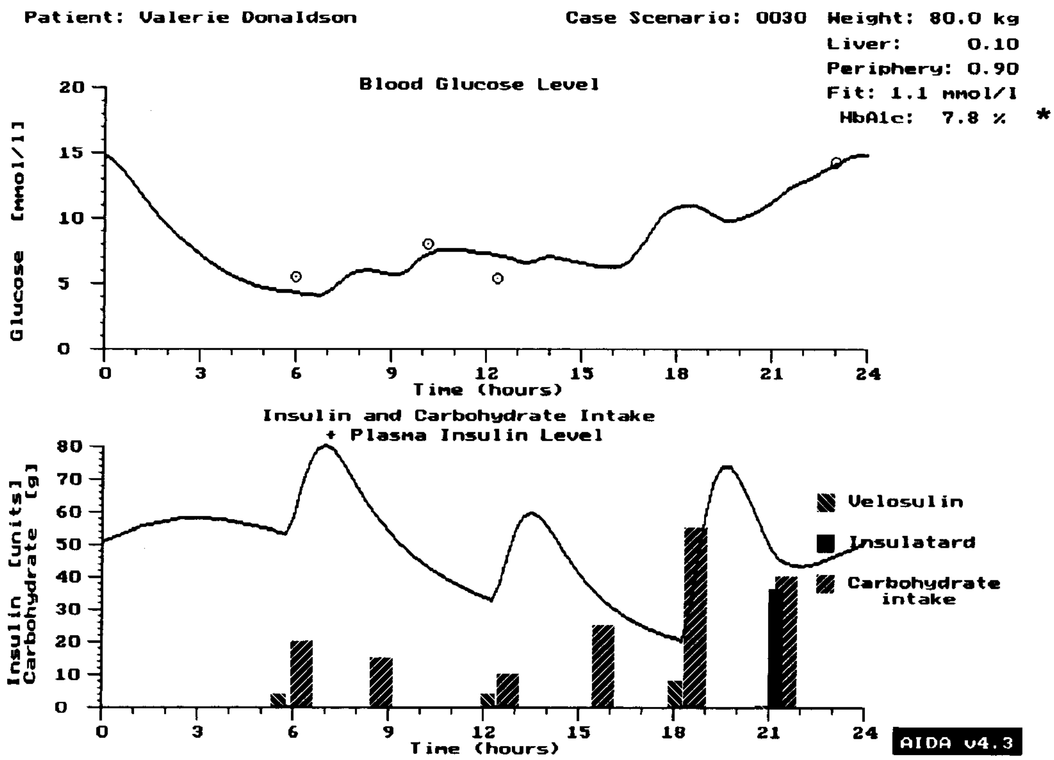
Glycosylated hemoglobin (HbA_{1c}) levels are widely regarded as a marker of medium-term blood glucose control and are extensively applied clinically as an indicator of a patient's average or integrated glycemic control over the preceding 2–3 months. Diabetologists, endocrinologists, diabetes specialist nurses and diabetes educators use assessments of HbA_{1c} levels to confirm overall blood glucose control; this test having the advantage of not being dependent on patient self-reported blood glucose data.

Furthermore, since the Diabetes Control and Complications Trial (DCCT),[11] the benefits of tight blood glucose control have become much more apparent and so more proactive patients also now use HbA_{1c} levels directly themselves as an indicator of their own glycemic control.

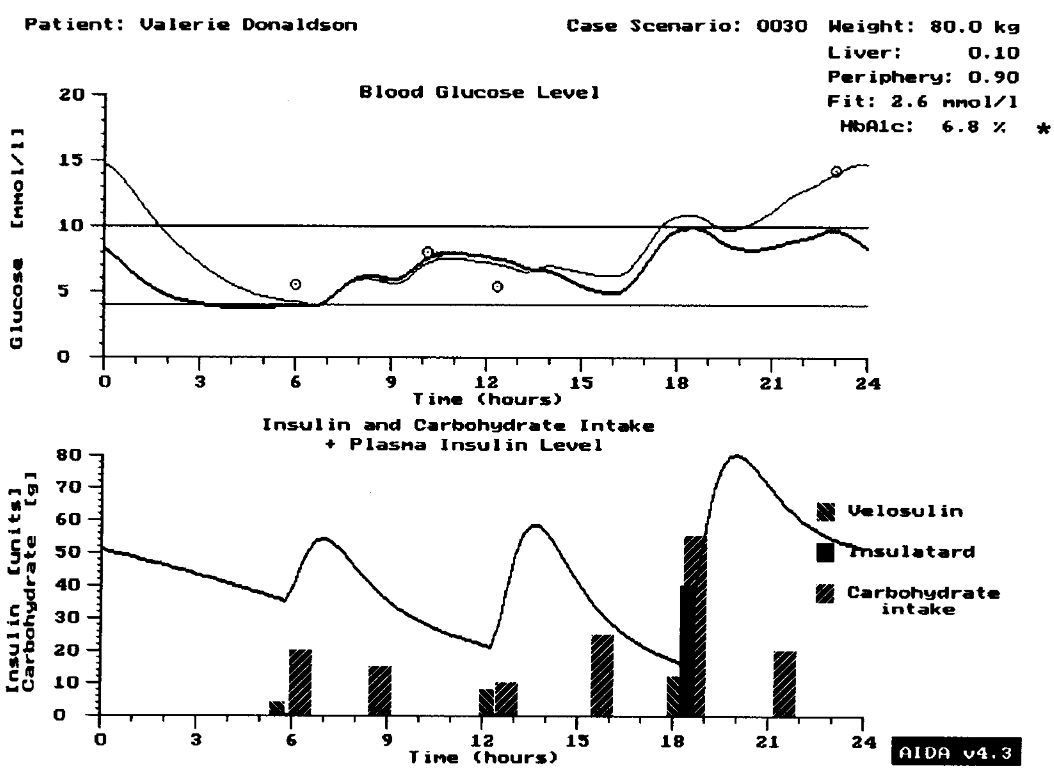
For all these reasons, it was felt that it would be useful to include an estimate or simulation of HbA_{1c} levels within the AIDA program. This would offer patients, their relatives, students and health-care professionals an indication of what the HbA_{1c} level might be if the simulated blood glucose profile was maintained for 2–3 months. It should be stressed that such HbA_{1c}

FIG. 3. **(A)** Baseline 24-h diabetes simulation from the AIDA system (shown in Figure 1A), but now simulated using AIDA v4.3. As can be seen the system predicts that if the simulated blood glucose control was maintained in the medium term, this would give a predicted glycosylated hemoglobin (HbA_{1c}) level of 7.8% (shown in the top right corner of the display*). (**B**) Demonstrates how, by adjusting the insulin and dietary regimen, it is possible to develop an educational therapy plan which can yield improved glycemic control (using the same case scenario as shown in Figure 3A). The most recent simulation is given by the bold (dark) curve, while the previous simulation is represented by the less dark line. Furthermore, a user-definable normoglycemic range (set at 4–10 mmol/L [72–180 mg/dL]) is shown superimposed. As can be seen, the adjustments lead to the previously raised overnight blood glucose level being brought more fully under control. Longer term this would also lead to a substantial improvement in the predicted glycosylated hemoglobin (HbA_{1c}) level (6.8%)—shown in the top right corner of the display*.

A


Patient: Valerie Donaldson
Case Scenario: 0030
Height: 80.0 kg
Liver: 0.10
Periphery: 0.90
Fit: 1.1 mmol/l
HbA1c: 7.8 %
*
Blood Glucose Level
Glucose [mmol/l]
Time (hours)
Insulin and Carbohydrate Intake
+ Plasma Insulin Level
Insulin [units]
Carbohydrate [g]
Velosulin
Insulatard
Carbohydrate intake
AIDA v4.3

B


Patient: Valerie Donaldson
Case Scenario: 0030
Height: 80.0 kg
Liver: 0.10
Periphery: 0.90
Fit: 2.6 mmol/l
HbA1c: 6.8 %
*
Blood Glucose Level
Glucose [mmol/l]
Time (hours)
Insulin and Carbohydrate Intake
+ Plasma Insulin Level
Insulin [units]
Carbohydrate [g]
Velosulin
Insulatard
Carbohydrate intake
AIDA v4.3

level estimations—like AIDA's main blood glucose simulations—are only intended for educational/teaching, self-learning or demonstration purposes, and not for individual patient prediction or therapy planning.[12]

SIMULATING HbA_{1c} LEVELS

The approach adopted to model HbA_{1c} levels within AIDA v4.3, using blood glucose data, is based on a relation first described by Nathan et al.[13] The Nathan formula relates measured HbA_{1c} levels to mean blood glucose (calculated based on patient self-monitoring blood glucose [SMBG] values). The formula applied within AIDA v4.3 is based on this approach—and is similar also to that described by Svendsen et al.[14]—but was modified slightly by inspection to provide a relationship between mean blood glucose and HbA_{1c} that would be suitable for computer-based simulation, and which would also be clinically realistic for as wide a range of simulated case scenarios as possible.[12]

For the AIDA simulations, the mean blood glucose was taken as the average (arithmetic mean) of the 96 simulated blood glucose data points during the 24-h period (one data point is produced by AIDA for every 15 min of the simulated day[5]). The formula then applied to calculate the HbA_{1c} level for the current day's simulation is provided by:

$$HbA_{1c} = (MBG + 86)/30 \quad (1)$$

with mean blood glucose (MBG) given in units of mg/dL (1 mmol/L of glucose = 18 mg/dL).[12]

Figure 2 shows mean blood glucose values and the associated HbA_{1c} levels using this approach, demonstrating the near linear relationship which this model assumes between HbA_{1c} and blood glucose over a wide range of blood glucose values.

Figure 3A shows the baseline simulation for "Valerie Donaldson" from Figure 1A—but now simulated using AIDA v4.3. As can be seen the system predicts that if the simulated blood glucose control was maintained in the medium term, this would give a predicted HbA_{1c} level of 7.8%. Figure 3B shows, using the same case scenario, how by adjusting the insulin and dietary regimen it is possible to develop an educational therapy plan that can yield improved glycemic control. As can be seen, as well as decreasing the previously raised blood glucose level overnight, longer term this leads to a substantial reduction in the predicted HbA_{1c} level (6.8%).

EVALUATING AIDA

Work has been commenced by Dr. Tatti and colleagues[6,15] to formally evaluate the educational utility of AIDA v4.3 in small group teaching sessions. These lessons generally involve six patients with diabetes and a teacher, or facilitator, who actually interacts with the computer. Such an approach avoids the need for patients themselves to be computer literate, and circumvents any requirement for patients to go through a learning curve to find out how to use the AIDA software.

These AIDA lessons have highlighted how useful it can be to have different components of an AIDA diabetes simulation displayed for different patients to monitor. In this respect, giving each participant a role seems to be particularly important for such lessons.[16] For instance the different simulated glucose fluxes within AIDA (net hepatic glucose balance, peripheral glucose uptake, glucose absorption from the gut, and renal urinary glucose excretion) plus blood glucose and plasma insulin levels can each be monitored by a different person, increasing their individual involvement.[16] In a similar way, one of the participants can also keep track of the simulated HbA_{1c} values during the course of a lesson.

This parameter is particularly relevant as it is a number to which most people with diabetes will be able to easily relate (having much experience of visits to their clinic where their HbA_{1c} level will have been discussed). Similarly health-care professionals will also be familiar with such values.

Therefore the inclusion of HbA_{1c} levels within AIDA seems to provide a useful "additional dimension" to the diabetes simulations, particularly during such small group diabetes teaching sessions (personal communication, Dr. Patrizio Tatti, Marino, Rome, Italy).

DISCUSSION

A new, novel feature has been added to the AIDA diabetes simulator by the inclusion of estimated HbA_{1c} levels for the diabetes simulations. AIDA v4.3 was first released for beta testing during July 2000—and then went fully live on the Internet for downloading in August 2000. Since then, the HbA_{1c} simulations incorporated within AIDA v4.3 seem to have been well received—judging from beta tester[12] and general user feedback comments.

However, while intuitively the benefits of the whole interactive educational diabetes simulation approach may seem self-evident, it is stressed that formal large-scale evaluation studies are still required, as for any other medical intervention, to demonstrate a definite clinical utility for the use of such software. In this respect preliminary, independent, randomised controlled trial (RCT) pilot study results involving a small number of patients with diabetes have been encouraging.[15] It is hoped that more healthcare professionals may become interested over time in teaching in their own clinics/centers using this novel educational tool, as well as possibly getting involved in more formally testing out the software in an RCT setting.

SYSTEM AVAILABILITY

AIDA v4.3 can be freely downloaded, without charge, from the Internet from http://www.2aida.org on the World Wide Web. The program runs on IBM PC or compatible 80386/80486/Pentium-based machines and requires approximately 3 Mb of hard disk storage space. AIDA can also be used on Apple Macintosh computers running PC emulation software such as Virtual PC or SoftWindows. Furthermore, a web-based version of the AIDA diabetes simulator, AIDA online, can also be accessed directly at http://www.2aida.org/online via the Internet. AIDA online allows diabetes simulations to be run and displayed in a standard web browser window from any type of computer (PC, Apple Mac, Unix workstation, WebTV, NT server) provided it has an Internet connection and a graphical display. No downloads or local installation are required to use AIDA online. People who wish to be automatically informed about updates and enhancements to the AIDA diabetes software range can subscribe (for free) to the AIDA registration/announcement list by sending a blank email note to: subscribe@2aida.org

Any readers who might be interested in collaborating by applying the standardized randomised controlled trial (RCT) protocol[6,15] themselves in an evaluation of AIDA in their own units for clinician/specialist nurse/educator-led patient teaching sessions are invited to contact the author. Further information about the evaluation of AIDA for patient use can be found at http://www.2aida.org/evaluate on the web.

FURTHER TOPICS

If you would like to suggest further topics or websites for future Diabetes Information Technology & WebWatch columns, please email information—with a brief description of the site or suggestion—to Dr. E.D. Lehmann: info-www@2aida.org (please write Diabetes WebWatch in the subject line). You can also fax information to: (503) 218-0828, quoting Diabetes Information Technology & WebWatch.

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