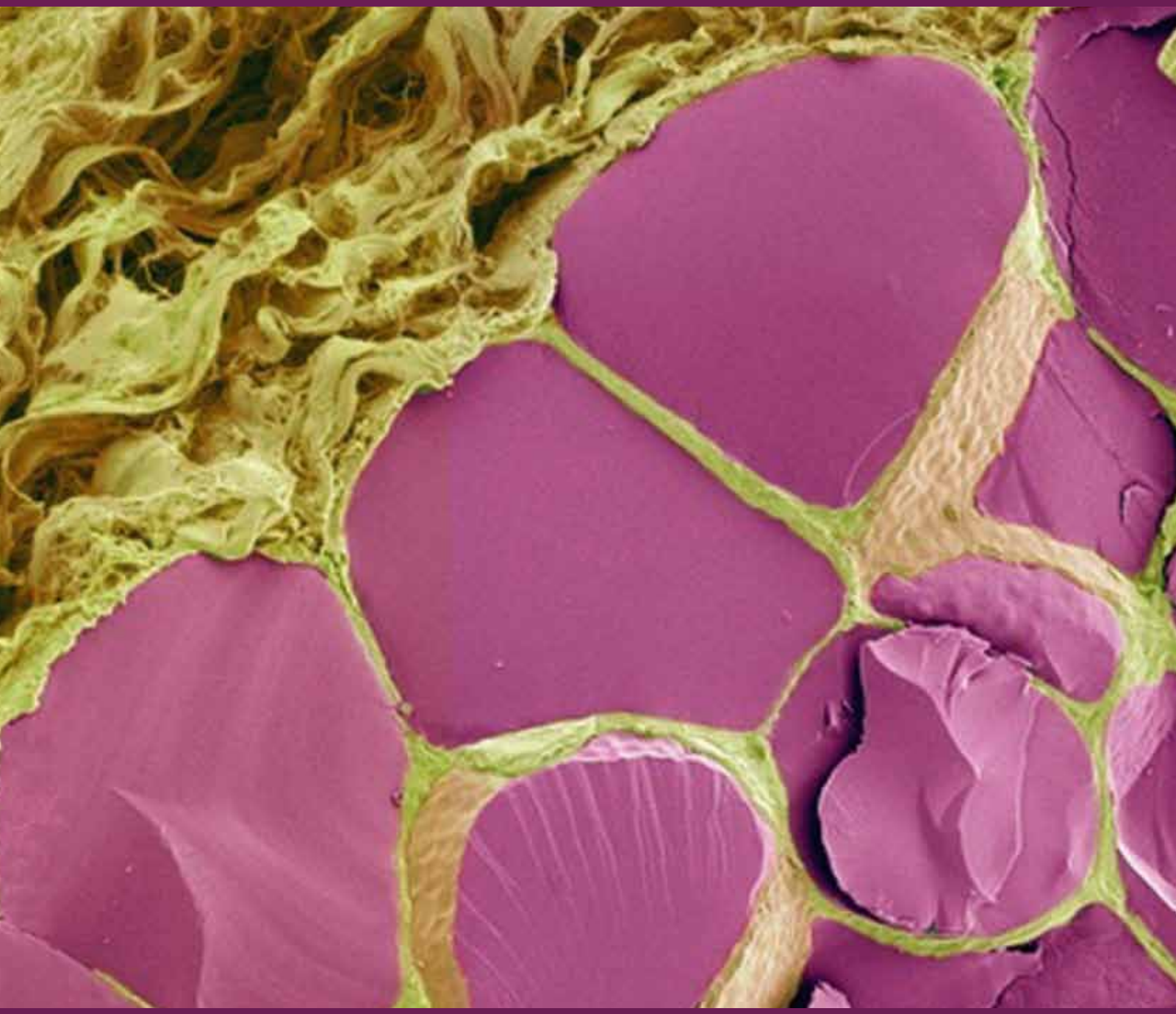
International Journal of Endocrinology

Application of Technology in Endocrine Disease

Guest Editors: Patrizio Tatti, Eldon D. Lehmann, Annabel E. Barber, Desiderio Passali, and Felice Strollo



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Editorial Board

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2014, Article ID 715029, 3 pages
http://dx.doi.org/10.1155/2014/715029

Editorial

Application of Technology in Endocrine Disease

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Received 24 December 2013; Accepted 24 December 2013; Published 12 February 2014

We live in a period of rapid change, in which many new technologies appear and are diffused through medical meetings, the Internet, specialized journals, the lay press, and media. While these innovations may bring a substantial improvement to the quality of care, sometimes, due to commercial pressures, technology can enter the market without adequate evidence of true benefit and without an analysis of the cost/benefit ratio. The converse is also true. Other potentially useful technologies can be underestimated due to insufficient commercial interest preventing further investment and development.

The present issue presents a selection of papers about the application of newer technologies in endocrinology. There have been numerous Special Issues devoted to the important topic of the application of information technology in clinical diabetes care [1–12], but to our best knowledge no attempts have been made at compiling a special issue regarding the application of technology in endocrinology.

The paper "*B-Flow twinkling sign in preoperative evaluation of cervical lymph nodes in patients with papillary thyroid carcinoma*" by G. Napolitano et al., from the Department of Health Science, University of Molise, Contrada Tappino, Campobasso, Italy, describes a new technique, B-flow imaging (BFI), to evaluate the presence of metastatic disease in lymph nodes. The authors report 99.7% specificity and 80.9% sensitivity for this technique which may be helpful in the preoperative planning of the intervention, prognostic staging, and individual therapy selection for patients.

The paper "*How to estimate fat mass in overweight and obese subjects*" by L. M. Donini et al., from the Medical Physiopathology Division, Food Science and Endocrinology Section, Food Science and Human Nutrition Research Unit, Experimental Medicine Department, Sapienza University of Rome, Italy, is of value to advance the understanding of the pathophysiology of obesity. This paper helps to make clear that body mass index (BMI), at the present state of our knowledge, is not more than a cursory evaluation, and not so useful to understand the pathophysiology and individualize the most appropriate treatment strategy. At the same time the report highlights the role of the other available techniques, including dual energy X-ray absorptiometry (DXA), body impedance analysis (BIA), and even the simple waist circumference (W) measurement. It is suggested that the widespread adoption of low-cost methods like BIA and W, in fact, could considerably help clinicians.

The paper "*Peripheral arterial tonometry to measure the effects of vardenafil on sympathetic tone in men with lifelong premature ejaculation*" by D. Francomano et al., from the Department of Experimental Medicine, Section of Medical Pathophysiology, Sapienza University of Rome, Italy, describes the use of peripheral arterial tonometry (PAT) to study the role of adrenergic overtone in men with lifelong premature ejaculation. This technique, coupled with intravaginal ejaculatory latency time (IELT), demonstrates a role of adrenergic hyperactivity, which can be reduced

by the use of vardenafil on demand. This may be a helpful contribution to future research into this problem.

The remaining papers in the special issue focus on diabetes.

The paper "*Dynamic interactive educational diabetes simulations using the world wide web: an experience of more than 15 years with AIDA online*" by E. D. Lehmann et al., from Imperial College, University of London, UK, describes the development of a web-based version of the widely available downloadable http://www.2aida.org/ AIDA educational simulator of glucose-insulin interaction in diabetes. This utilizes a server-based architecture with HTML FORM commands to submit numerical data from a web-browser client to a remote web server. AIDA online, located on a remote server at http://www.2aida.net/, passes the received data through Perl scripts which interactively produce 24-hour insulin and glucose simulations. AIDA online allows users to modify the insulin regimen and diet of 40 different prestored "virtual diabetic patients," on the Internet, or create new "patients" with user-generated regimens. Multiple simulations can be run, with graphical results viewed via a standard web-browser window. One of the relative strengths of AIDA online is that being totally Internet based; it can operate from any computer, anywhere, provided it has an Internet connection and a graphical display. This has led to widespread usage of the online simulator. To date, over 645,000 diabetes simulations have been run at AIDA online, from all over the world.

The remaining papers in this special issue deal with a nutritional algorithm developed by a group of experts that should gain wider acceptance. The algorithm supports the use of nutritional supplements in diabetes. This is a critical point because it is known that the diabetic population has subclinical or clinical malnutrition, correlated with the degree of hyperglycemia, the duration of the disease, and the medications used [13, 14].

This algorithm has a high degree of flexibility and the two papers in this issue show its applicability to different populations and dietary patterns. Transculturalization, as mentioned in the title, relies on the identification of appropriate, flexible guidance, which is available in the form of clinical practice guidelines (CPG). These guidelines, once reviewed for relevance and applicability by international experts, are abstracted and simplified in content and then condensed into a usable format. This process was applied to CPG in diabetes from the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and other international organizations. The use of this technique should help dealing with an epidemic that could affect more that 300 million people in the world in the coming years, causing an unsustainable social and economic burden. The numbers are staggering. The world prevalence of diabetes is approximately 6.6% and in some countries exceeds 10%. Total financial liabilities related to the disease exceed US$370 billion globally [15].

Complicating matters are various cultural, clinical, and financial issues that prevent simple solutions and mandate an individual approach to patient care. Despite stemming from this same cultural and ideological root, the final two papers in this issue have different scope and focus.

The paper "*Transcultural diabetes nutrition algorithm: a Malaysian application*" by Z. Hussein et al., from the Department of Medicine, Hospital Putrajaya Pusat Pentadbiran Kerajaan Persekutuan, Putrajaya, Malaysia, describes a comprehensive management strategy to try and improve glycaemic control, which includes medical nutrition therapy (MNT). This report is mostly tailored to the needs of a population with a different standard of diabetes treatment and an Eastern diet, and may represent a paradigm for other populations with similar characteristics. The authors highlight that evidence-based recommendations for diabetes-specific therapeutic diets are available internationally. However, Asian patients with type 2 diabetes mellitus (T2D), including Malaysians, have unique disease characteristics and risk factors, as well as cultural and lifestyle dissimilarities, which may render international guidelines and recommendations less applicable and/or difficult to implement. With these thoughts in mind, a transcultural Diabetes Nutrition Algorithm (tDNA) was developed to account for cultural differences in lifestyle, diet, and genetic factors. The initial evidence-based global tDNA template was designed for simplicity, flexibility, and cultural modification. This paper reports the Malaysian adaptation of the tDNA, which takes into account the epidemiological, physiological, cultural, and lifestyle factors unique to Malaysia, as well as the local guidelines and recommendations.

The other paper dealing with diabetes in the special issue, "*The transcultural diabetes nutrition algorithm: a Canadian perspective*" by R. Gougeon et al., from Crabtree Nutrition Laboratories, McGill University Health Centre/Royal Victoria Hospital, Montreal, QC Canada, describes the Canadian version of the transcultural Diabetes Nutrition Algorithm which supports and targets behavioural changes to improve nutritional quality and to promote regular daily physical activity consistent with the Canadian Diabetes Association's CPG, as well as supporting the concomitant management of obesity, hypertension, dyslipidemia, and dysglycaemia in primary care. This report is evidently addressed to a Western population with high sanitary standard and deals mostly with the topic of the Glycemic Index.

It has not been possible to cover all relevant technologies in this special issue. As promising as all these reports are, all novel technologies must be evaluated, and beneficial effects scientifically proven. A future special issue may usefully address the formal validation and evaluation of such new technologies. Also diabetes/endocrine technology topics that could usefully be addressed include, but are not limited to the following.

Endocrine

(i) New technologies for the diagnosis of thyroid nodules (e.g., the role of 3D ultrasound).

(ii) New technologies for the treatment of diabetic neuropathy (e.g., electrical stimulation for gastrointestinal paresis).

(iii) New diagnostic, noninvasive techniques for neuroendocrine tumors.

(iv) Evaluation of nanotechnologies.

(v) New technologies for the treatment of obesity.

Diabetes

(i) Evaluation of the technology for the treatment of diabetic foot ulcers.

(ii) Diagnosis and treatment of obstructive sleep apnoea and impact on metabolic disorders.

(iii) Meters with artificial intelligence for improved dosing recommendations and also artificial intelligence modelling, and educational and advisory software.

(iv) Blood glucose meters, including invasive and noninvasive devices.

(v) Communication protocols and systems for implementing a robust and effective telediabetes infrastructure.

(vi) New developments in continuous glucose monitoring with special focus on new sensor technologies.

(vii) Insulin delivery systems, including pump technology.

(viii) New tools and software for the "closure of the loop" in type 1 diabetes.

(ix) Methods which combine a continuous BGL sensor, insulin pump, and control algorithms for creating an artificial pancreas.

(x) The role of applications (apps) for smart phones and handheld devices in ambulatory diabetes care.

(xi) Diabetes management systems for transition from home to hospital and from hospital to home.

Acknowledgments

We, the guest editors, are grateful to all the reviewers who took time to assess the submitted papers. Their hard work has contributed greatly to ensuring that the final published papers have conformed to the high standards expected of this journal. We also thank the authors who have revised and improved their papers in the light of suggestions from the referees, resulting in clearer publications for journal readers.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2014, Article ID 151068, 12 pages
http://dx.doi.org/10.1155/2014/151068

Research Article

The Transcultural Diabetes Nutrition Algorithm: A Canadian Perspective

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Received 19 June 2013; Accepted 8 December 2013; Published 16 January 2014

Academic Editor: Annabel E. Barber

The Transcultural Diabetes Nutrition Algorithm (tDNA) is a clinical tool designed to facilitate implementation of therapeutic lifestyle recommendations for people with or at risk for type 2 diabetes. Cultural adaptation of evidence-based clinical practice guidelines (CPG) recommendations is essential to address varied patient populations within and among diverse regions worldwide. The Canadian version of tDNA supports and targets behavioural changes to improve nutritional quality and to promote regular daily physical activity consistent with Canadian Diabetes Association CPG, as well as channelling the concomitant management of obesity, hypertension, dyslipidemia, and dysglycaemia in primary care. Assessing glycaemic index (GI) (the ranking of foods by effects on postprandial blood glucose levels) and glycaemic load (GL) (the product of mean GI and the total carbohydrate content of a meal) will be a central part of the Canadian tDNA and complement nutrition therapy by facilitating glycaemic control using specific food selections. This component can also enhance other metabolic interventions, such as reducing the need for antihyperglycaemic medication and improving the effectiveness of weight loss programs. This tDNA strategy will be adapted to the cultural specificities of the Canadian population and incorporated into the tDNA validation methodology.

1. Introduction

Type 2 diabetes (T2D) is a chronic disease with hyperglycaemia as its characteristic feature, resulting from defects in insulin secretion and/or insulin action [1]. The disorder is associated with adiposity, particularly central abdominal adiposity [2], and multiple metabolic abnormalities that increase the risk of mortality from cardiovascular diseases (CVD) by two- to fourfold [3], the leading cause of death [4], shortening life by 5 to 15 years. In Canada, the prevalence of T2D is increasing at epidemic proportions, affecting more than three million Canadians, with 6 million others at elevated risk of developing the disease. Of particular concern are non-Caucasians who comprise more than 25% of the Canadian population (Figure 1) and are highly susceptible to T2D when adopting a Western lifestyle. Diabetes affects economic prosperity, costing the Canadian healthcare system $12.2 billion annually, a number that is projected to rise to $16.9 billion by 2020 [4].

Canadian census data show that more than 200 tongues are spoken in Canada, 60 being aboriginal. The mother tongue reported by 6.8 million Canadians (21% of the population) differs from English or French, the two official languages of the country. Another 4.7 million Canadians speak a language at home by order of prevalence: Punjabi, Chinese, Spanish, Italian, German, Cantonese, Tagalog, Arabic, and Mandarin (Statistic Canada). Challenged by this situation, the Canadian Diabetes Association (CDA) has begun to tailor its nutrition therapy tool, Just the Basics, to the cultural and personal tastes of individuals of varied ethnicities who have T2D (http://www.diabetes.ca/diabetes-and-you/nutrition/just-basics/Accessed January 24, 2013).

Through the support of the CDA, clinical practice guidelines (CPG) for nutrition therapy [4] were published in 2003 and 2008 and updated in 2013, to provide evidence-based recommendations for healthy food choices and lifestyles that improve glycaemic, metabolic, and weight control. Included in these guidelines is the recommendation to replace high-glycaemic index (GI) carbohydrate foods by low GI carbohydrate foods in mixed meals because low GI intake is associated with a lower glycaemic response and improvements in A1C [4]. A multitude of cultures and diverse geographic locations across Canada have challenged the effectiveness of nutrition therapy guidelines to promote sustained healthy eating habits in the diabetic population. In response, Mechanick et al. [5] have designed a global tDNA template for the optimization of nutritional care in prediabetes and T2D on a global scale with the intention that provided information will suit geographic and ethnocultural factors for individualization and implementation at regional and local levels worldwide. It is anticipated that tDNA will increase awareness of the benefits of dietary behaviour changes, which can be better achieved when recommended dietary patterns and food choices accommodate regional differences in genetic factors, food availability and preferences, lifestyles, and cultures. Thereafter, a task force was selected among Canadian health care experts in diabetes and nutrition to adapt the global tDNA template to Canadian mores, norms and population demographics (Figure 1). These experts, who are authors of this paper, are also key regional stakeholders in the implementation of the CDA CPG.

2. Methods

The process of modifying the tDNA to Canada involved a group of experts who reviewed and considered revising all of the topics outlined in the global template [5]. These reviewers also defined a vision for the Canadian tDNA and considered factors unique to the Canadian population and the guidelines and recommendations put forth by CDA in their revision, that is, ethnocultural lifestyle input; individual risk stratification with tables on classification by body composition; general recommendations on physical activity and healthy eating, with the related tables providing physical activity and nutritional guidelines; specific recommendations for obesity, hypertension, and dyslipidemia; criteria for bariatric surgery; description of an antihypertensive diet and other dietary patterns; and the glyceamic indices and load of common foods. During development of the Canadian version of tDNA, the task force established that their shared vision of the tDNA was to enable sustainable healthy lifestyle behaviours amongst healthcare providers and people with diabetes. It became evident that primary care providers would best be implicated in promoting a healthy lifestyle in their patients with T2D if they believed in its positive impact on glycaemic and metabolic control to the point that they themselves adapt and sustain a healthy lifestyle, the latter made achievable through resources and tools within the Canadian tDNA. There was also a need for defining simple assessment measures for lifestyle behaviour that put Canadians at risk of developing T2D,

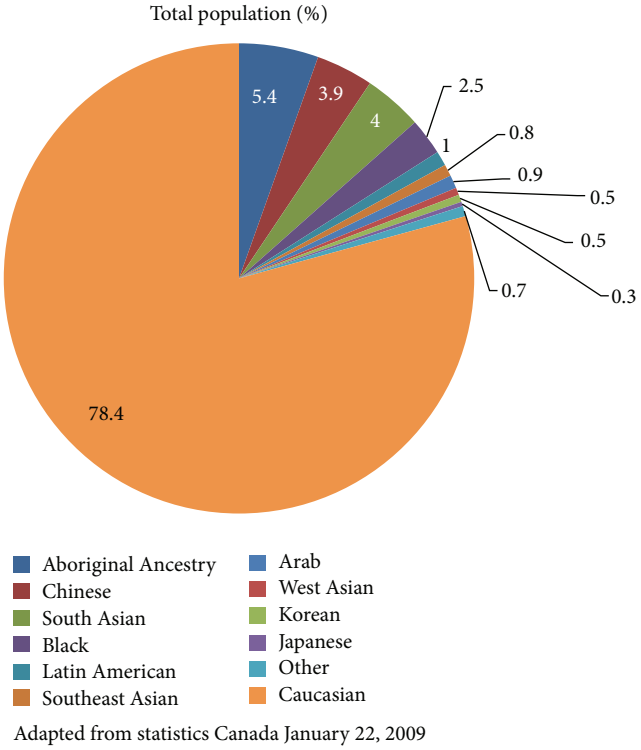

Figure 1: Canadian Population Demographics.

or associated complications, and also measures of lifestyle behavioural change.

Changes brought to the global tDNA template and different points of significance are highlighted in the results section of this report.

3. Results

As a result of our revision, the modified algorithm focused on the process of adapting healthy behaviours rather than weight loss; behaviour leading to improved diet and regular physical activity became the interventional target. Emphasis was placed also on increasing patient and provider awareness of the process of change and of improvements to lifestyle behaviour over time. The resultant objective of tDNA Canada became support of behavioural change through simple and effective dietary and physical activity advice at the primary care level. Additionally, a quick, simple, pragmatic, validated questionnaire to assess combined work and leisure time physical activity shown to be associated with mortality in a prospective population study was found to be feasible for use in clinical practice [6]. The algorithm was modified to better assist physicians in improving lifestyle habits of Canadian patients who present with diverse ethnic backgrounds, based on the existing Canadian guidelines for prevention and treatment of T2D. The global tDNA [5] adapted to fit current Canadian guidelines is presented in Figure 2.

As in the global tDNA, initially, ethnooncultural identification and geographic location are assessed concurrently with individual risk stratification, the latter described by Yusuf et al. [3]. In Canada, however, the general recommendations for counselling on care, physical activity, and healthy eating habits conform to CDA 2013 CPG [4] and are for all patients independent of the magnitude of their risk. Furthermore, the recommendations are extended to address patients' obesity, hypertension, dyslipidemia, and/or dysglycaemia with specific dietary approaches and metabolic targets. In all cases, follow-up evaluation is recommended at 1–3 months initially and at 3–6 months ongoing. The Canadian tDNA, like other cultural versions, includes and refers to tables that convey additional information adapted according to national or regional recommendations, in this case, Canadian CPGs. Examples are given in Tables 1–5.

Specific to the Canadian tDNA, Table 1 presents diabetes nutrition therapy in a manner that facilitates the selection of a strategy based on individualized targeted outcomes. Different dietary patterns evaluated in T2D populations, popular weight loss approaches, specific foods, varied macronutrient distributions, and meal replacements are listed with their specific effects on hemoglobin A1c (A1C), weight, blood pressure, lipid risk factors, inflammatory markers, hypoglycemia, and other advantages and disadvantages related to their impact on nutrients, gastrointestinal tract, or renal load. This approach is also promoted in the CDA CPGs [4].

Certain approaches from the global tDNA [5] were adapted to the many ethnicities in the Canadian population. Table 2 is an example that shows a list of common foods and their GI. Other modifications to the global tDNA were based on the recommendations from CDA CPG [4]. For example, Table 3 summarizes those for physical activity in the management of diabetes [4] and Table 4 the Dietary Approaches to Stop Hypertension (DASH) in diabetes adapted according to CDA CPG. Table 5 summarizes CDA CPG for bariatric surgery, which may be considered in patients with T2D and a BMI $\geq 35\,kg/m^2$ when lifestyle interventions have failed to achieve and maintain weight goals. Minimally invasive surgical approaches should be used by a well-established surgical team that includes experts in nutritional and psychological support. Bariatric surgery is now becoming an accepted option for the management of T2D and has been shown to be superior to medical management for its treatment [6]. Presently there is no overall consensus as to what kind of procedure is most effective, be it malabsorptive, restrictive, or combination surgery.

4. Discussion

Adopting healthy behaviour rather than only attaining sustained weight loss was defined as the main objective of the Canadian tDNA. This objective is consistent with CDA CPG, which recommend that self-management education incorporating knowledge and skill development, as well as cognitive behavioural interventions, should be implemented for people with diabetes (CDA CPG 2008) [4]. To optimize change, messages regarding nutrition recommendations and lifestyle modification should accommodate a person's culture [7]. The ethnic mosaic of the Canadian population provides a rich testing ground for learning how to adapt educational

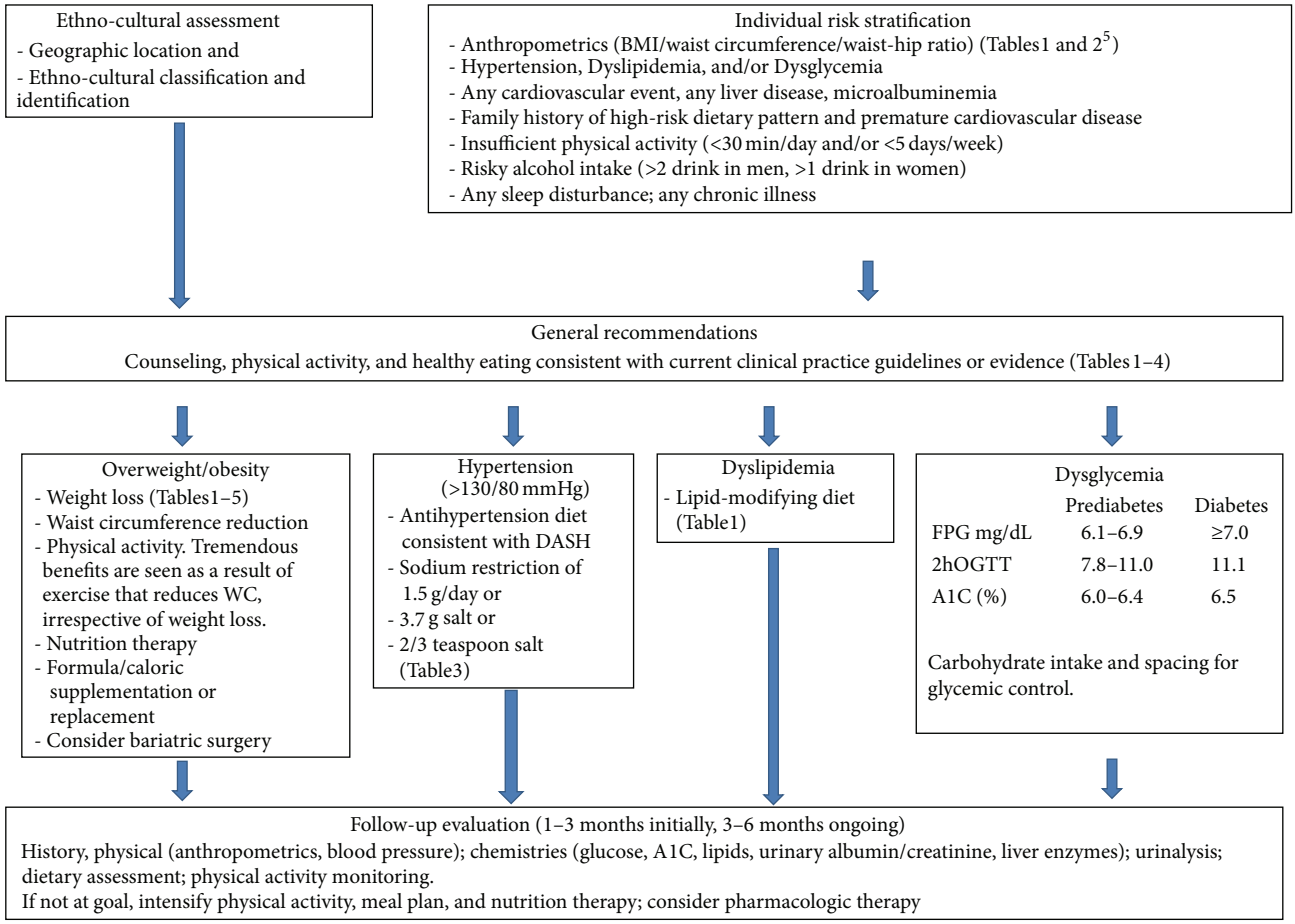

Figure 2: Canadian Transcultural Diabetes Nutrition Algorithm (tDNA) for prediabetes and type 2 diabetes.

tools to various cultures. At this time, the dietary education tool, Just the Basics, has been created for South Asian, Latin American, and the Aboriginal communities in Canada, using a consultative process within the respective cultural groups [8]. These tools were developed by reaching out to the ethnic communities through professional and community group networks to identify persons who could contribute to the adaptation of the educational materials. People with diabetes and their family members, as well as Aboriginal, Latin American, or South Asian dietitians, other dietitians experienced in working with cultural groups, and an advisory group of dietitians with expertise in diabetes management, participated in focus group discussions and pilot-tested the tools. The focus groups explored topics such as dietary patterns practiced in Canada, meaningful expressions of portion sizes, cultural holidays and values, preferred teaching and learning methods, classification of foods into food groups, and barriers to education [9]. Just the Basics provides clear initial messages to patients about healthy eating and physical activity for diabetes prevention and management, using culturally distinct foods and languages. Although these culturally adapted tools for the South Asian, Latin American, and Aboriginal populations need ongoing assessment of their ability to promote sustained behaviour change associated with optimal diabetes control, they provide the groundwork for creating tools tailored to other high-risk populations.

The Canadian tDNA is to promote low-GI carbohydrate foods within a healthy dietary pattern. GI provides an assessment of the quality of carbohydrate-containing foods based on their effect on postprandial blood glucose [10]. To decrease the glycaemic response to dietary intake, low-GI carbohydrate foods can replace high-GI carbohydrate foods. More detailed lists can be found in the International Tables of Glycaemic Index and Glycaemic Load Values [11]. Meta-analyses of controlled dietary trials of replacing high-GI carbohydrates with low-GI carbohydrates in the context of mixed meals have shown clinically significant improvements in glycaemic control over 2 weeks to 6 months in people with type 1 diabetes (T1D) or T2D [12–14]. Replacing high-GI carbohydrates with low-GI carbohydrates in mixed meals also has been shown to reduce total cholesterol over 2 to 24 weeks in people with and without diabetes [13], postprandial glycaemia and high-sensitivity C-reactive protein (hsCRP) over 1 year in people with T2D [15], and the number of hypoglycaemic events over 24 to 52 weeks in adults and children with T1D [14]. Similar benefits have been shown when low-GI diets are compared with different control diets. Dietary advice to consume a low-GI diet compared with

Table 1: Dietary strategies for diabetes nutrition therapies.

Interventions	HbA1c %	Wgt	BP	Lipid Risk Factors						Other Advantages	Disadvantage
				LDL-C	Apo-B	HDL-C	TG	Non-HDL-C	Ratio*		
Dietary patterns											
Low-GI/GL	↓ 0.3–0.5%					↑			↓	↓CRP, ↓Hypos, ↓Rx	
Veg diets	↓ 0.3–0.5%	↓	↔	↓				↓**			↓Vitamin B_{12}
Mediter diets	↓ 0.3–0.5%		↓			↑	↓		↓	↓CRP, ↓FPG, ↓Rx, ↓CV events	
DASH	↓ 0.5–1.0%	↓	↓	↓		↑				↓CRP	
Wgt loss diets											
Atkins	↔	↓				↑			↓		↑LDL, ↓micN, ↓adh
Protein power	↓ 0.5–1.0%	↓				↑	↓				↓micN, ↓adh, ↑RL
Omish		↓					↓		↓		↔FPG, ↓adh
Wgt watchers		↓							↓		↔FPG, ↓adh
Zone		↓							↓		↔FPG, ↓adh, ↑RL
Specific foods											
Dietary	↓ 0.3–0.5%			↓							GI side effects
Tree nuts	↓<0.3%			↓	↓		↓		↓		
Macronutrient											
Hi-CHO hi fiber	↓ 0.3–0.5%			↓							↓HDL, GI side effects
Hi-MUFA	↓<0.3%						↓				
Lo-CHO	↔						↓			Preserve lean mass	↓micN, ↑RL
Hi-protein	↔		↓				↓				↓micN, ↑RL
LC-N3-PUFAs	↔		↔	↔		↔	↓				CH_3–Hg exposure, EI
Meal replacements	↓ 0.3–0.5%	↓									Temporary intervention

Adapted from [4].

Glycaemic index (GI); monounsaturated fatty acids (MUFA); long-chain n-3 polyunsaturated fatty acids (LC-N3-PUFAs); Dietary Approaches to Stop Hypertension (DASH); weight (Wgt); blood pressure (BP); total cholesterol (TC); LDL cholesterol (LDL-C); HDL cholesterol (HDL-C); triglycerides (TG); non-HDL cholesterol (non-HDL-C); apolipoprotein-B (apo-B); fasting plasma glucose (FPG); C reactive protein (CRP); hypos (hypoglycaemic episodes); oral antihyperglycaemic agents (Rx); Mediterranean (Mediter); vegetarian (veg); adherence (adh); micronutrient (micN); renal load (RL); methyl-Hg (M-Hg); environmental impact (EI); gastrointestinal (GI).

*Lipid ratios include TC : HDL-C, LDL-C : HDL-C, and apo-B : apo-A1 (apolipoprotein-A1).

**Adjusted for medication changes.

Table 2: Common carbohydrate foods and their glyceamic indices (GI).

Food	GI
Cereals	
Biscuits	69
Cornflakes	81
Instant oatmeal	79
Rice congee	78
Rolled oatmeal	55
Millet porridge	67
Muesli	57
Common items	
Brown rice	68
Barley	28
Chapati	52
Corn	52
Corn tortilla	46
Couscous	65
Multigrain bread	53
Rice noodles	53
Spaghetti	49
Udon noodles	55
Wheat roti	62
White rice	73
White wheat bread	75
Whole wheat bread	74
Dairy products	
Ice cream	51
Skim milk	37
Soy milk	37
Rice milk	86
Whole milk	39
Yogurt	41
Fruits	
Apple	36
Banana	51
Dates	42
Mango	51
Orange	43
Peach	43
Pineapple	59
Watermelon	76
Legumes	
Chickpeas	28
Kidney beans	24
Lentils	32
Soy beans	16
Snacks	
Chocolate	40
Popcorn	65
Potato chips	56
Rice crackers	87
Soda	59
Vegetables	
Potato, boiled	78
Potato, fried	63
Potato, instant mash	87
Sweet potato	63
Carrots, boiled	39
Pumpkin, boiled	64
Plantain	55
Taro, boiled	53
Vegetable soup	48

Glyceamic index (GI) ranks carbohydrates according to their ability to raise blood glucose levels, with the following cut-offs: low-GI ≤ 55, medium-GI 56–69, and high-GI ≥ 70. Adapted from Mechanick et al. [5].

Table 3: Canadian Diabetes Association Physical Activity Recommendations for diabetes management.

(1) Patients with diabetes should accumulate a minimum of 150 minutes of moderate-to-vigorous intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise.
(2) People with diabetes (including elderly people) should also be encouraged to perform resistance exercise 3 times per week, in addition to aerobic exercise. Initial instruction and periodic supervision by an exercise specialist are recommended.
(3) An exercise ECG stress test should be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to undertake exercise more vigorous than brisk walking (Grade D LOE).

Adapted from the Canadian Diabetes Association Clinical Practice Guidelines Expert Committee.
Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes.2008;32 (suppl 1):S1-S201.

a high-cereal fibre diet in people with T2D has been shown to improve glycaemic control and HDL cholesterol over 6 months [16]. In another trial in which dietary pulses (e.g., beans, chickpeas, lentils, and peas) were emphasized to lower the GI of the diet, significant improvements in glycaemic control and blood pressure were reported over 3 months [17]. A low-GI diet compared with a low-carbohydrate, high mono-unsaturated fat diet, has been shown to improve beta-cell function over one year in people with T2D [18]. Moreover, low-GI diets compared with dietary advice based on the nutrition recommendations of varied diabetes associations have been shown to have advantages. For example, (a) dietary advice to consume a low-GI diet improved glycaemic control over 3 months in Japanese people with impaired glucose tolerance (IGT) or T2D when compared with the nutritional recommendations of the Japanese Diabetes Society [19], and (b) the need for antihyperglycaemic medications over one year was decreased in people with poorly controlled T2D when compared with the nutritional recommendations of the American Diabetes Association [20].

Table 4: Dietary Approaches to Stop Hypertension (DASH) for diabetes nutrition therapy.

Food groups	Servings per day			Serving size
	1600 kcal/day	2600 kcal/day	3600 kcal/day	
Grains	6	10-11	12-13	1 slice bread; 1 oz dry cereal; 1/2 cup cooked rice, pasta, cereal
Vegetables	3-4	5-6	6	1 cup raw leafy; 1/2 cup cut raw or cooked
Fruits	4	5-6	6	1 medium piece; 1/4 cup dried; 1/2 cup fresh, frozen, canned; 1/2 fruit juice
Low/nonfat dairy	2-3	3	3-4	1 cup milk or yogurt; 1.5 oz cheese
Lean meat, poultry, and fish	3–6	6	6–9	1 oz cooked, meats, fish; 1 egg
Nuts, seeds, and legumes	3/week	1	1	1/3 cup nuts; 2 tbsp peanut butter; 2 tbsp seeds; 1/2 cup cooked legumes
Fats and Oils	2	3	4	1 tsp soft margarine (nonhydrogenated); 1 tsp veg oil; 1 tbsp mayonnaise; 2 tbsp salad dressing
Sweets, added sugars	0	≤2	≤2	1 tbsp sugar; 1 tbsp jelly or jam; 1/2 cup sorbet, gelatin; 1 cup lemonade

Adapted from the Canadian Diabetes Association.
Canadian Diabetes Association, DASH diet summary, accessed at http://www.diabetes.ca/documents/about-diabetes/DASH_Diet_Summary.pdf on 11, 01, 2012.

Table 5: CDA's Clinical Practice Guidelines Suggestions for bariatric surgery.

(1) Adults with clinically severe obesity (BMI $\geq 40\ kg/m^2$ or $\geq 35\ kg/m^2$ with severe comorbid disease) may be considered for bariatric surgery when lifestyle intervention is inadequate to achieve healthy weight goals.

(2) Bariatric surgery in adolescents should be limited to exceptional cases and performed only by experienced teams.

(3) A minimally invasive approach should be considered for weight loss surgery when an appropriately trained surgical team and appropriate resources are available in the operating theatre.

The product of mean GI and total carbohydrate intake is known as glycaemic load (GL) and has also been explored in therapeutic studies. A low GL was found to improve the efficiency of weight loss advice over 4 weeks [21] and improve risk factors for coronary heart disease including high-density lipoprotein cholesterol (HDL-C), triglycerides, and C-reactive protein (CRP) over 4 weeks to 6 months [21–23] compared with a low-fat diet, in young overweight and obese adults without diabetes. A low GL diet has also been shown to have advantages for coronary heart disease in a systematic review and meta-analysis of prospective cohort studies [24] and for diabetes management itself in different analyses of the Nurses Health Study [25, 26]. The success of weight loss strategies using low-GL diets appears to be related to the degree of insulin resistance as assessed by the 30-min postprandial insulin loads [23].

The Canadian tDNA integrates and emphasizes physical activity. The recommendations are based on evidence from prospective observational studies showing that individuals who perform such levels of activity have reduced risk of premature total and cardiovascular mortality as well as reduced risk of developing T2D [27–30]. The relationship between level of physical activity and mortality/morbidity is semi-independent from the concomitant influence of well-established CVD risk factors such as lipids, blood pressure, diabetes, and smoking [28, 31]. Thus, even among individuals who are abdominally obese with other features of the metabolic syndrome, those who reported being very active exhibit a 50% reduction in coronary risk compared to similarly matched individuals who reported being very sedentary [32]. These results show that regular physical activity not only reduces the risk of developing T2D [33, 34] but also provides clinical benefits among patients with T2D or with the features of the metabolic syndrome. Some studies have used cardiorespiratory fitness (CRF) as an objective physiological marker of participation in vigorous physical activity and have shown that a high level of CRF is associated with a substantially reduced risk of premature mortality, CVD mortality, and CVD morbidity [35–37]. The substantial cardioprotection conferred by a high level of CRF has even been reported among patients with T2D [38]. For instance, Church and colleagues [38] have shown that overweight/obese but fit patients with diabetes were at lower mortality risk than nonobese but unfit patients with diabetes. All the above observations clearly highlight the critical importance of recommending regular physical activity and better cardiorespiratory fitness in patients with T2D. In addition, regular physical activity produces substantial benefits in high-risk individuals with prediabetes, reducing their risk of converting to T2D and developing detrimental cardiovascular outcomes [33, 34].

In addition to aerobic training, moderate-to-high intensity resistance training is beneficial in order to maintain lean body mass, particularly in the aging population of patients with T2D [39–41]. As there is a dose-response relationship between level of physical activity and clinical outcomes, guidelines from the Canadian Society of Exercise Physiology

have emphasized the greater health benefits that are expected from a greater volume of weekly physical activity [27]. In line with the Canadian recommendations, it is herein proposed to reduce the time devoted to sedentary behaviour, to increase the level of moderate-to-vigorous physical activities and exercise, and also to perform resistance exercise training for all major muscle groups. Unfortunately, accelerometer data obtained from the 2007–2009 Canadian Health Measures Survey have revealed that only about 15% of Canadian adults accumulate 150 minutes of moderate-to-vigorous physical activity per week, and this statistic is probably even worse among patients with T2D [8]. Because lifestyle modification is a cornerstone of the management of cardiometabolic risk in patients with T2D, it is proposed that efforts and resources should be devoted to help patients afflicted by a societal metabolic disease recalibrate their nutritional and physical activity/exercise habits.

Furthermore, interventions such as motivational interviewing, which is a specific way of helping people recognize and formulate an action plan to address specific lifestyle changes, can be useful for clients who are reluctant or ambivalent about changing behaviour [42]. The strategies used for motivational interviewing are more supportive than confrontational, and the overall goal is to increase a person's intrinsic motivation to change rather than having change imposed by healthcare practitioners [42]. Motivational interviewing, when administered by general practitioners who received training in this treatment modality, has been shown to positively affect attitudes for change in people with T2D [42].

Indeed, it must be remembered that patients find adherence to appropriate dietary patterns exceptionally difficult to maintain consistently and that recommended dietary patterns are not well followed. Furthermore, in the past, diabetes nutrition therapy has emphasized individual macronutrient and micronutrient components and their adequacy. Although studying individual nutrients may lead to an understanding of important biological mechanisms, it has been recognized more recently that providing practical advice or identifing strategies on how people eat is not sufficient. Rather, assessment of dietary patterns offers a comprehensive and complementary approach to apply nutritional principles to "real life" [43] and to identify and validate those that support optimal glycaemic control in people with T2D, regardless of extant pharmacological management. Such assessment has been suggested to be important for advancement of efficacious and effective clinical and public health interventions [43]. Analyses of food patterns would include the possibility that interactions or synergistic effects among individual foods or nutrients are examined [43].

Studies reviewed by Kris-Etherton et al. provide evidence that food-based approaches and dietary patterns reduce risk for cardiovascular disease [44]. For instance, the Breast Cancer Detection Demonstration Project [45] evaluated 42,254 women and demonstrated that all-cause mortality decreased by quartile of recommended food score. The recommended food score was the sum of the number of foods as recommended by current dietary guidelines (fruits, vegetables, whole grains, low-fat dairy and lean meats, and poultry) that were consumed. The age-adjusted relative risk for all-cause mortality in persons in the upper quartile was 0.69 (95% confidence interval 0.61–0.78); for the second and third quartiles the relative risks were 0.82 (95% confidence interval 0.73–0.92) and 0.71 (95% confidence interval 0.62–0.81), respectively. The study demonstrated that as the quality of the dietary pattern improved (on the basis of current dietary guidelines) an associated health benefit was gained. Other reviewed [44] dietary patterns associated with lower or higher risk of chronic disease (resp.) include the Prudent Pattern compared to the Western Pattern, dietary patterns identified in the Nurse's Health Study and the Physician's Health Study. The Prudent Pattern was characterized by a higher intake of vegetables, fruits, legumes, whole grains, and fish while the Western Pattern by a higher intake of processed meat, red meat, butter, high-fat dairy products, eggs, and refined grains. Relative risk for coronary heart disease (CHD) decreased from the lowest to highest quintiles of Prudent Pattern score (relative risk 1.0 and 0.70, 95% confidence interval 0.56–0.86; $P = 0.0009$ for trend), whereas CHD risk increased with increasing quintile for Western Pattern score (relative risk 1.0 and 1.64, 95% confidence interval 1.24–2.17; $P < 0.0001$ for trend). These analyses may provide useful evidence for making specific food-based dietary recommendations within the context of the existing dietary guidelines; however, their impact as part of clinical treatment for diabetes has not been studied.

The Dietary Approaches to Stop Hypertension (DASH) Study demonstrated that a dietary pattern high in fruits, vegetables, and low-fat dairy products, coupled with sodium restriction, reduced hypertension and, consequently, is included here as a dietary intervention for hypertensive patients with T2D (Table 1). Moreover, the Lyon Diet Heart Study showed that dietary patterns have a marked beneficial impact on important risk factors for CVD, as well as morbidity and mortality end-points. These results support the potential positive implications for clinicians and patients of using a dietary pattern approach that emphasizes "what to eat" (i.e., plant-based foods, selected unsaturated fats) rather than "what to restrict" (i.e., total fat, saturated fat, sodium, and sugars) and give more explicit instructions that can be put into practice over the long term. Because evidence continues to emerge about the importance of regularly including particular foods (i.e., nuts, legumes, and vegetables) relative to the risk of developing diabetes and/or other chronic diseases, especially CVD, the Canadian tDNA makes reference to these items (Table 1) in its algorithm. However, background food intake patterns are not usually reported in studies in which one or two foods/nutrients are manipulated, and this information is required in order to understand the potential for interactions between foods and nutrients. Furthermore, it is unlikely that emphasizing a single food or set of foods (e.g., only low GI foods) will significantly and positively impact glycaemic control unless the changes in total intake reflect a significant change in underlying regular dietary patterns [46]. Thus, an emerging issue that must be resolved is that inclusion of particular foods is made within a diet that confers the optimal dietary pattern for risk reduction in a way that promotes

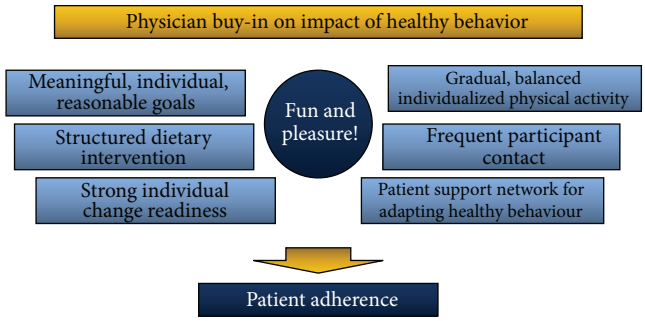

Figure 3: Drivers of adherence for the Canadian tDNA.

a healthy body weight (i.e., it does not exceed energy requirements).

Validated evaluation tools and simple/efficient processes for monitoring/surveillance are essential to the success of tDNA. Establishing efficacy is important, but it is also essential to identify techniques, tools, and environmental factors that contributed to, or detracted from, the success of implementing the intervention [47]. Nutrient intake, although important, does not capture the complexity of behavioural changes that people make to implement the dietary advice they received. Details are critical so that programmes can be expanded and adapted when warranted. For the field to advance, we must know what study participants were asked to do and what they actually did and we must move beyond "intention to treat" analyses. Assessment of dietary and physical activity behaviour and behaviour changes requires evaluation tools that are validated, reliable, and easy to use in various clinical practice settings [48]. The tools should be adapted to the cultural specificities of the clients and the Canadian guidelines. An inventory of validated tools, their selection according to accessibility and appropriateness, their adaptation to geographic and ethnocultural specificities, and their modification to improve clarity, simplicity, and user-friendliness remain to be achieved before validation of the tDNA is undertaken in a clinical setting. The tDNA and its tools can only be of use when patients adopt and adhere to the recommendations. This is optimized if the physicians and their patients buy-in on the impact of healthy behaviour on diabetes management and points to the importance of their involvement at each step of the tDNA. Figure 3 summarizes what is to be accomplished when primary caretakers adopt the Canadian tDNA and its tools in a clinical practice; at its core, we promote to always aim at making the relationship to food and physical activity fun and pleasurable.

5. Conclusions

Adapting the global tDNA template to a Canadian society led to the recognition that primary care practitioners need to participate as active and key promoters of healthy lifestyle behaviour with other members of the health professional team. Their involvement entails the development of simple, quick, and effective methods to assess nutritional and physical activity behaviours that put patients at risk and requires the implementation of strategies to help change thi behaviour in a sustainable manner. The foods in the environment of Canadians with T2D should be nutritionally adequate, culturally acceptable through appropriate food and distribution systems, physically and economically accessible at all times, and safe and secure in order to enable adoption of behaviour that promotes optimal diabetes care and make healthy food choices the norm. Furthermore, simple tools should be put in place to first evaluate sedentary behaviour and physical activity habits of patients and then support economically viable solutions to help patients increase their physical activity habits and regular exercise level. Above all, primary care practitioners should buy-in on the impact of healthy lifestyle behaviours on diabetes management by adopting this behaviour themselves. The Canadian tDNA is a first step.

Disclosure

The paper of this article was created and enriched solely by task force members through a process of ongoing literature searches, independent contributions and reviews, and group interactions for consensus.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

Financial support was provided by Abbott Nutrition International. Other support may have been provided to task force members as follows. Jean-François Yale has received financial support for advisory boards, lectures, and research from Sanofi, Eli Lilly, NovoNordisk, Merck, Bristol-Myers Squibb, Astra Zeneca, Boehringer Ingelheim, Janssen, Medtronic, Abbott, Takeda, and GlaxoSmithKline. Thomas PP Ransom has received financial support for advisory boards, lectures and research from Merck & Co., Novartis, Boehringer Ingelheim, Bristal-Myers Squibb, AstraZeneca, Eli Lilly, GlaxoSmithKline, Novo Nordisk and Sanofi-Aventis. Jean-Pierre Després declares associations with the following companies: Abbott, AstraZeneca, GlaxoSmithKline, Merck, Novartis, Pfizer Canada, Sanofi, Theratechnologies, and Torrent Pharmaceuticals. Cyril Kendall has received research grants, travel funding, consultant fees, and honoraria, or has served on the scientific advisory board for Abbott Laboratories, Advanced Food Materials Network, Agrifood and Agriculture Canada (AAFC), Almond Board of California, American Peanut Council, American Pistachio Growers, Barilla, California Strawberry Commission, Calorie Control Council, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, The Coca Cola Company (investigator initiated, unrestricted), Danone, General Mills, Hain Celestial, International Tree Nut Council, Kellogg, Kraft, Loblaw Brands Ltd, Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, Peanut Institute, Pepsi-Co, Pulse Canada, Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate

& Lyle, and Unilever. David Jenkins has served on the Scientific Advisory Board of Sanitarium Company, Agriculture and Agrifood Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), Loblaw Supermarket, Herbal Life International, Nutritional Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer Care, Orafti, Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Pulse Canada, Saskatchewan Pulse Growers, and Canola Council of Canada; received honoraria for scientific advice from Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, International Tree Nut Council Nutrition Research and Education Foundation and the Peanut Institute, Herbal Life International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California Strawberry Commission, Hain Celestial, Pepsi, and Alpro Foundation; has been on the speakers panel for the Almond Board of California; received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program (ABIP) through the Pulse Research Network (PURENet), Advanced Food Materials Network (AFMNet), Loblaw, Unilever, Barilla, Almond Board of California, Coca-Cola, Solae, Haine Celestial, Sanitarium Company, Orafti, International Tree Nut Council Nutrition Research and Education Foundation and the Peanut Institute, the Canola and Flax Councils of Canada, Calorie Control Council, Canadian Institutes of Health Research, Canada Foundation for Innovation, and the Ontario Research Fund; and received travel support to meetings from the Solae, Sanitarium Company, Orafti, AFMNet, Coca-Cola, The Canola and Flax Councils of Canada, Oldways Preservation Trust, Kellogg's, Quaker Oats, Griffin Hospital, Abbott Laboratories, Dean Foods, the California Strawberry Commission, American Peanut Council, Herbal Life International, Nutritional Fundamental for Health, Metagenics, Bayer Consumer Care, AAFC, CAPI, Pepsi, Almond Board of California, Unilever, Alpro Foundation, International Tree Nut Council, Barilla, Pulse Canada, and the Saskatchewan Pulse Growers. Dr Jenkins' wife is a Director of Glyceamic Index Laboratories, Toronto, Ontario, Canada. Albert Marchetti has received financial support for research and the development of educational materials in diabetes from Eli Lilly, Takeda, GlaxoSmithKline, Bristol-Myers Squibb, and Abbott Nutrition International. Osama Hamdy has received financial support as a Consultant from Abbott Nutrition and as a Speaker from Amylin/Eli Lilly and Abbott Nutrition. Jeffery I Mechanick has received honoraria for lectures and program development from Abbott Nutrition International.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2014, Article ID 692893, 25 pages
http://dx.doi.org/10.1155/2014/692893

Research Article

Dynamic Interactive Educational Diabetes Simulations Using the World Wide Web: An Experience of More Than 15 Years with AIDA Online

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Received 2 July 2013; Accepted 8 August 2013; Published 6 January 2014

Academic Editor: Patrizio Tatti

Background. AIDA is a widely available downloadable educational simulator of glucose-insulin interaction in diabetes. *Methods*. A web-based version of AIDA was developed that utilises a server-based architecture with HTML FORM commands to submit numerical data from a web-browser client to a remote web server. AIDA online, located on a remote server, passes the received data through Perl scripts which interactively produce 24 hr insulin and glucose simulations. *Results*. AIDA online allows users to modify the insulin regimen and diet of 40 different prestored "virtual diabetic patients" on the internet or create new "patients" with user-generated regimens. Multiple simulations can be run, with graphical results viewed via a standard web-browser window. To date, over 637,500 diabetes simulations have been run at AIDA online, from all over the world. *Conclusions*. AIDA online's functionality is similar to the downloadable AIDA program, but the mode of implementation and usage is different. An advantage to utilising a server-based application is the flexibility that can be offered. New modules can be added quickly to the online simulator. This has facilitated the development of refinements to AIDA online, which have instantaneously become available around the world, with no further local downloads or installations being required.

1. Introduction

AIDA v4 (accessible freely at http://www.2aida.org) is a downloadable program that permits the interactive simulation of plasma insulin and blood glucose (BG) profiles for teaching/demonstration/self-learning/research purposes [1]. The software incorporates a compartmental/physiological model describing glucose-insulin interaction in insulin-dependent diabetic patients (lacking endogenous insulin secretion). The graphical interface of the downloadable software allows nonspecialist users to interact with the model. AIDA v4 permits the effects of insulin dosage and dietary adjustments to be simulated for a typical patient's BG profile, with the working hypothesis being that patients, relatives, students and health-care professionals (HCPs) should be able to experience metabolic adjustments without risk of hypoglycaemia. AIDA v4 also incorporates a knowledge-based system that can suggest changes in insulin dose for users unsure about what to simulate next [2, 3].

Although a range of other interactive simulation programs of glucose-insulin interaction in diabetes have been described in the literature [4–12], to date, most of these do not seem to have been distributed so widely via the internet or been made particularly widely available. Indeed, in a number of cases, it would seem that readers are entirely dependent on the authors' own descriptions of their prototypes in research articles, since no versions appear to be available for general use by others [5, 7, 8, 12].

By contrast, with AIDA, multiple updates and versions of the software have been freely available on the web since 1996, and before that made available to researchers on diskette [13–15]. This has led to a substantial experience with the software worldwide, with over 426,000 downloads of the program taking place since the program's original internet launch.

The burgeoning popularity of the world wide web means that more people are surfing the net than ever before. This surge in popularity has led people to increasingly consult web sites as sources of *bona fide* medical information. Although there is currently a vast amount of educational material that is available on the internet, it is helpful to have *interactive* resources which engage students in the learning process. In this respect, it has been found that students learn best through active learning and discovery rather than by simply listening or reading [16, 17]. Interactive multimedia has changed the teacher/student relationship from one of "*the sage on the stage*" to the "*guide on the side*" and provides tools for students to collaborate together on projects or to work independently at their own pace and for teachers to present new types of materials [18–25].

In days gone by most computers were mainframes, and most applications were run centrally on a large host computer. Networks connected "dumb" terminals with the central mainframe. With the development of personal computers (PCs), the pendulum swung towards "distributed computing" with significant processing taking place locally on individual's desktop/notebook PCs. With the massive expansion of the internet, it has become possible once again for centralisation of functionality to be considered. Nowadays, a range of applications can operate across the internet, from distant servers. While most internet users do not have "dumb" terminals-there is a move back to using less and less complex devices for accessing the internet (e.g., mobile phones/smartphones, WebTV, etc.). It is interesting how things seem to have moved almost full circle.

With the recent move towards "cloud" computing, the interest has focused less on a single central server and more on distributed services that can be hosted on a range of servers, with more resources (bandwidth, central processing units [CPUs], memory, and disk space) commissioned as usage requires.

Using AIDA v4 as an example, work has been done to show how it is possible to move from purely static, informational resources on the web to using the internet to provide more interactive and dynamic information about clinically relevant situations in diabetes care. The purpose of the AIDA online diabetes simulator has not been to provide individual patient BG prediction or medical advice or therapy planning but instead to provide an interactive educational web-based tool to help people with diabetes and their relatives/carers, as well as HCPs and students, to better understand how meal (carbohydrate) and insulin interactions can affect BG levels; that is the intended role—for self-learning/teaching/demonstration/education purposes.

While the downloadable AIDA software has been widely applied, there may be a number of practical and theoretical limitations to the standalone AIDA PC software approach. (i) People who wish to make use of the program need to download an archive file and then install it on their hard disk. This requires a certain modicum of computer knowledge or experience. (ii) Some people might be concerned about the theoretical risk of receiving some sort of virus when downloading an executable file from the internet (notwithstanding the fact that the AIDA PC software has repeatedly been shown to be virus free). (iii) The software requires an IBM-compatible DOS/Windows PC (or an Apple Mac running SoftWindows or Virtual PC emulators or a PowerPC Macintosh). People without access to one of these computers or operating systems cannot run the standalone AIDA v4 downloadable software. (iv) The availability of enhancements or upgrades to the PC software can take time to reach end users, since further downloads and local installation are required to obtain the latest version/release. This issue could be addressed with an autoupdate facility, but such functionality is currently not yet available within AIDA v4. (v) The downloadable software, being DOS based, has a user interface that is not totally adherent to the principles of a windows graphical user interface (GUI) with which end users will be most familiar.

For all these reasons, the value of the internet has been recognised for making a diabetes simulator even more widely available than via just a downloadable program. Indeed, users might wish to try out the simulator online to see what it is all about, before going to the "trouble" of downloading and installing a standalone version.

Therefore, it was hypothesised that an even wider audience might benefit from the AIDA diabetes-simulation approach if it did not require any local download or installation, could run on a wider range of computers, and would offer a standard windows GUI for user interaction.

To address these issues, the authors set out to collaborate on the development of a web-based version of the AIDA diabetes simulator, called AIDA online, which would be totally internet based and which therefore would be able to operate from any computer, anywhere in the world, provided it had a connection to the internet and a graphical display. The intention was that—via such a web-based simulator—enhancements and upgrades could be made available instantaneously, worldwide. Furthermore, no download or local installation would be required. In fact, it would not even be necessary to have a computer to use AIDA online, with usage being possible through any internet-enabled device, for example, WebTV or a smartphone.

2. Materials and Methods

2.1. Design Considerations. Recognising that the new target audience may be less computer "savvy" than AIDA v4 DOS

users, it was planned for the input variables for the web-based simulator to be somewhat simplified with pull-down menu options used for ranges of values (e.g. "increased," "normal" and "reduced") instead of absolute numbers. Along similar lines, clickable terms were planned to allow unfamiliar users to see the definitions of various terms via an online glossary and also permit users to see some of the assumed values used in the simulations.

In order to make the diabetes simulator available to as many people as possible who could get on the internet, "portability" and "accessibility" were important design considerations. Given this, it was desired to make the simulator as browser friendly as possible. Web programmers distinguish "client-side" and "server-side" processing. In client-side processing, the browser asks the server to send it the program and then runs it locally. Java applets and JavaScript work like this [26].

In server-side processing, the web browser asks the server to run a program. The server does and returns the results [27]. So, with "server-side" processing, the user types data into a form, and this is sent to a web server, which calculates the results and sends them back as HTML (HyperText Markup Language) data. The developer only needs to write the program once and connect it to a web server. Then, anyone with a browser can run the program. There are no problems with porting the program to different machines [28]. Clearly, such a centralised approach might lead to issues with load on the server, although this has not been a problem to date with the web-based version of AIDA.

Haag et al. [29] have suggested that in contrast to conventional computer-assisted instruction (CAI) programs, web-based training (WBT) programs can be considered as four main types: client-based; remote data and knowledge; distributed teaching; and server-based. Using this classification, the web-based version of AIDA would be considered a "server-based WBT program."

In earlier days, JavaScript was not supported by many browsers. Based on this, a decision was taken to make use of "server-side" processing and translate the original AIDA v4 program source code from Pascal into Perl (Practical Extraction and Report Language) and avoid Java and Javascript.

2.2. Practical Extraction and Report Language (Perl). Educational models written in Perl allow a wide variety of internet browsers to access and run simulations without requiring time-consuming downloading of lengthy files, utilising compilers, or using local disk storage space. Perl v5.0 was selected for this work for a variety of reasons, the most compelling being its portability between platforms and its widespread acceptance by web browsers. Perl is the language used in CGI (Common Gateway Interface) scripts, which are used by web servers to allow for communication with the outside world, and therefore must be recognised by web browsers. Furthermore, Perl places a minimal load on the user's system and is compatible with all major web browsers that are currently in use.

Perl is a high-level, general-purpose, nonproprietary, interpreted, and dynamic shell scripting/programming language that does not require a special linker [30]. It is a relatively simple language where variables and commands are passed to the script and output is sent directly back. In other words, Perl can be run from the command line of different platforms like DOS or UNIX and of course via the web [31].

Another reason, which was nearly as important, was the ease with which Perl could be learned. Designed to be a user friendly language and written by one person, Perl takes many of the good attributes of languages like C++, GREP, shell scripting (sh), and others to make it user friendly. Conversely, Java, for example, has been written like C and has a much steeper learning curve for first time users. This consideration factored into the decision to use Perl for this work.

Furthermore, Perl can be used without modification on multiple computer platforms. As a scripting language, it does not require compilation in order to be executed. Perl is distributed under the GNU General Public License and is maintained by a worldwide network of volunteers, a factor which also contributed to its choice for the implementation of AIDA online, which is itself a free web resource implementation of a freeware PC program.

2.3. AIDA Online. Designed to be accessible and usable by anyone who desires to learn more about diabetes, AIDA online has been developed to provide a windows-compatible easy-to-use web-based interface for the AIDA v4 diabetes simulator. The method of interaction between the user and the program is an important aspect of the simulator which merited consideration. The simplest method is to utilise the interaction built into HTML through the FORM function. This allows input by the user through both text and buttons, allowing a page designer to guide the user through the steps required to fill in all the necessary information to run the program. Default values can also be given to input areas to allow for the creation of a simple default example to help lead the user through what needs to be done by them to fill out the form. Using a form also lends itself to the next step, which is displaying output. Using forms is supported by the use of Perl, that can be used to create an output HTML page "on the fly," which will incorporate both text and graphs to provide the required information for the user.

AIDA online has been designed to allow the user to run multiple simulations in order to compare the results of changes made to a patient's diet and/or insulin regimen. The design plan was for results to be viewed through the use of several different graphs that display the BG and insulin concentrations over a 24 hour period, the results of two different simulations being viewed on graphs at the same time. It was also planned for the graphs to be able to display glucose absorption, renal excretion, peripheral glucose utilization, and net hepatic glucose balance data (fluxes within the AIDA v4 model).

One of the authors, EDL, collaborated on this work with two design project students (DKDW and CAN) at North Carolina State University [25] and made the AIDA v4 Pascal source code available for translation into Perl.

Under EDL's direction, the existing AIDA v4 Pascal source code was translated, and an online version of AIDA was developed in order to produce a more accessible version of the simulator for a wider (different) audience. The result of this work has become a widely utilised resource for HCPs and educators, students, patients, and relatives/carers of people with diabetes. It is freely available to anyone with internet access and has the ability to engage people from a wide variety of educational, social, and cultural backgrounds.

2.4. How AIDA Online Works. The AIDA online website utilises two divisions of a web server, the HTML public domain area and the cgi-bin script/program area (Figure 1).

The HTML area hosts all static web pages including most of the forms that post information directly as input to programs stored in the cgi-bin area of the host (AIDA online) web server. This area also hosts the graphics files and temporary numerical data files produced by the simulation engine. This allows the user, if required, to download the information produced by the simulator into local storage.

The cgi-bin Perl scripts (programs) which actually run the simulations are executed in realtime, so that they can output dynamic information (data and graphs) which can be viewed immediately through a web browser. The Perl scripts have been set up to accept input from the web server (HTML form submission) as well as from static text files stored at the website. The main output from these scripts is formatted in HTML. This allows the user's web browser to view and download the output of the AIDA online scripts. The HTML output does not actually exist physically as files but rather is created dynamically in realtime, upon demand (generated "on the fly"). The Perl scripts' other outputs include physical text files that store data used in the generated plots. There are a total of three scripts used to generate AIDA online simulations (cases.cgi, intro.cgi, and simulate.cgi). Two scripts (cases.cgi and intro.cgi) are used to process user preferences in order to set up forms for the users' input. The third script (simulate.cgi) actually computes the AIDA diabetes model and can be considered the "simulation engine", generating the simulations.

The HTML area is also used to store all static web pages that provide information, help, and directions to the simulator.

The simulator requires several parameters that allow users to customise their simulations. For example, users can select their preferred units for BG display (mmol/L versus mg/dL), select the insulin types to be used, and decide whether or not they would like to see the advanced fluxes plots underlying the simulations (net hepatic glucose balance [32], peripheral glucose utilization, renal excretion of glucose into the urine, and glucose absorption from the gut) as part of their simulation runs.

As in AIDA v4, users can choose from 40 existing, prestored scenarios or create a new case from "scratch." An abbreviated description of the cases is provided initially on the "Options" web page. However, if the user needs a further description or more details, a link is given to a web page where each of the 40 sample cases is described in full.

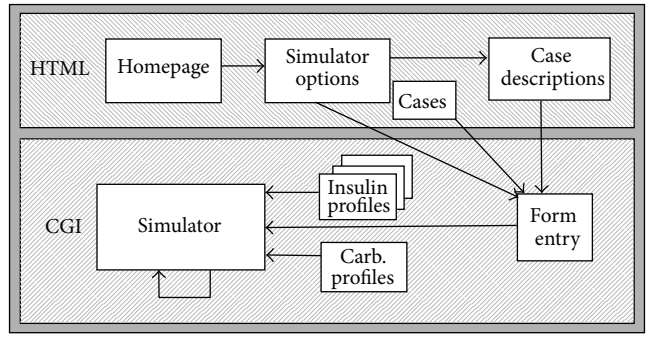


Figure 1: Basic structure of AIDA online. HTML = HyperText Markup Language. The AIDA online homepage (http://www.2aida.net) presents the user with various simulator options and case scenarios. A series of dedicated (Common Gateway Interface) cgi-bin scripts written in Perl v5.0 are used to read case scenario data and insulin and carbohydrate profiles from various databases. The plasma insulin and blood glucose (BG) profiles are computed using a further Perl script which contains the AIDA v4 model differential equations (and which makes use of some temporary storage space on the AIDA online server) [11]. Output from the simulator is returned to the user in HTML format for display by a web browser.

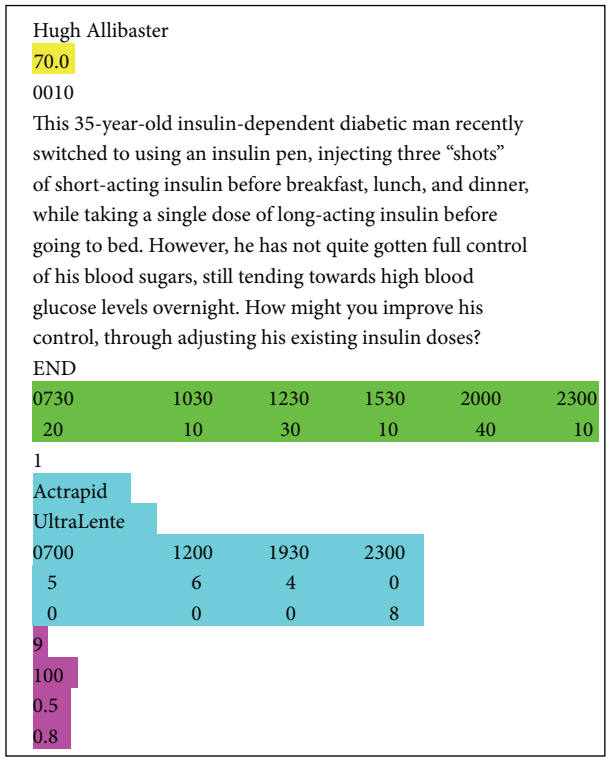
The case details page allows the user to choose a case and return to a similar customisation page to proceed with a simulation.

Once the user has selected a case scenario, a cgi-bin Perl script is invoked. This script is passed the preferences of the user and the sample case, if one has been chosen. If an existing case is chosen, the script populates an HTML template form with data extracted from static text files obtained from AIDA v4, which are stored on the AIDA online web server for that individual case scenario (Figure 2(a)). This form would be left blank if the user decides to start a new case. Using this form, clinical and nutritional data are submitted to the AIDA online simulation engine.

When the user opts to run the simulation, this HTML form data and the user's preferences are passed to the simulation engine, implemented in Perl, and which makes use of the same model as that adopted for the downloadable AIDA v4 simulator [2] to generate the BG and plasma insulin profiles.

Based on the user's time of carbohydrate intake and amount, as in AIDA v4, the simulator reads prestored values from a static text file—effectively a large lookup table—containing precomputed carbohydrate gut absorption profiles generated by one of the authors (EDL) and taken from AIDA v4. The same process occurs with the insulin injections. The time, amount, and type of insulin injections are used to determine which file and what value to extract. This data is then used by the simulator to calculate the BG and plasma insulin levels as well as each of the four fluxes at 15-minute intervals, using an Euler integration method, during a simulated 24 hour day, as per the original AIDA v4 model [2].

An early prototype version of AIDA online incorporated observed BG data points—for example, "Glucostix" measurements—as in the downloadable version of AIDA,



(a)

```
<INPUT COLOR = "WHITE" TYPE=hidden SIZE=0 NAME="run" VALUE="1">
<INPUT TYPE= HIDDEN SIZE=1 NAME="glucfile" FONT COLOR="WHITE" VALUE= "glucose15546.dat">
<INPUT TYPE= HIDDEN SIZE=1 NAME="insulinfile" VALUE="insulin15546.dat">
<INPUT TYPE= HIDDEN SIZE=1 NAME="garfile" VALUE="gar15546.dat">
<INPUT TYPE= HIDDEN SIZE=1 NAME="pgufile" VALUE="pgu15546.dat">
<INPUT TYPE= HIDDEN SIZE=1 NAME="renalfile" VALUE="renal15546.dat">
<INPUT TYPE= HIDDEN SIZE=1 NAME="hepaticfile" VALUE="hepatic15546.dat">
<INPUT TYPE= HIDDEN SIZE=1 NAME="units_select" VALUE="18">
<INPUT TYPE= HIDDEN SIZE=1 NAME="display" VALUE="1">
<INPUT TYPE= HIDDEN SIZE=1 NAME="insulin_type" VALUE="1">
<INPUT TYPE= HIDDEN SIZE=1 NAME="bounds_limits" VALUE="0">
```

(b)

Figure 2: (a) Data from an ASCII (American Standard Code for Information Interchange) text file for an example case scenario (number 0010: Hugh Allibaster) from the AIDA online database. Depending which case scenario the user selects, these data are read in and used as the basis for an initial (baseline) simulation. Forty case scenarios exist in AIDA online, data imported from AIDA v4. Colour key, highlighted in figure. Yellow: weight (in kg). Green: meal times and grams of carbohydrate. Cyan: preparations, times, and dosages of insulin injections. Magenta: renal threshold of glucose, creatinine clearance rate, and hepatic and peripheral insulin sensitivity parameters, respectively. (b) Hidden fields in the dynamically generated HTML web pages produced by the AIDA online cgi-bin Perl scripts. These fields are used to store parameters and case details to be transferred between simulation runs. "units_select" value = 18 for mg/dL blood glucose units; value = 1 for mmol/L. Premixed/biphasic "insulin_type" value = 2. "display" value = 1 is standard display; "display" value = 2 is advanced/fluxes display. "run" value = 1 is the simulation run number (1 = first, baseline simulation). "run" value number increments for each subsequent simulation. "bounds_limits" value = 1 would show the user-defined normoglycaemic ranges. 5 digit number is a PID = process identification number generated by the web server for each separate process/simulation.

but these were not retained when AIDA online went "live" on the web, in order to try and reduce the amount of user entered data required to run a simulation and thereby simplify user interaction with AIDA online.

Storage data files used by AIDA online were previously processed and saved in the same location as the Perl script. Eight of the data files represent the different insulin absorption profiles based on the type of insulin injected and the dosage. Four of the eight files represent the "active" insulin absorption, while the other four pertain to the plasma insulin profiles [4]. A different file represents the glucose absorption data based on the amount of carbohydrates ingested.

The data arrays of absorption profiles stored in these files are the product of a precomputation program written by Lehmann and Deutsch [2]. The storage file was originally written in binary for the DOS version of AIDA which allowed for fast access to the data. However, for AIDA online, a decision was taken to have the storage files written in an ASCII (American Standard Code for Information Interchange) text file format to accommodate future easier upgrades, if necessary. Also, to compensate for any increase in search time, the storage arrays were divided up into nine files so that there would be a faster access rate. ASCII text files are used to store precomputed plasma (_pa) and active (_act) insulin profiles as shown below for the four classes of insulin preparations catered for by AIDA online; Actrapid = short-acting; NPH + Lente = intermediate-acting; and UltraLente=long-acting insulin preparations; CAR = carbohydrate absorption profiles from the gut.

Actrapid_act

Actrapid_pa

NPH_act

NPH_pa

Lente_act

Lente_pa

UltraLente_act

UltraLente_pa

CAR.

The amount of carbohydrates ingested in each meal determines the offset (0–80 grams) for fetching the appropriate absorption profile from the carbohydrate storage file. The data retrieved from the carbohydrate storage, along with the meal times, are used to calculate the glucose absorption profile over the 24-hour period. For each meal, the absorption of glucose into the blood stream from the gut is calculated over a period of several hours after ingestion. The type of insulin determines which of the eight insulin storage files to read, while the dosage determines the offset (0–40 IU) within that file. There are different forms of insulin injections offered as choices in the web-based simulator, as in PC AIDA v4: soluble short-acting insulin preparations (10 types), intermediate-acting preparations (19 types), long-acting preparations (4 types) [4], and a mixture of short- and intermediate-acting biphasic preparations (18 types).

Upon completion of the main computation process, over a simulated 24 hour period, the data is stored in six separate files from time 0 to 24 hours in preparation for graphing.

2.5. Gnuplot Graphing Program. AIDA online makes use of an open access graphical program, called *gnuplot*, to generate the AIDA online graphs in real time. The plots are displayed on a line graph with a frequency of 15 minute data points.

Gnuplot is a portable command-line driven graphing utility for Linux and many other platforms. The source code is freely distributed. It was originally created to allow scientists and students to visualise mathematical functions and data interactively, but, it has grown to support many noninteractive uses such as web scripting [33].

The six ASCII text files created by AIDA online and stored in the HTML area contain the x, y values for the graphical plots. Once these files have been closed, the simulator makes system calls that pass these files to the *gnuplot* graphing program, which takes in the x, y coordinates from the ASCII text data files and produces a graphic file.

In the original AIDA online version 1 development, *gnuplot* would produce a .PPM (Portable Pixel Map) graphical file. However, web browsers did not support the .PPM file type produced, so the simulator would make another system call to a separate program called ppmtogif to convert the .PPM graphics file into a common .GIF (Graphics Interchange Format) file supported by web browsers.

The .GIF file is stored along with the data files in a temporary directory within the HTML area. This ensures that (i) the files can be accessed by the user for download which may assist data retrieval and (ii) the files are kept in the directory for approximately 6 hours before being deleted by an automated timed cronjob in order to save server hard disk space. With all the calculations and plot creations completed, the simulator displays its output in HTML format to the user's web browser. The HTML output automatically contains references to the newly created plots and data files for the user's browser to display.

The form page allows for a choice of which plots will be viewed. Once the simulator has finished its execution, the user also has the opportunity to download any of the plots as well as the actual data files [34].

The AIDA online website is designed so that multiple simulations can be run in succession. Each run of the simulator returns not only the graphs but also a new form already filled in with the data previously submitted. This allows the user to make changes to the input data based on their observations from the simulation graphs. When the user submits the new regimen data, new graphs are generated and a further data form is returned. Graphs containing the new information are overlaid on the previous plot. The user can therefore visually assess a change in the shape of the curves.

A key feature of the AIDA online diabetes simulation approach is the ability to visualise and compare graphical simulation results before and after a change in the regimen. This is achieved by the simulator submitting in the background not only the changed data and preferences but also references to the data files that were produced during the original simulation run. This is all done automatically, completely transparently for the user.

One of the ways in which user preferences are stored and communicated between simulation runs is via the use of hidden fields in the dynamically Perl-script generated HTML code. As shown in Figure 2(b), a series of parameters and variable values are recorded via this approach.

For a subsequent simulation, the simulator then goes through the same process as the original simulation run. However, this time, the previously stored data files are passed with the new data to the *gnuplot* graphing program.

The new graphs will then contain values for the two different simulations. This allows the user to see the changes made from the previous run.

The present AIDA online simulator is set up to handle two separate data files at a time. The user can continue to submit changed data, but the new simulation will only contain the present and most recent previous simulation data. AIDA online was initially developed and run on a SuSE Linux 6.1 (SuSE Inc, CA, USA) world wide web server on a dual Pentium II/450 MHz (Intel, CA, USA) with 256 Mb RAM and 36 Gb DASD (Direct Access Storage Device). The web server software used was Apache 1.33 (Apache Group, CA, USA).

The Apache web server development effort has aimed at creating a robust, commercial-grade, and freely-available source code implementation of an HTTP (HyperText Transfer Protocol) web server [35]. The Apache web server used on the Linux platform utilises a multithreading algorithm that allows multiple simultaneous processes to be run. For AIDA online, when the simulator is invoked, a Process Identification (PID) number is assigned. The files (graphics and data) are stored uniquely with the PID as part of the filename so even if multiple users from different parts of the world submit simulations at the same time, the simulations can all be processed separately. This explains how it is possible to run a diabetes simulation from, for example, Auckland, New Zealand, simultaneously with a simulation from Basel, Switzerland on a computer originally in Durham, North Carolina—and now in London, UK—all in a matter of seconds [36].

The AIDA online simulations can be run from any machine (PC, Apple Mac, Linux, Unix server, WebTV, smartphone, etc.) from anywhere in the world, provided the device has access to the internet and a graphical display.

There is also a free registration/announcement list that AIDA online users can subscribe to at the website (or by emailing subscribe@2aida.org) so that they can be immediately notified by email about any enhancements or modifications to the system as they become available worldwide. Furthermore, people can also follow developments with AIDA online on Facebook at https://www.facebook.com/www.2aida.org and/or at http://www.facebook.com/aida.diabetes.simulator1 or on Twitter at http://www.twitter.com/aida_diabetes.

The total elapsed time for a single simulation varies. There are basically two periods of delay between data being submitted by the user and the full results being presented back to the user. Firstly, the time for the simulator to be invoked and run depends on the amount of load on the server. However, the time used by the simulator is rarely more than 1 second. Secondly, there is a time delay for the transfer of the HTML page and graphics files back to the end user. The HTML (text only) file itself is only 9 kb (kilobytes) in size. By contrast, the standard simulation produces 17 kb, and the advanced (fluxes) simulation produces 25 kb of graphics data. While the total elapsed time for the user may initially have depended on the speed of the connection to the internet and geographical location, these file sizes are tiny compared with usual web transfers, so apparent simulator response times for users, wherever they are in the world, are generally very rapid (typically 1-2 seconds). There is also a http://www.sitemeter.com/ embedded graphic on the main AIDA online simulation web page which helps to monitor visitors running simulations and provides some anonymised insight into ongoing AIDA online usage. Loading this embedded graphic may delay the apparent simulation time—but the simulations are still incredibly quick, even via a home broadband connection.

Designed to be accessible and usable by anyone who desires to learn more about diabetes, AIDA online version 1 was initially made available on a Shodor Education Foundation web server in the Eastern United States (in North Carolina).

Shodor (http://www.shodor.org) is a North-Carolina-based research and education organisation dedicated to the advancement of science and maths education, specifically through the use of modelling and computers [37].

However, since then, with the development and release of AIDA online version 2 (AIDA online^2), the main AIDA online facility was relocated by one of the authors (EDL) to London, England, and the web-based simulator has been updated further since, and merged in with the rest of the AIDA (http://www.2aida.org) website.

AIDA online^2 has seen glycosylated haemoglobin (HbA_{1c}) calculations as reported by Lehmann [38, 39] for AIDA v4—based on work by Nathan et al. [40]—incorporated into the web-based simulations, together with user-definable upper and lower normoglycaemic limits (bounds) which can be overlaid on the BG graph to assist users in identifying out-of-range high and low BG values.

The main AIDA online^2 website currently resides on a shared web server with an Intel Xeon single core processor running at 2 GHz with 4 Gb of RAM. The current operating system is SuSE Linux Enterprise Server 10 (SuSE Inc, CA, USA).

2.6. Interacting with AIDA Online. Writing the program in Perl and then utilising a fast Linux server allows many users to access AIDA online simultaneously. The main educational utility seems to lie in AIDA online's ability to compare results from different simulation runs. For instance, by modifying the inputted insulin injections, users can learn to exert more control over the BG level of the simulated "virtual diabetic patient." The working hypothesis underlying use of AIDA online is that, while modifying the input parameters, users—whether they be patients, carers, students, or HCPs—can also learn more about how to manage glucose concentrations in insulin-dependent diabetes mellitus (IDDM). The advantage of using multiple injection times and different insulin types becomes apparent as different regimens can be compared. Modifying carbohydrate inputs can also demonstrate the importance of maintaining a strict diet. Large swings in meal carbohydrate intakes result in obvious swings in BG levels that require adjustments to be made to insulin injections to correct the perturbations in the simulated patient. As has been highlighted previously by Blanchard et al., the advantage of having multiple preprogrammed simulated "patients"

allows the user to see the effect of these changes on different body types that have various insulin sensitivities [41].

2.6.1. Using AIDA Online to Perform Simulations. AIDA online is accessed directly at http://www.2aida.net or from the main AIDA website (http://www.2aida.org) via menu options on the left frame menu. Selecting "Online Simulation" takes the user through a short selection procedure, in which a case scenario may be chosen—if desired—and various preferences are determined. A summary of the key features of the AIDA online web-based diabetes simulator at http://www.2aida.net is as follows.

Availability and Functionality

(i) Accessible via the AIDA website at http://www.2aida.org or directly at http://www.2aida.net.

(ii) Standard web browser software using mouse to navigate (by contrast to the downloadable standalone PC version of AIDA, also available at the website, which is DOS based and employs key and tab functions).

(iii) Simulated blood glucose (BG) and plasma insulin levels are derived and displayed in graphical format.

(iv) Carbohydrate intake and insulin injection data are also displayed graphically.

(v) Simulated glycosylated haemoglobin (HbA_{1c}) value derived.

(vi) Forty different case scenarios are available. Dedicated cases can also be created and simulated.

(vii) Data entry forms allow the user to change various values and rerun simulations.

Options

(i) BG units: choose either mmol/L or mg/dL.

(ii) Display: choose either "Standard" or "Advanced."

(iii) "Standard" displays the simulated BG and plasma insulin curves.

(iv) "Advanced" displays the simulated BG and plasma insulin curves, together with graphs of the model's glucose fluxes (glucose absorption from the gut, glucose excretion from the kidneys, glucose utilisation in the periphery, and the net hepatic glucose balance: the production or utilisation of glucose by the liver).

(v) Insulin types utilised (when defining new case only): choose either "Standard" or "Premixed."

(vi) Display upper and lower bounds/limits (the user can define upper and lower normoglycaemic ranges to be indicated on BG graphs): choose either "Display bounds" or "Do not display bounds."

Data Entry Forms (user defined)

(i) Six data entry points for the timing and quantity of carbohydrate intake over a 24 hour period.

(ii) Insulin(s)—choose from a selection of short-acting and from a selection of intermediate- or long-acting preparations; up to four injections per day of each insulin type can be entered, along with the time and dose in units for each injection.

(iii) Body weight is user defined (in kg or lb).

(iv) Kidney function: renal glucose threshold can be "high," "low," or "normal" and renal function can be "reduced" or "normal."

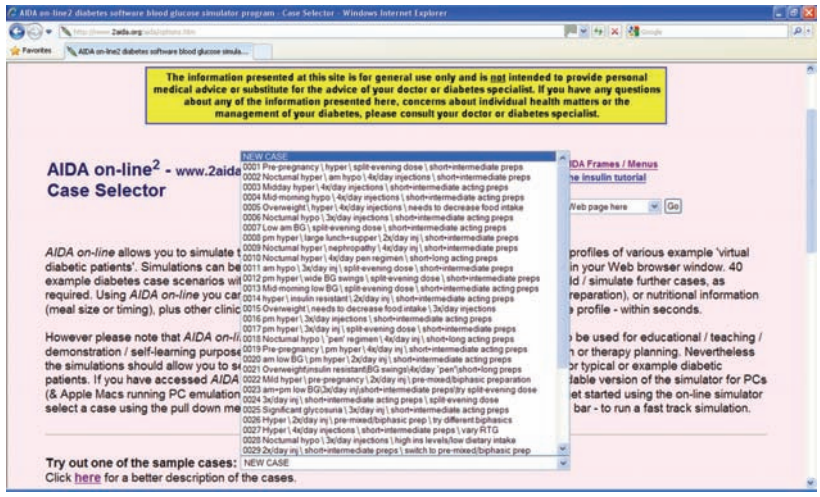
(v) Hepatic and/or peripheral insulin sensitivity may be normal or reduced.

There are currently 40 different case scenarios to choose from as a starting point; each presents a virtual patient with IDDM on a given insulin regimen, experiencing real-life problems associated with BG control. Alternatively, as outlined above, a "new" case may be defined by the user (Figures 3(a) and 3(b)). If the user wishes to have further details about the case scenarios, these can be accessed on the options.htm page via the "*Click here for a better description of the cases*" link (see at the bottom of Figure 3(a)), which loads the cases.htm page (Figure 3(c)) giving full details of each case scenario.

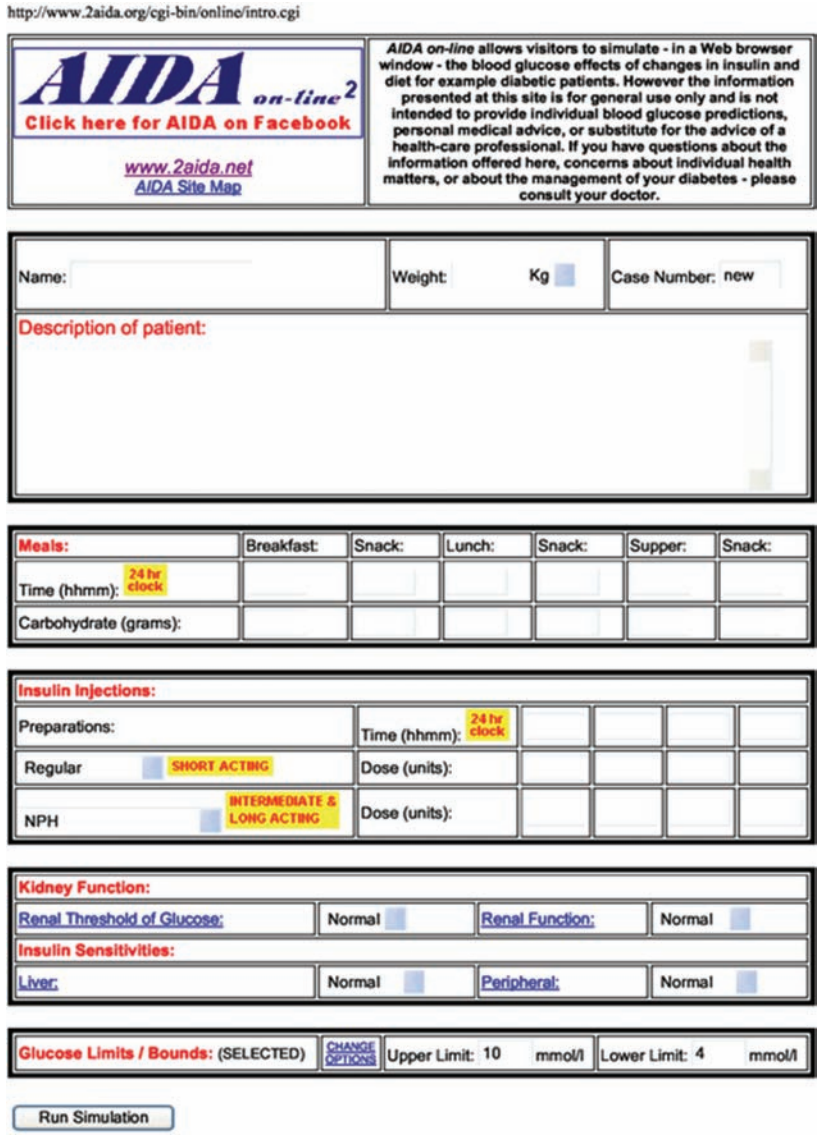
The compartmental design of the AIDA model allows for a number of variables to provide a more tailored and realistic simulation. Hepatic and peripheral insulin sensitivities are modifiable into three categories (increased, normal, and reduced), as is the renal threshold of glucose (the level of BG at which sugar spills into the urine). Renal function is also modifiable into two levels, normal and reduced creatinine clearance (Table 1), which is then used for an estimate of the glomerular filtration rate (GFR).

The final two variables are probably of most interest to casual users, and these are the carbohydrate intake and insulin injections. Carbohydrates are input with a time of ingestion and a total number of grams. The insulin input allows for a time of injection, dosage, and type of insulin (short acting, intermediate acting, and/or long acting, with a variety of brand names to choose from). Additional input variables include the patient's name, weight, and definable limits of the recommended, allowed, normoglycaemic range.

Having selected a case scenario via the pull-down menu on the options.htm page (Figure 4(a)) or via the cases.htm page (Figure 3(c)) and/or indicated preferred options, the (Continue) button is clicked and a Perl script (intro.cgi) stored in the cgi-bin area is invoked. A new dynamically generated page is loaded, giving a description of the selected case (see Figure 4(b)). Data entry forms are displayed, with prestored entries shown for carbohydrate intake (amount and time) and insulin dosage (type, amount, and time), according to the selected case scenario. If the "New Case" option has been selected, then this form is presented blank (Figure 3(b)). There are up to six data entry times for carbohydrate intake (for breakfast, midmorning snack, lunch, afternoon snack, supper, and bedtime snack) and up to four data entry times for each of two insulin types, to cover a 24-hour period, which enables a wide range of insulin regimens to be accommodated.

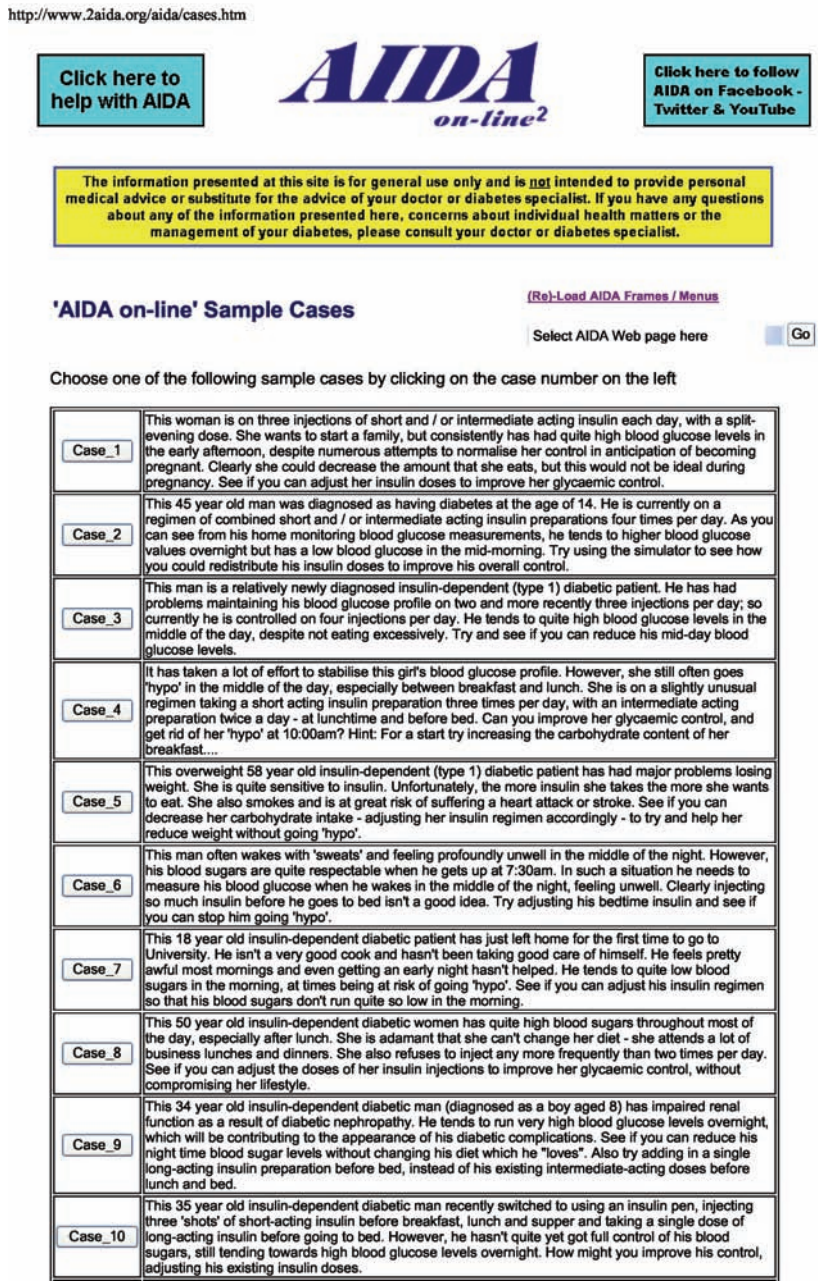


(a)



(b)

Figure 3: Continued.



(c)

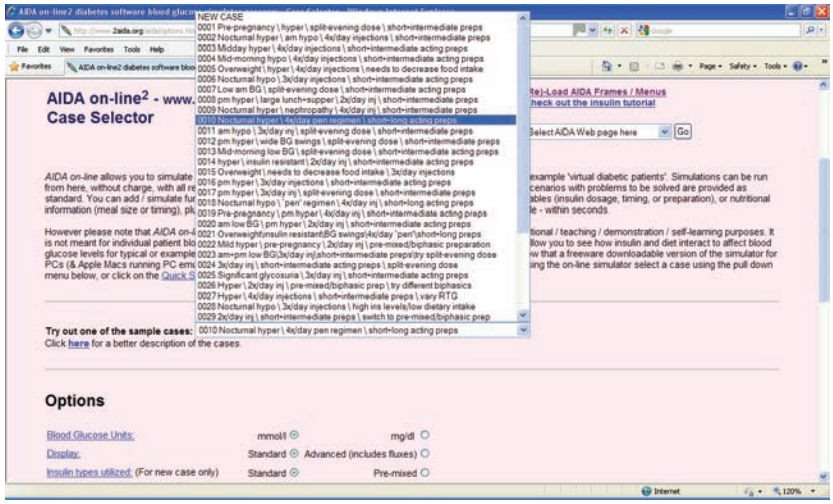
Figure 3: (a) AIDA online^2 main options.htm Case Selector screen shown accessed via Internet Explorer on a Windows XP personal computer. The display shows how a list of summaries of each case scenario can be accessed via a pull-down menu. In this example, a NEW CASE is highlighted. (b) AIDA online^2 intro.cgi dynamically generated HTML page created based on the NEW CASE selected shown in (a). As can be seen, all the fields are blank, allowing the user to create a new case from scratch. (c) AIDA online^2 cases.htm fixed HTML web page giving further details of each of the first ten AIDA online case scenarios (imported from AIDA v4).

Preselected data pertaining to the chosen case scenario can be modified at this stage, if desired, prior to running the simulation.

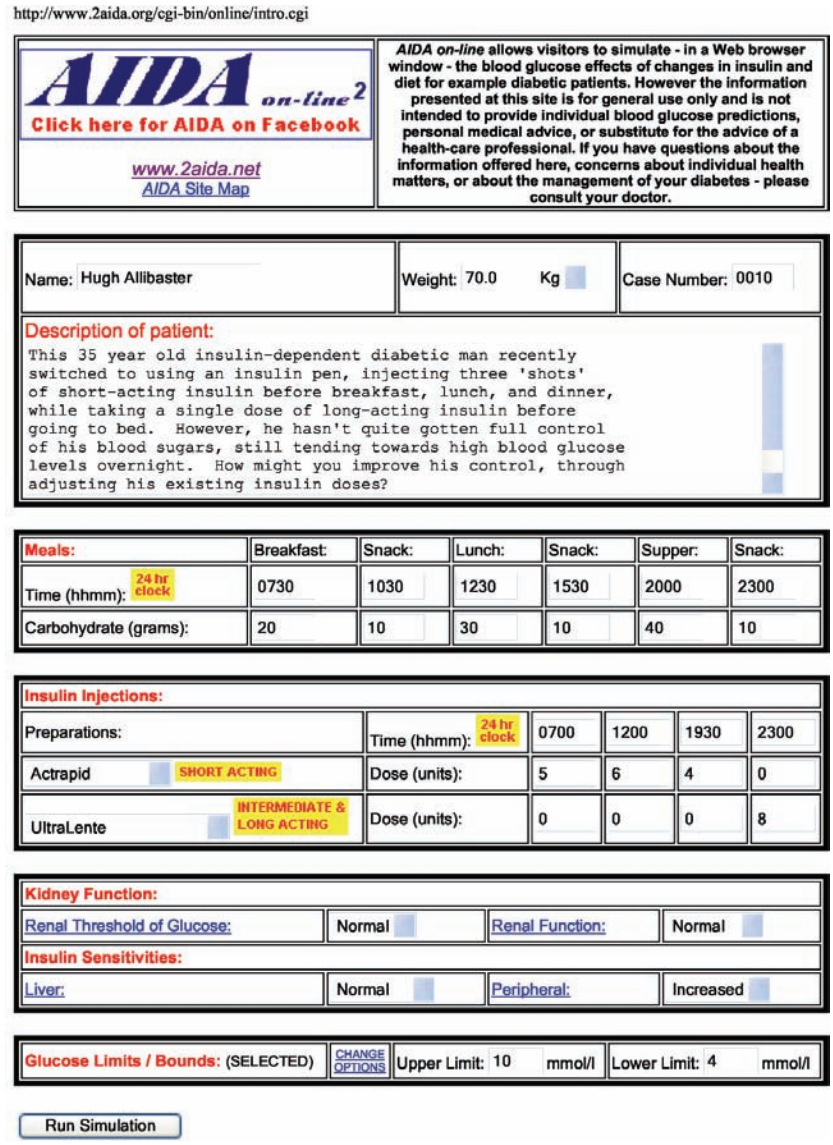
A number of other parameters can also be changed, as outlined previously and in Table 1, and these help in further defining the virtual patient's clinical situation.

When all of the data entries have been made and the (Run Simulation) button is clicked (Figure 4(b)), then the simulation is performed in real time.

If the online simulator is accessed directly from the popup window that is automatically generated when the AIDA website is loaded or if "Quick Simulation" is selected from the left frame menu, then the user is taken straight into a preselected case example (case number 0001, "Joy Wilson" in the AIDA online case scenario database), in which the baseline simulation has already been performed (see http://www.2aida.org/aida/example.htm). This route provides an ideal introduction to AIDA online for first time users.

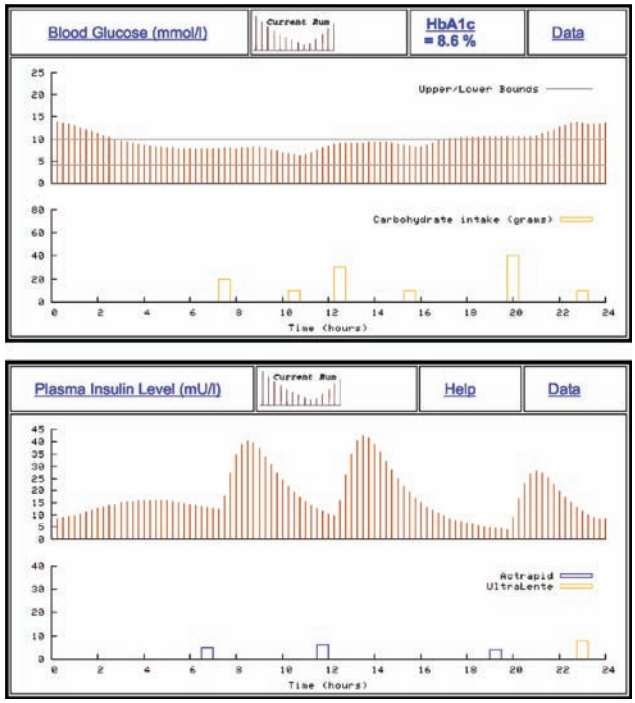


(a)



(b)

Figure 4: Continued.



(c)

http://www.2aida.org/cgi-bin/online/simulate.cgi

Name: Hugh Allibaster	Weight: 70.0 Kg	Case Number: 0010

Meals:	Breakfast:	Snack:	Lunch:	Snack:	Supper:	Snack:
Time (hhmm): 24 hr clock	0730	1030	1230	1530	2000	2300
Carbohydrate (grams):	20	10	30	10	40	10

Insulin Injections:					
Preparations:	Time (hhmm): 24 hr clock	0700	1200	1930	2300
Actrapid SHORT ACTING	Dose (units):	5	6	4	0
UltraLente INTERMEDIATE & LONG ACTING	Dose (units):	0	0	0	8

Kidney Function:			
Renal Threshold of Glucose:	Normal	Renal Function:	Normal
Insulin Sensitivities:			
Liver:	Normal	Peripheral:	Increased

Glucose Limits / Bounds: (SELECTED)	CHANGE OPTIONS	Upper Limit: 10 mmol/l	Lower Limit: 4 mmol/l

Run Simulation

(d)

Figure 4: (a) AIDA online[2] options.htm Case Selector screen showing Case Scenario 0010 highlighted. Options to select the "Blood Glucose Units" and "Standard" versus "Advanced (includes fluxes)" display are shown lower down the page. (b) AIDA online[2] dynamically-generated HTML web page, produced by intro.cgi Perl script, populated with information and data for case scenario number 0010 (Hugh Allibaster). Clicking on the (Run Simulation) button at the bottom of the web page will submit the data shown to the simulate.cgi script to run the simulation engine and generate a graphical simulation (as shown in Figure 4(c)). (c) Baseline simulation using AIDA online[2] with data shown in Figure 4(b) for Hugh Allibaster (case scenario 0010). Top panel: Blood glucose (BG) level and carbohydrate intake over a 24 hour period. User definable normoglycaemic ranges ("Upper/Lower Bounds": 4–10 mmol/L [72–180 mg/dL]) are shown superimposed. Lower panel: Plasma insulin level and injections of Actrapid (short-acting) and UltraLente (long-acting) insulins. The HbA_{1c} value (8.6%) gives an indication—for educational purposes—of the glycosylated haemoglobin level predicted by the AIDA model, if the current glycaemic control were to be maintained in the medium- to long-term. (d) Scrolling down the simulate.cgi page shown in Figure 4(c) yields a dynamically-generated HTML data entry form populated with the data used for the simulation, which—for a baseline (initial) simulation—will be identical to that shown in Figure 4(b). The user can now change any of the data values and run a further simulation by clicking on the (Run Simulation) button at the bottom of the screen.

Table 1: Parameter pre-set values for the AIDA online (http://www.2aida.net) web-based diabetes simulator.

	Low/reduced	Normal	High/increased
RTG (mmol/L)	7	9	11
CCR (mL/min)	40	100	—
Hepatic insulin sensitivity	0.2	0.5	0.8
Peripheral insulin sensitivity	0.2	0.5	0.8

RTG: Renal threshold of glucose. CCR: Creatinine clearance rate.

Once a simulation is run, a new page is loaded, which gives the simulated BG and plasma insulin levels for the 24-hour period (Figure 4(c)). The first panel shows BG fluctuations plotted against time, with a dotted line indicating preferred limits (normoglycaemic range), if this option was selected. Directly below, on the same chart, carbohydrate intake is quantitatively indicated across the 24-hour period. The bars at the bottom of the graph, showing the carbohydrate intake, help the user to visually line up the changes in the BG graph based on carbohydrate intake.

The second panel shows simulated plasma insulin levels over the same 24-hour period; injected insulin doses are indicated below, on the same chart. Once again, the bars below the plasma insulin levels are similar to the carbohydrate graph, except showing insulin injections.

This graphical presentation of both user-defined and simulated data clearly illustrates the relationship between meal times, carbohydrate consumption, and associated BG excursions, insulin injections, and plasma insulin levels. By the same token, the graphs provide an uncomplicated presentation of the characteristics of various insulin types, particularly in terms of their action profiles.

A key feature of AIDA online is the facility that enables one simulation to be compared with the previous. Thus, the HTML data forms are reproduced on the same page below the simulation panels, allowing the user to make any number of changes to the input data (Figure 4(d)). Re-running the simulation derives similar graphs; however, the BG and plasma insulin levels from the previous simulation are also shown. Taken together, the two panels illustrate how various features of the insulin-diet regimen interact, and the user can observe and identify specific effects arising from any changes made prior to rerunning the simulation. In addition, the computed glycosylated haemoglobin (HbA_{1c}) value gives a predicted indication of overall BG control, and this helps to guide the learning process, especially when simulations are rerun repeatedly (Figures 5(a), 5(b), and 5(c)).

The user has the option to view several additional graphs that help explain how the BG simulations are derived. These additional graphs include glucose absorption rate, renal excretion of glucose into the urine, peripheral glucose utilization, and net hepatic glucose balance (Figure 6(a)), which are "fluxes" in the original standalone PC AIDA v4 program.

Throughout the simulation web pages are HTML links to an online glossary (Figure 6(b)), which gives clear but concise explanations of basic terms—for the newcomer—such as BG level, plasma insulin level, and HbA_{1c}. So, clicking on underlined links shown, for instance, in Figures 4(a)–4(d), 5(a)–5(c), and 6(a) all link to the online glossary for further explanations. More advanced scientific concepts associated with the model used in the simulations are also described. Thus, for those users already familiar with the relevant basic concepts, glucose flux options are described, and HTML links provide access to graphical representations of the model of glucose utilisation that is used (also available by selecting "Model Graphics" from the left frame menu). Furthermore, there are links to graphs showing insulin absorption and elimination for various types of insulins covered by the simulator. Additional detailed technical information about the AIDA model is also freely available to users at the AIDA website, accessible directly at http://www.2aida.org/technical. A summary of how AIDA online works is also explained via a link at the bottom of the online simulation web page.

Employing standard web-browser technology, AIDA online is easy to use, and simulator response times are generally very rapid.

2.6.2. Caveats and Warnings. It is emphasised that the model upon which AIDA online is based is not sufficiently accurate for individual patient BG prediction or therapy planning [15, 42, 43]. The user is therefore reminded that the simulation approach is suitable only as an educational tool and not for generating individual therapeutic advice or treatment planning. The general caveats displayed at the AIDA website can be seen at the top of Figures 3(a) and 3(c), and the AIDA online specific caveats can be seen top right in Figure 3(b).

2.6.3. Applications of AIDA Online. Current applications of AIDA online are numerous and wideranging, as exemplified through the variety of user-generated feedback received which has on the whole been very positive. Independent user reviews of AIDA/AIDA online have been published previously elsewhere [44, 45], and user feedback can also be found at the AIDA website at http://www.2aida.org/aida/online-reviews.htm and is referred to in the results section of this paper.

To make the most effective use of AIDA online, it may help for the web-based simulator to be incorporated into structured learning materials. One way in which the simulation approach may be tied in with "static" textual educational material to effectively enhance the learning experience is illustrated at the AIDA website by the interactive Diabetes/Insulin Tutorial [46]. However, use of AIDA online is not limited to personal or individual distance learning via the internet; it also has the potential to be used successfully in a variety of settings, including group education sessions [44].

As has been highlighted by DeWolf [47], computer-assisted education has the potential to accommodate different *speeds* of learning. Some diabetes education sessions have often been provided to groups of patients/students and have necessarily been administered at the *average* learning speed of the group. However, computers can also offer education directly to individuals, allowing individuals to control

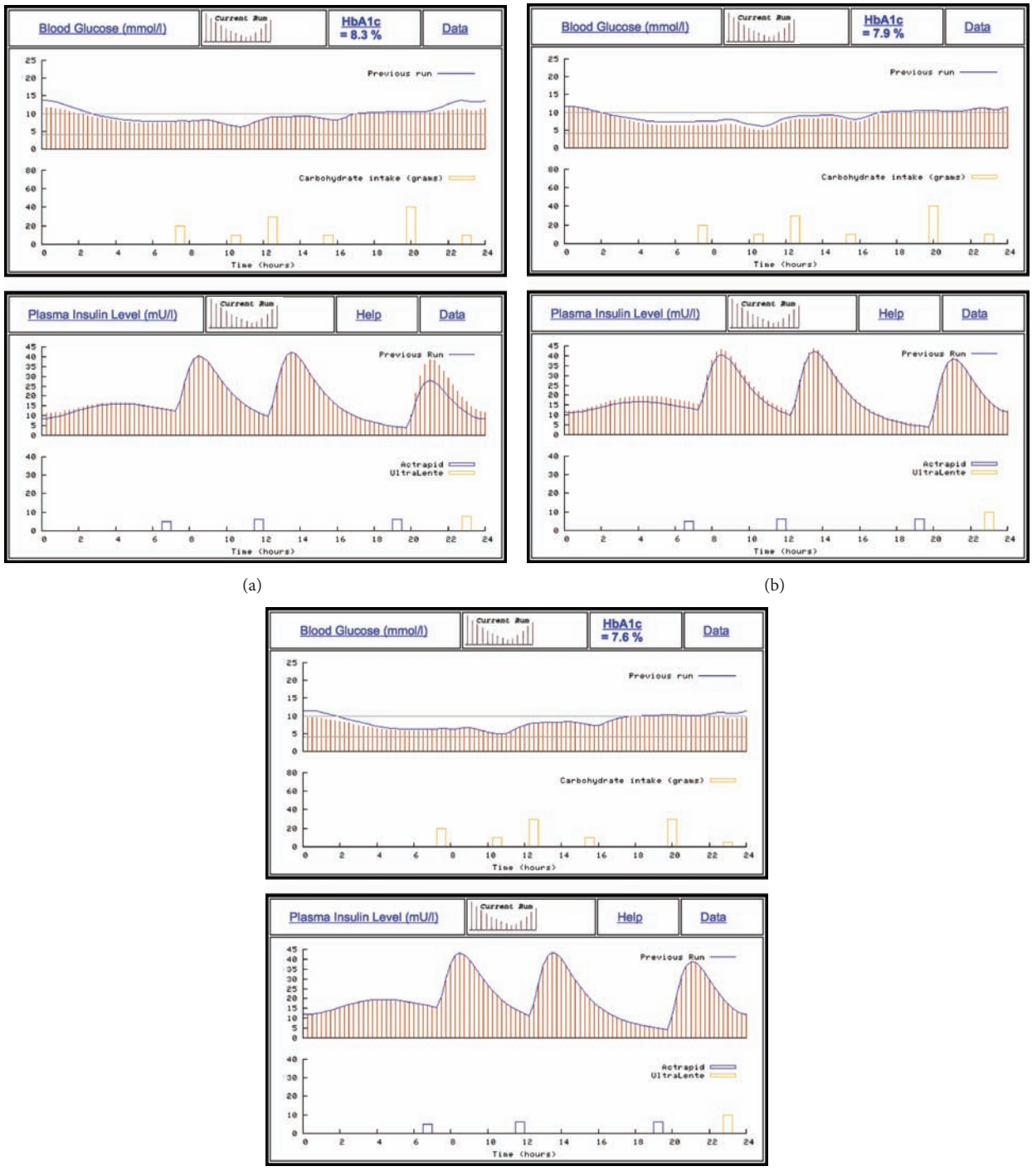
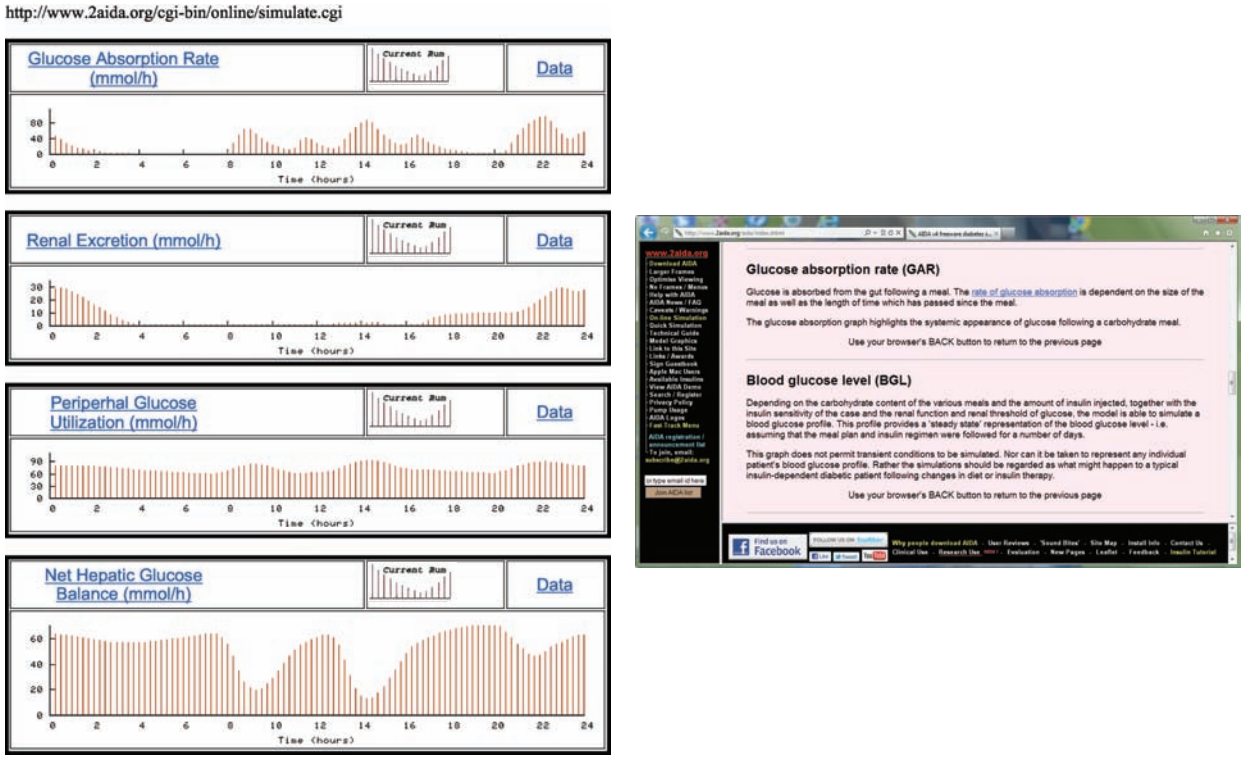


FIGURE 5: (a) AIDA online[2] simulation of the case shown in Figure 4(c) in which the evening (7:30 pm) Actrapid dose has been increased by 2 units from 4 units to 6 units. The current simulation run is shown as the vertical red lines, with the previous run shown for comparison as the solid blue lines. The higher plasma insulin peak in the evening and the reduction in blood glucose (BG) overnight are clear to see, although the BG profile still remains elevated compared with the user defined normoglycaemic range. The glycosylated haemoglobin (HbA_{1c}) level—if this control were maintained in the medium-to-long-term—is expected to improve from 8.6% (Figure 4(c)) to 8.3%. (b) AIDA online[2] simulation of the case shown in (a) in which the evening (11 pm) Ultralente dose has been increased by 2 units from 8 units to 10 units, resulting in some further improvement in the blood glucose (BG) profile, with an expected glycosylated haemoglobin (HbA_{1c}) of 7.9% (improved from 8.3% in (a)). The current simulation run is shown as the vertical red lines, with the previous run shown for comparison as the solid blue lines. (c) AIDA online[2] simulation of the case shown in (b) in which the bedtime snack has been decreased by 5 grams from 10 grams to 5 grams and supper has been decreased by 10 grams from 40 grams to 30 grams (in one simulation). This results in further improvement in the simulated blood glucose profile with a predicted glycosylated haemoglobin (HbA_{1c}) of 7.6%. Once again, the current simulation run is shown as the vertical red lines, with the previous run shown for comparison as the solid blue lines.



(a) (b)

Figure 6: (a) Advanced Display option showing fluxes for the baseline simulation from Figure 4(c). "Glucose Absorption Rate" shows glucose absorption following carbohydrate ingestion in meals; "Renal Excretion" shows the passage of glucose into the urine, above the renal threshold of glucose; "Peripheral Glucose Utilization" demonstrates the utilization of glucose in the periphery, while "Net Hepatic Glucose Balance" shows the production or utilization of glucose by the liver. (b) Screenshot from AIDA online^2 showing two of the entries in the online glossary—directly accessible at http://www.2aida.org/glossary—which is linked to the online simulator output. In this way, users can click on HTML links to obtain explanations about terms they do not understand or concepts with which they are unfamiliar.

the pace of their own learning and at the same time receive immediate feedback. AIDA online can service both group and individual teaching sessions [47].

2.7. Technical Issues. There have been some technical issues with AIDA online, particularly in the early years. The original web-based simulator made use of a program called ppmtogif. This converted .PPM format files generated by *gnuplot*, which could not be viewed by browsers, into .GIF format files, which are very well supported by web browsers.

While .GIF files have been very widely used on the internet, there were unfortunately some issues about programs which produce .GIF files online needing to be licenced prior to use. The licence fee, apparently, cost US$5,000, and therefore, the ppmtogif program could no longer be provided with a GNU public licence [48].

Given this, when AIDA online was moved from North Carolina to London, UK .GIF files could no longer be generated in realtime by the web-based simulator. As a result, the initial release of AIDA online version 2 (AIDA online^2) was modified to make use of .JPG (Joint Photographic Experts Group) and .PNG (Portable Network Graphics) image files, avoiding any problems with dynamically generating .GIF files. Subsequent versions of AIDA online^2 have been modified further to just concentrate on .PNG format graphics, which actually reduce the file sizes, contributing further to the apparent speed of AIDA online^2 (Table 2).

Table 2: Gives typical values for file sizes (in kb) for data and image files made displayable/accessible by the AIDA online simulator. The small file sizes help explain the rapid data transfer via the internet, and contribute to the apparent speed of AIDA online. Reducing the file sizes with .PNG files with the move to the AIDA online version 2 (AIDA online^2) simulator in London, UK ensured reduced bandwidth and increased apparent speed for simulations.

	.JPG	.GIF	.PNG	.DAT
Preparation	8.7	1.6	1.2	
Plasma Insulin	15.1	2.8	1.5	2.3
Carbohydrate	9.2	1.7	1.3	
Glucose	15.1	2.3	1.3	2.2

JPG: Joint Photographics Experts Group; GIF: Graphics Interchange Format; PNG: Portable Network Graphics; DAT: ASCII text format data file.

3. Results

The conversion of the AIDA v4 Pascal program from the DOS-based standalone, downloadable version to Perl has been successful, and AIDA online has been accessible via http://www.2aida.net for a number of years.

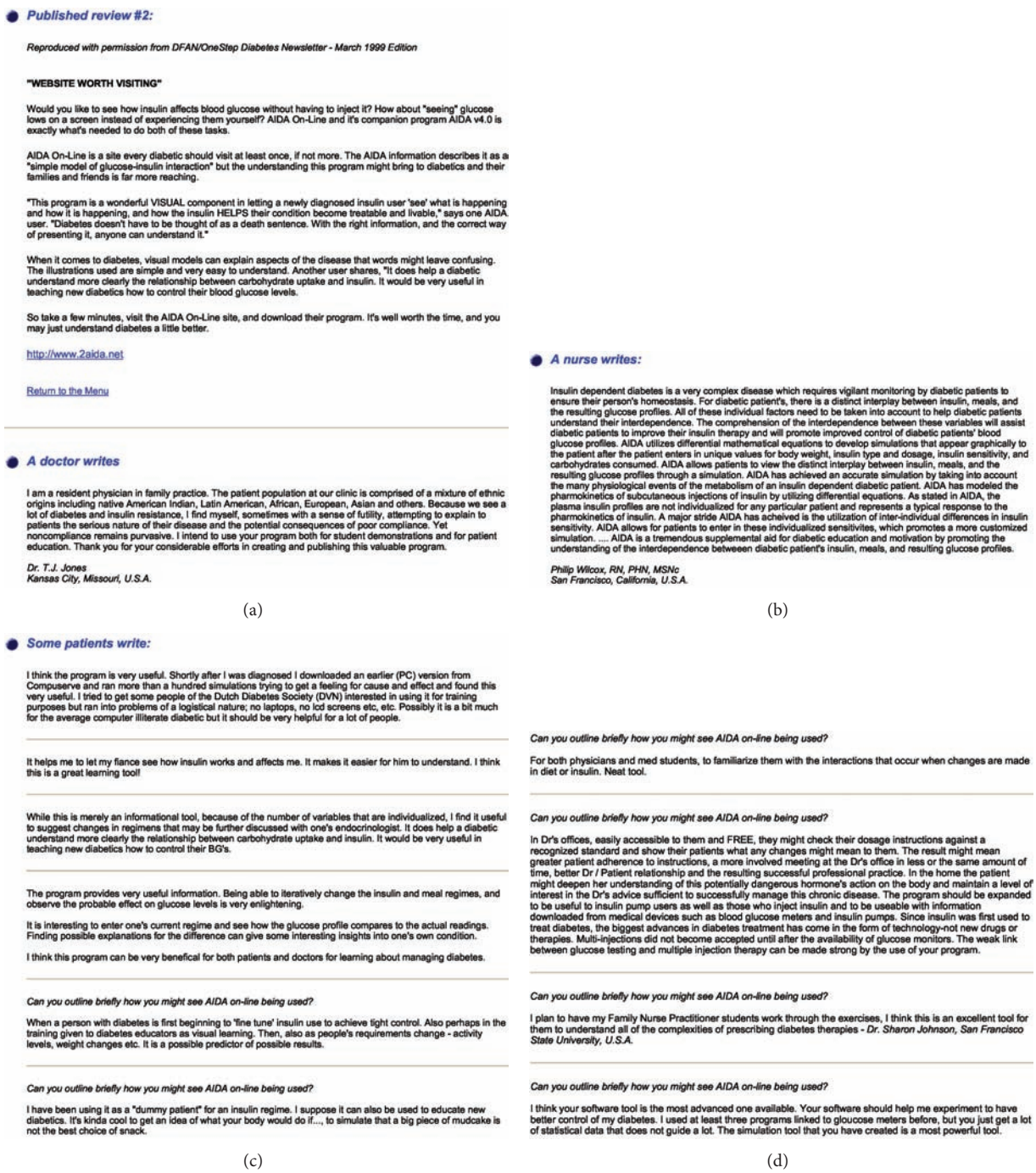


Figure 7: Independent user reviews of AIDA online, reproduced from the AIDA online website (http://www.2aida.org/aida/online-reviews.htm).

The purpose of developing a world wide web accessible glucose-insulin simulator has been to provide an educational opportunity for as many people as possible (patients with diabetes, their relatives, students, and HCPs). In this respect, AIDA online has exceeded all expectations. A range of user comments/reviews can be found in Figures 7(a), 7(b), 7(c), and 7(d).

AIDA online^{beta} first went "live" on the internet for beta testing in December 1997. AIDA online version 1 was formally launched in August 1998, following 8 months of extensive beta testing by the authors and others.

AIDA online has been thoroughly tested with a range of web browsers and works well with Microsoft Internet Explorer, Mozilla Firefox, Google Chrome, and Apple Safari, as well as with Netscape Navigator (in earlier years).

Since records began, over 637,500 diabetes simulations have been run at AIDA online (Figure 8). Since AIDA online was relocated to a server in London, UK, visitors

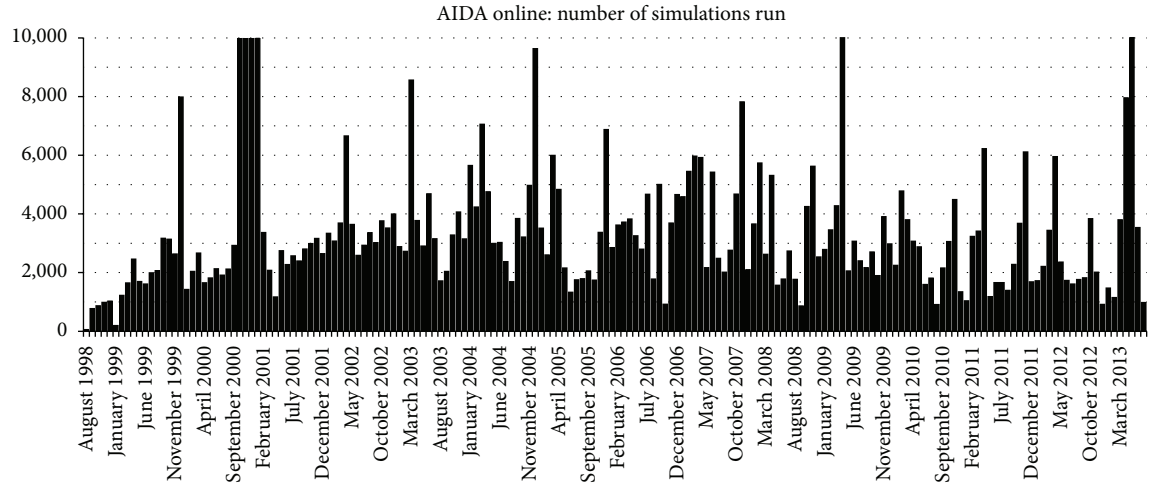


Figure 8: Usage of AIDA online showing the number of simulations run per month versus time. (a) January 1999—server hosting "AIDA online" version 1 crashed, and therefore the facility was unavailable for much of the month. (b) October 2000 to January 2001—simulated blood glucose data harvested from AIDA online by researchers at NASA for training and testing an insulin-dosage adjustment decision support prototype. Over 68,000 simulations were run during this time. Further information available at http://www.2aida.org/nasa.

to the website have been logged from over 115 countries, including (in alphabetical order): Andorra, Argentina, Armenia, Aruba, Australia, Austria, Bahrain, Belarus, Belgium, Bermuda, Bhutan, Bolivia, Bosnia-Herzegovina, Brazil, Brunei Darussalam, Bulgaria, Canada, Chile, China, Christmas Island, Cocos (Keeling) Islands, Colombia, Comoros, Costa Rica, Croatia (Hrvatska), Cuba, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, Estonia, Ethiopia, Faroe Islands, Fiji, Finland, France, French Polynesia, Georgia, Germany, Gibraltar, Greece, Guam, Guatemala, Hong Kong, Hungary, Iceland, India, Indonesia, Iran, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kazakhstan, Kuwait, Latvia, Lebanon, Lesotho, Lithuania, Luxembourg, Macau, Macedonia (Former Yugoslav Republic), Malaysia, Malta, Mauritius, Mexico, Moldova, Morocco, Nepal, Netherlands, New Caledonia, New Zealand (Aotearoa), Nicaragua, Nigeria, Norway, Oman, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia/Russian Federation, Samoa, San Marino, Saudi Arabia, Singapore, Slovakia/Slovak Republic, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Sweden, Switzerland, Taiwan, Thailand, Tonga, Trinidad and Tobago, Turkey, USSR (former), Ukraine, United Arab Emirates, United Kingdom, United States of America, Uruguay, Venezuela, Yemen, and Yugoslavia (former), as well as from nonprofit organizations, unknown IP addresses, US commercial, educational, government and military IP addresses, and dot.net and dot.arpa (old Arpanet) addresses. Independent comments about the simulations have been very encouraging [44, 49–51]. On average, more than 3,200 simulations have been run each month at AIDA online (in 2011–2013).

Figure 9 shows a series of simulations using case scenario 0026 in the AIDA online database. The case details for this scenario record that "*This young woman is on a twice daily insulin regimen, injecting a biphasic preparation which has a premixed 30% to 70% ratio of short versus intermediate acting insulin. While this does not permit quite as much flexibility in selecting a dose—it does save on having to mix insulin in the syringe. Use the simulator to see what would happen if you switched this woman onto other biphasic preparations with, say, premixed 10/90, 20/80, 40/60, or 50/50 percent constituents. . .*"

The simulations given in Figures 9(a), 9(b), and 9(c) demonstrate the usage of AIDA online with premixed (biphasic) insulin injections containing different proportions of short-acting and intermediate-acting insulin preparations.

4. Discussion

The work overviewed in this paper shows how it has been possible to make use of the internet not just as a static repository of information but also as an interactive medium to perform quite complex dynamic simulations in a clinically useful manner. Translating the original PC AIDA v4 Pascal source code into Perl and then utilising a fast web server have allowed many users to access AIDA online simultaneously. The authors are not aware of any diabetes simulation facility as sophisticated as AIDA online that is available anywhere else on the internet.

The main educational utility of AIDA online lies in the ability to rapidly compare results from different diabetes simulations. By modifying the simulated insulin injections, users can learn to exert more control over the BG level of the simulated patient. For instance, possible advantages of using multiple injections and different insulin types can become apparent as different therapeutic combinations are compared. Modifying carbohydrate inputs can also demonstrate the important contribution of diet to BG control. In this respect, large swings in meal carbohydrate intake result in obvious swings in the BG level, which requires insulin injections to be adjusted for the simulated virtual diabetic patient. Having multiple, prestored, example "patients" allows users to see

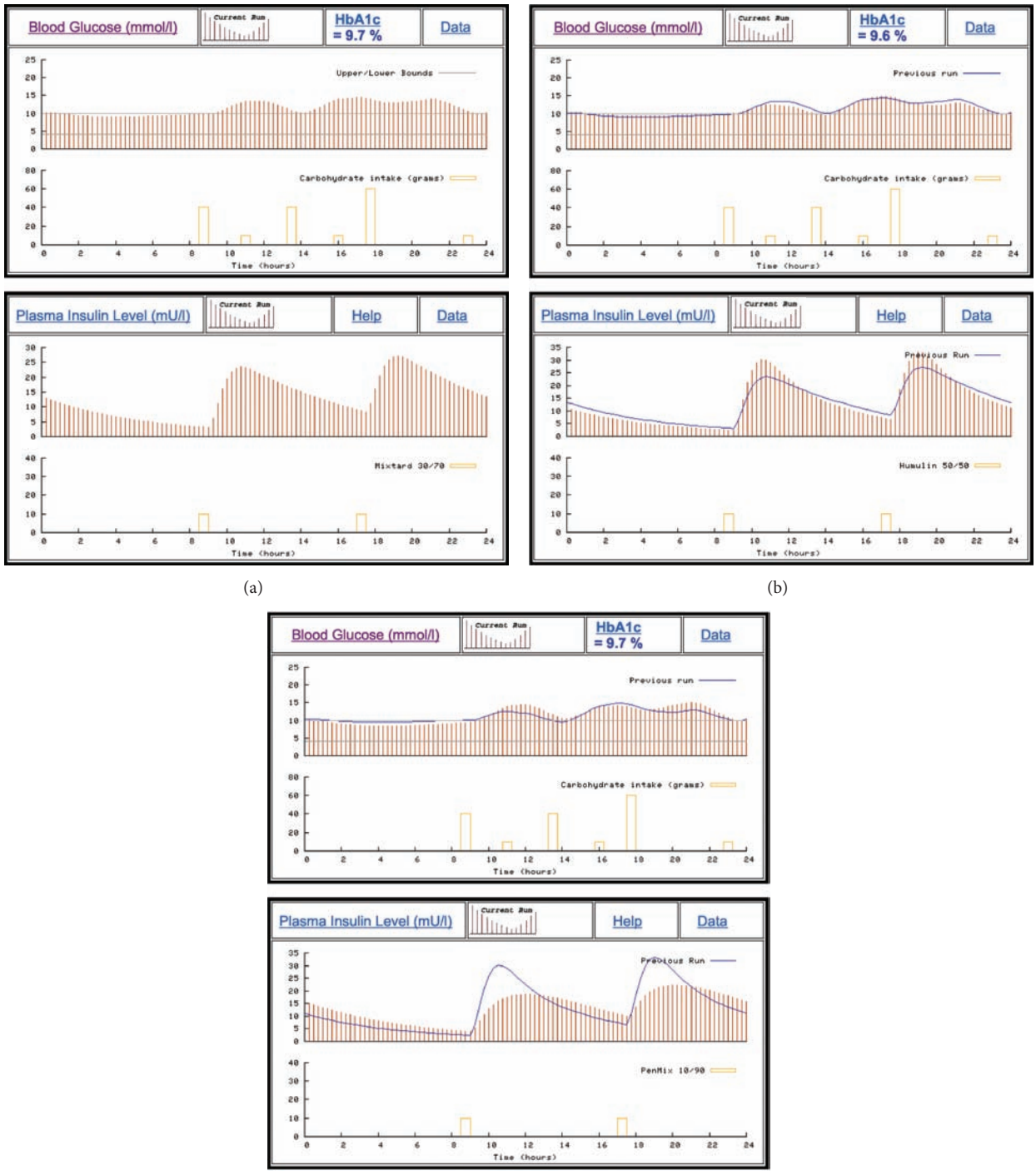


Figure 9: (a) Gives a baseline simulation for case scenario 0026 in the AIDA online database, showing a premixed (biphasic) insulin injection regimen with Mixtard 30/70 being injected twice a day. Mixtard 30/70 is a premixed mixture of 30% short-acting insulin and 70% intermediate-acting insulin. (b) Demonstrates the effect of switching the insulin type from Mixtard 30/70 shown in (a) to Humulin 50/50 (50% short-acting and 50% intermediate-acting insulin) with proportionally more short-acting insulin. The current simulation run is shown as the vertical red lines, with the previous run shown for comparison as the solid blue lines. (c) Demonstrates the effect of switching the insulin type from Humulin 50/50 shown in (b) to PenMix 10/90 (10% short-acting and 90% intermediate-acting insulin) with proportionally more intermediate-acting insulin. The current simulation run is shown as the vertical red lines, with the previous run shown for comparison as the solid blue lines.

the effects of these changes on different patients with different sensitivities to insulin.

The hope is that patients, their relatives, and students can learn how to balance insulin and diet in diabetes by modifying the simulations. The concept underlying this diabetes simulation approach is that patients with diabetes may also improve their ability to actually manage their own diabetes by experimenting in this way. Clearly, this hypothesis remains to be tested in a clinical randomised controlled trial (RCT) setting [52, 53]. However, it is hoped that the relatively widespread use—and widespread availability—of the AIDA PC and AIDA online diabetes simulation approaches will encourage the undertaking of such clinical trials.

There are potential advantages and limitations to both the downloadable and web-based versions of AIDA. However, in reality, the two simulators complement each other remarkably well. One benefit of AIDA online has been to allow visitors to the AIDA websites to try out the simulator—on the web—before downloading a copy to use locally on their PC/Mac. Although not specifically studied, the working hypothesis for this complementary approach is that if people like what they see using AIDA online, they may be more likely to download the standalone (PC) version for further use locally on their home/office computer.

AIDA online extends the concept of the downloadable AIDA PC software by making the simulator accessible via the world wide web from any device (e.g., UNIX based, Apple Mac, or network server computer), smartphone, or WebTV anywhere in the world provided it has internet access and a graphical display. There is no longer a need to have a PC nor to download and install software on a local machine. Furthermore, upgrades to AIDA online require only one version of the program to be changed, and these changes then automatically become accessible to anyone from anywhere in the world. In addition, many users have asked for a windows-based, mouse-controlled "point and click" version of AIDA [54]. AIDA online provides just such an easy to use simulator with a standard user interface accessible in a familiar web browser format.

4.1. Limitations. There are some obvious limitations to AIDA and the underlying model. Physical activity is currently not addressed and assumed to be constant over the course of the steady-state simulation period. It is recognised that different carbohydrate types are absorbed at different rates by the body, but for the purpose of the model, all carbohydrates are considered equal. In addition, although there are modifiable variables for medical conditions, such as renal disease, they are not able to be specifically tailored to exactly recreate a specific patient's condition. Some of this is done intentionally, to keep patients from feeling that they can model their own particular treatment regimen and expect the results obtained to exactly mimic their own BG values. However, the more variables (parameters) included in a model, the more complex it becomes.

One of the not-so-obvious limitations of the model results not from the model itself, but from the patient's own day to day variances, be it diet, insulin dosing, BG data collection, or otherwise, which can affect their own BG readings. Many of these variables (such as exercise, stress levels, or food intake) can change minimally and not be noted by the patient. This was especially notable during the validation process for the original AIDA model [15].

These and other limitations may help to explain why there has been difficulty in applying these models to individual patient therapy planning in clinical practice. However, this does not negate the educational benefit of allowing users to see how carbohydrate intake and insulin usage will affect BG levels on an ongoing basis throughout the day and allow users the opportunity to see how plasma insulin and BG levels interact over a 24-hour time period.

Other limitations of the AIDA online approach relate to the fact that a user clearly needs continuous internet access to use the web-based simulator. In earlier times, this was fine for those in academic/work establishments with continuous web access and for those with unmetered access, for example, in first world countries. However, broadband/dial-up usage does remain an issue for those who still pay by the minute for internet access, for example, via dial-up in certain parts of the world, or who only have time-limited satellite-based internet access, for instance, in some parts of Africa. As there are still many parts of the world with intermittent/no web access, it is recognised that a web-based application like AIDA online will be only of limited benefit in those places, and perhaps the downloadable standalone PC version of the simulator will actually remain of more use in those areas.

Interestingly, the centralised versus distributed computing idea of AIDA online versus AIDA v4 revisits a number of early discussions about PCs versus central servers in years gone past. Things seem to have gone full circle now with "cloud" computing.

4.2. Other Considerations. At present—with its current level of usage—AIDA online does not require a dedicated server. However, potentially one web-based server could have difficulty supporting the extent of usage which has been reported with the downloadable AIDA PC software. For instance, a detailed survey of AIDA v4 users has revealed that 16,790 simulations were run by 200 users [54]. Over a similar period—around the same time—over 16,700 downloads of the AIDA PC software were logged at the main AIDA website. If the survey usage was typical for most AIDA v4 PC downloads, this would suggest that in the region of $16{,}700 \times (16{,}790/200) = 1{,}400{,}000$ simulations might have been run on these 16,700 downloaded copies of the PC software.

From past experience, 2,600 AIDA online simulations run per month account for approximately 610 Mb of website data traffic each month (Dr. E. D. Lehmann, personal communication).

Over a comparable two-year period, based on the AIDA v4 PC survey data [54], AIDA online would have needed to support roughly 23 times as many simulations (approximately 58,300 simulations/month) to run as many simulations as are estimated to have been executed by the AIDA PC software. This would equate to approximately 14 Gb of data traffic per month (23×610 Mb). While these are only estimates,

14 Gb of data transfer per month just for AIDA online would be perfectly feasible to support in internet/web/computing terms. However, together with static HTML traffic from the Diabetes/Insulin Tutorial and AIDA online glossary and PC AIDA v4 software downloads which independently account for 4-5 Gb of data traffic each month (Dr. E. D. Lehmann, personal communication), careful consideration may need to be given to the web hosting company used to permit such an ongoing level of sustained activity.

Furthermore, as an unfunded, not-for-profit, and non-commercial venture, the cost of a dedicated server may be hard to justify just to run AIDA online. Therefore, the web-based simulator is currently hosted on a *shared* server, which substantially reduces the hosting cost.

However, in order to render the graphical simulations, AIDA online relies on local access on the same server to the *gnuplot* program. Access to *gnuplot* is not always included as standard on shared Linux servers; *gnuplot* needs to be compiled on the server for installation, which requires root access. This clearly is possible with a dedicated server, where root access and installation are feasible, but on shared servers, this necessitates the support and cooperation of the web host. Fortunately, *gnuplot* is accessible as part of the "Ruby on Rails" open-source web framework (http://www.rubyonrails.org), which appears to be supported on more shared Linux servers, and in this way, it seems to be possible to find web-hosting companies that will support longer-term access to *gnuplot* even on shared Linux server platforms.

Clearly, at times, the number of simulations run at AIDA online will be high, for example, when people are running diabetes education classes making use of the web-based simulator. At other times, the load on the server will be much lower. It is difficult to predict these surges in usage, but to maintain its position as a well-established, much used web-resource, the AIDA online simulation facility needs to be able to cater for peak demand.

With only one web server running the online simulator if this server goes down, there would be no online diabetes simulations. One solution would be to make use of "mirror sites," but in the early days of AIDA online, cost may have been an issue. However, web hosting costs have fallen dramatically since, so hosting multiple AIDA online simulators on different shared web servers now becomes more practical.

This consideration is of importance particularly if the intention is to encourage third party websites to link to AIDA online and the Diabetes/Insulin Tutorial [46]. For such links, it becomes imperative to offer a good "service," because if AIDA online becomes unavailable, then the service at the other websites will also be restricted. Clearly, other website owners will not wish to make a commitment to using interactive educational simulations, however good, unless they can be assured that the service will be reliable.

Therefore, in the longer term, if AIDA online is to be used even more extensively, a distributed network of mirrored low-cost shared web server accounts might be an appropriate way to proceed. This could be less costly and more flexible than one large dedicated (expensive) server and could help to ensure that the web-based simulator would remain available irrespective of local geographic server issues. One might even consider porting AIDA online to a "cloud" computing cluster, so that usage of the simulator could be scalable and increased, as required by user demand.

Obviously, keeping AIDA online working on multiple servers would raise issues about longer-term maintenance, aside from cost. However, it seems preferable to keep AIDA online operating on a number of separate, distributed web-servers—in different geographical locations—to ensure the web-based simulations can continue to operate irrespective of local issues with any one single web server. For this reason, the process of mirroring AIDA online[2] has started, and one of the authors (EDL) has set up a mirror server for AIDA online[2] in California, USA.

4.3. Future Developments. The authors believe that the full potential of such web-based interactive educational diabetes simulators is yet to be fully realised. As a result, AIDA online and the AIDA website form part of an ongoing development. A number of simple refinements are already planned, but with collaboration and further resources, the novel web-based simulator could be incorporated into a wider range of diabetes educational resources in a number of innovative ways and make an even more significant contribution to the rapidly evolving field of web-based learning.

4.3.1. New Insulins. Recent years have seen the successful introduction of a number of insulin analogues with markedly different action profiles compared with earlier insulin preparations. As these types of insulin are becoming ever more popular with patients and HCPs alike, it will be pertinent to adapt AIDA online to accommodate use of these newer insulins. Such work has been done for AIDA v4 [55–58], and now the concept needs to be ported to an updated release of AIDA online[3] (version 3).

4.3.2. Insulin Pump Therapy. Insulin pumps are increasingly being recognised as an effective way to provide physiological insulin replacement in people with IDDM. As it stands, the AIDA model does not explicitly cater for continuous subcutaneous insulin delivery; however, user feedback has indicated that useful insight can still be gained from the software by using basal levels of insulin and adding in insulin boluses, Ways in which AIDA and AIDA online can be applied for insulin pump simulations, derived from: http://www.2aida.org/pump, are as follows.

To set up a near "basal" level of insulin administration, it is possible to make two entries within AIDA online using a long-acting insulin preparation (e.g. Ultratard, Humulin-U, or Ultralente). These two "injections" need to be set 12 hours apart (say in the morning and evening).

As AIDA and AIDA online are currently limited to 4 insulin administrations (injections) per day, if a user can make one of these long-acting entry times correspond to a meal (and therefore a bolus), that will permit 3 boluses to be given to AIDA / AIDA online, at other times. For example, if a user would like to simulate a basal regimen with 10 units/day, with AIDA or AIDA online the user could enter 4 units of Ultratard in the morning (at 7 am) and 6 units in the evening

(at 7 pm). This would give a background insulin profile that is slightly elevated in the morning, which might be fairly typical for a patient who does not have too much of a blood glucose (BG) rise in the morning.

If a user would like to simulate a bigger morning BG rise (e.g., as in the "dawn phenomenon"), then with AIDA/AIDA online, it is possible to use a slightly more lopsided ratio. For instance, for the 10 units/day Ultratard example given above, a user could split the dose to 3 units in the morning and 7 units in the evening, for the basal background. However the user would need to be careful to not split the basal dose, say 1 unit am and 9 units pm, since the simulator will need some morning long-acting insulin to help flatten out the basal curve in the afternoon.

For the bolus doses, AIDA/AIDA online will allow users to give the simulator up to 4 boluses (injections) of short-acting (regular) insulin, although one limitation is that 2 of these will need to be at the same times as the basal doses. Nevertheless, by giving the simulator a basal and bolus dose together (for instance in the morning), this will still leave users with at least 2 more (and possibly 3) boluses to "play with" later in the day.

It is hoped that in this way—by experimenting with different basal and bolus regimens—users might be able to learn a bit more about balancing insulin and diet in diabetes, even with an insulin pump.

A version of the simulator software which would enable pump regimens to be more completely simulated could be planned. Ultimately, it is hoped that AIDA online may be usefully incorporated into insulin pump training programmes, as a means of illustrating some of the principles of physiological insulin therapy.

4.3.3. Enhancing Structured Education Resources. Flexible insulin therapy is increasingly being recognised as an effective approach to insulin treatment. The Diabetes Control and Complications Trial (DCCT) [59] demonstrated the long-term benefits of intensive insulin treatment; however, the increased risk of hypoglycaemia and increased staff resources used in the DCCT have perhaps limited the adoption of this approach even more widely. However, more recent evidence suggests that appropriate training in insulin adjustment can improve HbA_{1c} without significantly increasing the risk of severe hypoglycaemia [60, 61]. Diabetes self-management skills training enables patients to adapt insulin doses on a daily basis, in order to accommodate increased dietary freedom. This approach originated in Germany but is now widely adopted in many countries. The Dose Adjustment For Normal Eating (DAFNE) trial in the UK [60] has led to the approach receiving increased support, and this educational material is even being adapted for school-age children [62]. Modular outpatient education for flexible insulin treatment adapted for pregnancy has also been shown to improve pregnancy outcome [63].

Web-based diabetes simulators, such as AIDA online, could conceivably be used in such skills-based training programmes to aid understanding of the relationships between insulin dose/timing and meal content/timing. Further refinement of the software to allow for the effects of exercise and/or illness or stress would obviously confer even greater potential. Additionally, the use of web-based resources in training programmes such as those used in the DAFNE approach may help to address the perceived problems associated with staffing levels, time, and resources.

The interactive educational Diabetes/Insulin Tutorial at the AIDA website [46] demonstrates how AIDA online can be integrated with "static" informational material to provide an even more engaging educational resource. It is envisaged that this concept could be expanded further. In particular, AIDA online could potentially be integrated with teaching materials for various different specific audiences, with the text and format of the informational material being tailored appropriately to the target audience. For example, AIDA online could be used in structured training programmes for diabetes HCPs, educators, and students. Specific educational materials could be directed towards various patient populations: teenagers, young women considering pregnancy, patients with low health literacy, patients with noninsulin dependent diabetes mellitus (NIDDM) beginning insulin treatment, and so on. An interactive learning game for school-age children may also be of tremendous value. While it is noted that the AIDA simulator model is based on data for adults with an absolute insulin deficiency, it can still be used effectively to demonstrate the *principles* of insulin adjustment even if some endogenous insulin secretion is still occurring.

AIDA online can also be run across the internet from third-party websites, in a separate "pop-up" or new web browser window. This increases the possibilities for further collaborative intelligent use of the simulator in web-based diabetes education resources.

In particular, there are large numbers of static graphical/fixed textual diabetes educational resources on the internet but not so many online diabetes simulators. In Reed and Lehmann [46], the concept is developed of one simulation engine being able to service a number of educational websites. So, for instance, not all diabetes educational websites need to have the complexity of running AIDA online locally, with (common gateway interface) cgi-bin programs/scripts and *gnuplot* available. With the interconnected web, each educational diabetes resource does not need to run its own copy of the simulator locally.

Therefore, a Diabetes/Insulin Tutorial has been developed at http://www.2aida.info and integrated with AIDA online, which can also now be accessed at other websites—for example http://medweb.bham.ac.uk/easdec/aidadevelopment/tutorial.htm—and the tutorial has even been translated into other languages—for example, Spanish ("Tutorial sobre Insulina y Diabetes") at http://www.um.es/grupo-cirrosis/Insulintutorial/tutorial87.htm Further collaborative website developments like this are expected.

Refinement of the simulator to incorporate the effects of exercise, illness, and stress would be useful. Additional benefits may also be derived from adding in functions to allow for some variation in the glycaemic index of carbohydrates consumed.

The AIDA model thus far has been centred on people with IDDM and focuses on the diet and insulin interactions instituted by the patient/student. Of necessity, many of the interactions have been simplified. This is the nature of modelling to present as simple and as accurate a version of an event as possible.

The validation work performed on the original downloadable AIDA software precluded using this method as a treatment planner but was found to be sufficiently accurate to warrant use as an educational tool [15]. The same issues apply to AIDA online, and this fact is extensively noted at the AIDA website to try and prevent patients from directly applying data from AIDA online simulations to their personal treatment plans (e.g. see caveats in Figures 3(a) and 3(b)).

By focusing predominantly on insulin therapy and carbohydrate intake, while unobtrusively accounting for some of the significant medical modifiers, AIDA online allows users to experiment with various regimens and see how they may affect the overall glucose-insulin balance.

This is done by providing a relatively simple interface for the user to input/modify times and amount of carbohydrate intake, as well as insulin dosages, and providing a wide variety of insulin types to choose from. The simulation can then be run in either a basic (standard) or advanced mode, with the difference being in the number and type of graphs that are displayed.

As part of future work, it is intended to increase the number of AIDA online case scenarios available on the web. Already, three extra cases have been generated, which are accessible directly at http://www.2aida.org/aida/fast-track8.htm, http://www.2aida.org/aida/fast-track1.htm, and http://www.2aida.org/aida/fast-track14.htm These just now remain to be included in the main AIDA online case scenario database. Additional case scenarios will be added, particularly when new cases are generated for the lispro/glargine release of AIDA v4 (v4.5c) and once the new insulin analogues (lispro and glargine [55–58]) have been incorporated into AIDA online version 3 (AIDA online^3).

4.3.4. Other Possible Developments. There are other ideas for further work that warrant consideration. Eventually, if arrangements could be made to track users (teachers) at AIDA online, it would be possible to have a tutorial or series of lessons that teachers could go through to be credentialed to teach with the simulator. The idea could be developed to get teachers up to speed with using the diabetes simulations and what AIDA is about. Potentially, this could even form part of continued medical education (CME). Technically, it is likely to be less challenging to track users of an online simulator than a downloadable/offline simulator like AIDA v4.

One could even envisage a logon Perl script to monitor usage of AIDA online by patients as part of a RCT with HbA_{1c} measured before and after lessons with the simulator, possibly using home HbA_{1c} monitoring kits. Something similar (without HbA_{1c} monitoring) has been tried for a small number of medical students by DeWolf [47], but the approach might be more powerful with hundreds, or thousands, of people with diabetes accessing AIDA online and the accompanying Diabetes/Insulin Tutorial [46].

There have also been suggestions to permit some user selectable different colours to be chosen for the graphs in AIDA online. Allowing grey scale or other colour schemes to be selected may assist patients with visual impairments/colour blindness to maximize their access to and the usability of the web-based simulations, and this is planned to be investigated as part of future development work with AIDA online.

4.4. Conclusions. In terms of its functionality, the current version of AIDA online^2 is similar in many ways to the PC version of AIDA (v4.3d). However, with its improved mouse-based user interface—and the fact that only one version of the program needs to be changed to distribute updates—it is envisaged that AIDA online^2 may become more amenable to further upgrades and improvements in functionality, in due course.

It is recognised that making use of a simulator in a standard web-browser window, which most people know how to use, could also potentially help decrease the "learning curve" for generating simulations, compared with a downloadable version of the program.

Nevertheless, the designated purpose of the standalone PC software and AIDA online remains the same. In this respect, AIDA online should be solely regarded as an educational tool which some patients and HCPs have found fun and interesting to use. It is provided free of charge—from a not-for-profit website at: http://www.2aida.net—as a non-commercial contribution to continuing diabetes education, in the hope that more people may find it of some use.

A number of verification, validation, and clinical evaluation studies have been performed with the downloadable versions of AIDA v4 (e.g., see [15]). Thus far, relatively little evaluation work has been done with AIDA online, aside from a small study by DeWolf investigating the value of the web- based simulator as an educational tool for medical students [47] and an assessment of AIDA online for teaching high school students [64]. Part of the reason for the relatively limited assessment of the AIDA online version of the simulator, to date, may simply be its self-evident use.

However, in view of the fact that the mathematical model underlying AIDA online is the same as that in the downloadable software, going forward evaluation work for AIDA online may benefit from focusing particularly on human factor assessments, as well as identifying optimal ways to actually apply AIDA online in clinical/teaching settings.

One major advantage to utilising a server-based application (as opposed to a downloadable program) is the flexibility that is offered. New modules can be added to the simulator which become available instantaneously around the world. This has facilitated the development of AIDA online version 2 (AIDA online^2), as well as various more recent refinements to the web-based simulator.

5. System Availability

The most up-to-date version of AIDA online (version 2) is available without charge at the http://www.2aida.net website. Following completion of further programming and bench testing work, it is expected that new, improved versions of AIDA online will become available in due course. People who wish to be automatically informed by email about updates to AIDA online are welcome to join the very low volume AIDA registration/announcement list by sending a blank email note to subscribe@2aida.org or by following AIDA on Facebook at http://www.facebook.com/www.2aida.org and/or at http://www.facebook.com/aida.diabetes.simulator1 or on Twitter at http://www.twitter.com/aida_diabetes.

Conflict of Interests

The authors confirm that they do not have any financial relation with any of the commercial entities mentioned in this paper, that might lead to a conflict of interests. The AIDA PC software referred to in this report is an independent, noncommercial development which is being made available free of charge via the internet, at a dot org (.org) not-for-profit website, as a noncommercial contribution to continuing diabetes education. The AIDA online simulator described in this paper is also an independent, noncommercial, collaborative development which is being made available without charge via the internet at its linked http://www.2aida.net not-for-profit website, as a noncommercial contribution to continuing diabetes education. There are no patents or trademarks protecting the AIDA PC software or AIDA online.

Acknowledgments

Dr. Eldon D. Lehmann acknowledges the warm and close collegial collaboration in earlier years with Dr. Tibor Deutsch (originally from the Computer Centre, Semmelweis University, Budapest, Hungary, and more recently at the Department of Medical Imaging and Instrumentation, Faculty of Health Sciences, Semmelweis University, Budapest, Hungary) that led to the codevelopment, testing, initial distribution, and enhancement of the original PC AIDA v4 model [1–3, 13–15, 42, 43, 55–58]. Dennis K. DeWolf, Christopher A. Novotny, and Robert R. Gotwals acknowledge the kind oversight and support of the following in the North Carolina State University (NCSU) Senior Design Project (SDP) which forms part of the work described in this paper: Dr. Susan M. Blanchard-SDP Organiser in the Department of Biological and Agricultural Engineering (BAE), NCSU, NC 27695, USA; Professor Roger P. Rohrbach, Head of the BAE Department at NCSU; and Dr. Robert M. Panoff, President and Executive Director, Shodor Education Foundation, Durham, NC 27701, USA.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2013, Article ID 679396, 7 pages
http://dx.doi.org/10.1155/2013/679396

Review Article

Transcultural Diabetes Nutrition Algorithm: A Malaysian Application

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Received 27 June 2013; Accepted 27 September 2013

Academic Editor: Patrizio Tatti

Glycemic control among patients with prediabetes and type 2 diabetes mellitus (T2D) in Malaysia is suboptimal, especially after the continuous worsening over the past decade. Improved glycemic control may be achieved through a comprehensive management strategy that includes medical nutrition therapy (MNT). Evidence-based recommendations for diabetes-specific therapeutic diets are available internationally. However, Asian patients with T2D, including Malaysians, have unique disease characteristics and risk factors, as well as cultural and lifestyle dissimilarities, which may render international guidelines and recommendations less applicable and/or difficult to implement. With these thoughts in mind, a transcultural Diabetes Nutrition Algorithm (tDNA) was developed by an international task force of diabetes and nutrition experts through the restructuring of international guidelines for the nutritional management of prediabetes and T2D to account for cultural differences in lifestyle, diet, and genetic factors. The initial evidence-based global tDNA template was designed for simplicity, flexibility, and cultural modification. This paper reports the Malaysian adaptation of the tDNA, which takes into account the epidemiologic, physiologic, cultural, and lifestyle factors unique to Malaysia, as well as the local guidelines recommendations.

1. Introduction

Globally, the prevalence of prediabetes and type 2 diabetes (T2D) is increasing as a consequence of social, epidemiologic, and demographic shifts, such as population aging and urbanization [1, 2]. The majority of people with these conditions now live in low- and middle-income countries, including many Asian nations, where substantial increases in incidence

rates are anticipated by the year 2030 [2]. According to the fourth Malaysian National Health and Morbidity Survey (NHMS IV) carried out in 2011, the prevalence of T2D in Malaysian adults ≥30 years of age had risen to 20.8%, affecting an estimated 2.8 million individuals [3] as compared with the third National Health and Morbidity Survey (NHMS III), which reported a prevalence of 14.9% in 2006 [4]. The heterogeneous nature of Asian populations gives rise to unique T2D features. For example, Asians tend to develop T2D at a lower body mass index (BMI), at younger age, and with a lower waist circumference than Caucasians [5, 6], and their course of illness is punctuated with earlier chronic complications [7–9] and frequent postprandial hyperglycemia [10]. These and other clinical features must be recognized and factored into lifestyle recommendations in order to tailor management to individual needs and improve the effectiveness of preventive and therapeutic efforts at the primary care level.

2. Methods and Materials

The universal tDNA template for patients with prediabetes and T2D was established by an international task force of experts during a two-year process that included planning and developmental meetings, evidence collection and review, consensus building, and algorithm construction and face validation [11]. The initial global template was designed for simplicity, flexibility, and cultural modification. A comparable process was used by an appointed Malaysian task force to adapt the algorithm to meet the needs of practitioners and patients in Malaysia. The regional version emerged through the modification of general tDNA recommendations to account for cultural, lifestyle, food, diet, and genetic differences that exist among the Malaysian people.

2.1. Perspectives Unique to Malaysia. Among the major ethnic groups in Malaysia, Indians (24.9% in 2011 and 19.9% in 2006) had the highest prevalence of T2D, followed by Malays (16.9% in 2011 and 11.9% in 2006) and Chinese (13.8% in 2011 and 11.4% in 2006) [3, 4]. These epidemiologic differences could be due to the genetic makeup, diet, and cultural variants among these major ethnic groups.

The overall prevalence of abdominal obesity in Malaysia, measured by waist circumference, has been reported between 55.6% and 57.4% [13, 14]. Epidemiologic studies investigating abdominal obesity in Malaysia have consistently shown an ethnic trend similar to that seen in T2D with prevalence being highest among Indians (65.5–68.8%), followed by Malays (55.1–60.6%), Chinese (49.5–51.1%), and other indigenous groups (44.9–48.3%) [13, 14]. The prevalence of abdominal obesity is increased among patients with T2D and is observed in 75% of T2D patients in Malaysia. Moreover, in the DiabCare Malaysia 2008 study, the most recent study in an ongoing initiative to monitor diabetes control in Malaysia, undesirable waist circumference was reported in a higher proportion of women (≥80 cm in 89.4%) than men (≥90 cm in 73.7%) with T2D [15]. The study patients with T2D, 72% of whom were obese, had a mean BMI of 27.8 kg/m^2.

Glycemic control in Malaysia continues to deteriorate despite initiatives by the Ministry of Health to increase awareness and also expanded accessibility of glycosylated hemoglobin (A1c) testing across the country. The DiabCare Malaysia 2008 study reported a mean A1c of 8.66%, compared with 8.0% [16] in 2003, a mean fasting glucose of 8.0 mmol/L, and an elevated mean postprandial glucose of 12.7 mmol/L in Malaysians with T2D. Furthermore, only 22% of the patients achieved the glycemic target of A1c <7%, the lowest rate since 1998 [15]. Data from the online registry database Adult Diabetes Control and Management (ADCM) revealed ethnic differences in glycemic control and complication profiles among Malaysians. Chinese patients had the lowest mean A1c levels, while Malaysian Indians had the highest [17].

Only 16.4% of the Malaysian patients adhere to the dietary regimen provided by dietitians [20]. Interestingly, patients were found to adhere to the advice of "eat lots of food high in dietary fiber such as vegetables or oats" but found it difficult to eat five or more servings of fruits and vegetables per day. Self-care practices among the majority of patients with suboptimal glycemic control are obviously inadequate. A large proportion of Malaysian T2D patients consume four or more meals a day and more than two carbohydrate portions per snack [21].

The current Malaysia Clinical Practice Guidelines (CPGs) for the management of T2D contain recommendations without any specific reference to glycemia-targeted specialized nutrition (GTSN), that is, oral nutritional products that facilitate glycemic control and may be used as meal and/or snack replacements or supplements as part of the medical nutrition therapy (MNT) [18]. With the increasing prevalence of prediabetes and T2D and the continued deterioration of glycemic control among patients in Malaysia, there is a clear need for a simple MNT algorithmic decision-making tool to address these issues. This paper summarizes the Malaysian adaptation of the universal tDNA template [11]. See Figure 1. Specific Southeast Asian and Asian Indian tDNA versions have also been published [22, 23].

3. Results: Transcultural Factors for Malaysia

3.1. Assessment of Body Composition and Risk of Disease Progression. The World Health Organization (WHO) Western Pacific Regional Office and the International Diabetes Foundation (IDF) define overweight and obesity in Asians as BMI greater than 23 kg/m^2 and 25 kg/m^2, respectively [24]. Lower cutoff values are required for Asian populations because Asians generally have a higher percentage of intra-abdominal fat compared with Caucasians of the same age, sex, and BMI [25]. Furthermore, Asian populations have higher cardiovascular and T2D risk factors than Caucasians at any BMI level [25, 26], thereby highlighting the rationale for defining Asian-specific cutoff values for anthropometric measures.

The Malaysian CPG for the management of obesity categorizes overweight as BMI of 23.0–27.4 kg/m^2 and obesity as BMI of 27.5 kg/m^2 and above [28]. Waist circumference cutoff values for abdominal obesity are 90 cm for men and 80 cm for women [24]. Similarly, these cutoff values are also found in the CPG for the management of T2D in Malaysia [12] and are used as the standard throughout this paper.

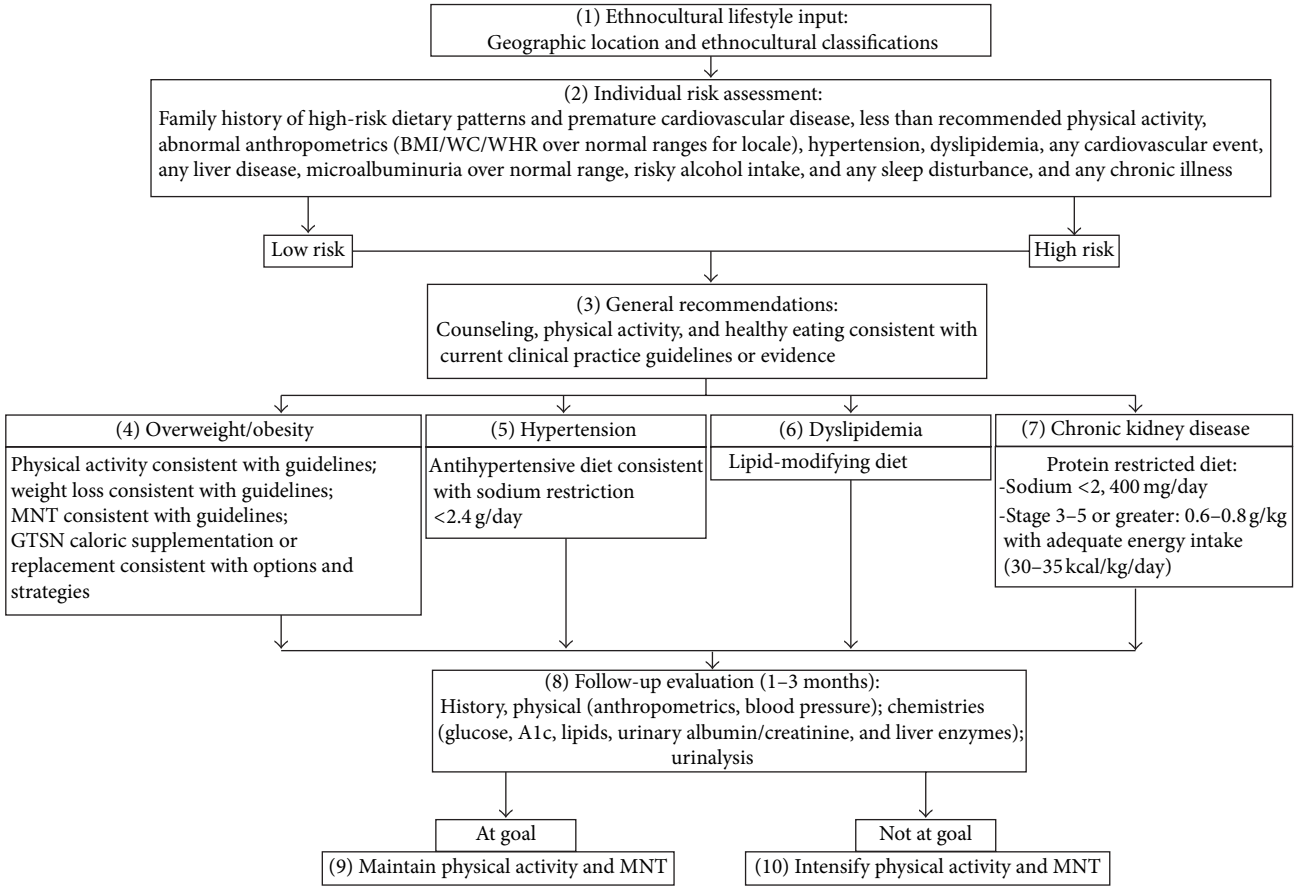

Figure 1: Transcultural Diabetes Nutrition Algorithm (tDNA): Malaysian application.

3.2. Physical Activity in T2D Management. Physical activity and exercise have been shown to lower blood glucose levels, improve glucose and insulin utilization, and improve carbohydrate metabolism [29, 30]. Benefits of physical activity have been demonstrated in both Caucasian and Asian patients with T2D [31–34]. The Malaysian CPG for the management of T2D recommends physical activity as an integral feature in every stage of T2D management [12]. These recommendations are echoed in the Malaysian tDNA application (Table 1).

3.3. MNT and Weight Loss in T2D Management. MNT plays an integral role in T2D management and indeed is recommended by the American Diabetes Association as an important component of individual weight loss programs for T2D patients [35]. The benefits of MNT on glycemic control in Asians with prediabetes and T2D have been demonstrated in clinical trials [36–39]. On-site registered dietitian-led management of MNT has been shown to improve glycemic control in poorly-managed patients with T2D in primary care clinics in Taiwan. Patients with A1c levels ≥7% who received on-site diabetic self-management education had significantly greater improvements in fasting plasma glucose and A1c levels after one year than control subjects or subjects with A1c levels <7% [36]. A lifestyle intervention that includes MNT was found to be effective in preventing or delaying the development of T2D in middle-aged Japanese patients with impaired glucose tolerance [40, 41].

The Malaysian Dietitians' Association (MDA) has formed an expert committee, comprising dietitians from primary care, hospitals, and academia, to compose MNT recommendations for T2D. The first version was published in 2005 [42] and updated in 2013 [43]. Building on the MNT guidelines recommended by the MDA, the Malaysian CPG for the management of T2D, and taking into consideration similar Malaysian CPGs for hypertension and dyslipidemia, this panel recommends the nutritional considerations outlined in Table 2 [12, 18, 19].

Weight loss is an important therapeutic objective for T2D patients to reduce insulin resistance. Moderate weight loss of just 5–10% of body weight in patients with T2D has been shown to decrease insulin resistance and improve other metabolic risk factors [38, 44, 45]. GTSN formulae are a component of MNT that contain nutrients to facilitate weight management and glycemic control. These formulae are available in Malaysia and may be utilized with nutritional counseling as meal and/or snack replacements for overweight and obese patients and those with suboptimal glycemic

Table 1: Physical activity guidelines for the management of type 2 diabetes[a] [12].

All patients	Frequency	Exercise 5 days a week with no more than 2 consecutive days without physical exercise
	Intensity and type	(i) Moderate-intensity activities include walking down stairs, cycling, fast walking, doing heavy laundry, ballroom dancing (slow), noncompetitive badminton, and low-impact aerobics (ii) Vigorous activities include jogging, climbing stairs, football, squash, tennis, swimming, jumping rope, and basketball
	Duration	150 min per week of moderate-intensity aerobic physical activity and/or at least 90 min per week of vigorous aerobic physical activity
Overweight or obese patients (BMI > 23)		Gradually increase physical activity to 60–90 minutes daily for long-term major weight loss

BMI: body mass index.
[a]Patients should be assessed for complications that may preclude vigorous exercise. Age and previous physical activity level should be considered.

Table 2: Nutrition guidelines for the management of type 2 diabetes [12, 18, 19].

Calories	For overweight and obese individuals, a reduced calorie diet of 20–25 kcal/kg body weight is recommended to achieve a weight loss of 5–10% of initial body weight over a 6-month period
Carbohydrate	45–60% daily energy intake
Protein	15–20% daily energy intake
Fat	25–35% daily energy intake
Saturated fat	Less than 7% of total calories
Cholesterol	Less than 200 mg/day
Fiber*	20–30 g/day
Sodium	<2,400 mg/day

*Should be derived predominantly from foods rich in complex carbohydrates including grains (especially whole grains), fruits and vegetables.

control, including persons with high insulin requirements. These formulae are also indicated as a supplementary nutrition for patients with diabetes and acute concurrent illness who are unable to maintain optimal nutrition due to reduced appetite and calorie intake. Recommendations for the use of meal replacements will be incorporated in the revised MNT guidelines from the MDA.

3.4. Nutritional Management of Patients with Concomitant Hypertension, Dyslipidemia, and/or Chronic Kidney Disease (CKD). Data from the ADCM's online registry database showed that as many as 57% of the Malaysian patients with T2D experience concomitant hypertension [46]. Among the ethnic groups in Malaysia, more Malay patients (62.3%) have concomitant hypertension than Chinese (19.6%) or Indian (17.0%) patients. In patients with T2D, hypertension is defined as blood pressure >130/80 mmHg on two readings 2-3 weeks apart [12]. Pharmacotherapy for hypertension should be initiated in patients with T2D when the blood pressure is persistently >130 mmHg systolic and/or >80 mmHg diastolic [12]. For patients with concomitant hypertension, salt intake should be restricted to <6 g/day (sodium 2 g) [18].

The ADCM also revealed that as many as 38% of the patients with T2D in Malaysia suffer from concomitant dyslipidemia [47]. Malays were more likely to have uncontrolled low-density lipoprotein cholesterol (LDL-C) and triglycerides compared with Chinese and Indians; however, Indians were twice as likely to have inadequate high-density lipoprotein cholesterol compared with Malays [47]. A recent study that investigated the ethnic differences in lipid metabolism among Malaysian patients with T2D demonstrated that Malays had significantly higher serum levels of glycoxidation and lipoxidation products compared with those of Chinese and Indian patients [48]. For T2D patients with dyslipidemia, lifestyle modification focusing on the reduction of saturated fat (<7% of total calories), trans fat (avoid), and cholesterol (<200 mg/day) intake has been recommended [12, 19]. In accordance with the Malaysian CPG for dyslipidemia, patients over the age of 40 without overt cardiovascular disease (CVD) should be treated with lipid lowering drugs, regardless of the baseline LDL-C levels, while all patients with overt CVD, irrespective of age, should be treated with lipid lowering drugs [19].

For T2D patients with concomitant CKD, limited protein intake and daily sodium <2400 mg are recommended. For those with CKD stages 3–5, daily protein should be limited to 0.6–0.8 g/kg in a diet with adequate energy intake (30–35 kcal/kg/day) [49].

4. Conclusions

The following recommendations, statements, figures, tables, and graphs represent the conclusions of the Malaysian transcultural Diabetes Nutrition Algorithm (tDNA) task force and constitute the current Malaysian tDNA application, which accommodates local differences in lifestyle, foods, and customs and incorporates established local Clinical Practice Guidelines (CPGs) to meet the needs and preferences of type 2 diabetes (T2D) patients in Malaysia.

Recommendation 1. Medical nutrition therapy (MNT) is an integral component of the management of T2D and must be prioritized in view of poor glycemic control among patients in Malaysia. Individualized care plans are essential

Table 3: Glycemia-targeted specialized nutrition (GTSN) for the management of prediabetes and type 2 diabetes.

Overweight (BMI > 23 kg/m^2) or obese (BMI > 27.5 kg/m^2)		Use meal and/or snack replacements[a] as part of a meal plan to reduce total calorie intake (i) Calorie reduction of 500–1000 calories per day (to lose 0.5–1.0 kg per week), using 1-2 servings of a GTSN formula[b] to replace 250–500 calories from meals (ii) Reassess every 1–3 months
Normal weight (BMI 18–23 kg/m^2)	Controlled diabetes (A1c ≤ 6.5%[c])	The use of meal replacements should be based on clinical judgment and individual assessment[d]
	Uncontrolled diabetes (A1c > 6.5%[c])	Use 1-2 servings of a GTSN formula per day to be incorporated into a meal plan
Underweight (BMI < 18 kg/m^2)		Use 1–3 servings of a GTSN formula per day as supplementation based on clinical judgment and individual assessment of desired rate of weight gain and clinical tolerance

BMI: body mass index; A1c: glycosylated hemoglobin; GTSN: glycemia-targeted specialized nutrition.

Recommendations were rated and assigned numerical and alphabetical descriptors according to levels of scientific substantiation provided by the 2010 American Association of Clinical Endocrinologists protocol for the development of Clinical Practice Guidelines [27].

[a]Meal and snack replacements are nutritional products used as replacement for meals or snacks to replace calories in the diet. It is suggested that products used should meet the American Diabetes Association nutritional guidelines.

[b]Glycemia-targeted specialized nutrition formulas are complete and balanced products with at least 200 calories per serving used as part of a meal plan to help control calorie intake and achieve glycemic control.

[c]Glycemic (A1c) targets should be individualized for each patient based on local CPGs.

[d]To avoid hypoglycemia or postprandial hyperglycemia, individuals who may have muscle mass and/or function loss and/or micronutrient deficiency may benefit from a nutrition supplement. Individuals who need support with weight maintenance and/or a healthy meal plan could benefit from meal replacement.

in order to increase adherence and compliance with MNT recommendations.

Recommendation 2. Personalized nutrition counseling by a dietitian is recommended and should be individualized according to personal nutritional needs, concomitant disease, severity of T2D, cultural preferences, and patient cooperation. If access to a dietitian is not possible, all newly diagnosed patients should receive basic nutrition and dietary counseling from either doctors or diabetes educators.

Recommendation 3. Values for body mass index (BMI) cutoffs in the Malaysian CPGs are recommended for use in the Malaysian tDNA.

Recommendation 4. The Malaysian CPG for the management of T2D recommends physical activity as an integral feature in every stage of T2D management [12]. These recommendations are adopted in the Malaysian tDNA (Table 1).

Recommendation 5. Overweight and obese individuals should achieve a weight loss of 5–10% of the initial body weight over a 6-month period (Table 2).

Recommendation 6. The nutritional recommendations outlined in Table 2 (adapted from the Malaysian Dietitians' Association's MNT guidelines and the Malaysian CPG for the management of T2D) should be implemented as part of the Malaysian tDNA.

Recommendation 7. Patients with T2D and concomitant hypertension should limit salt intake to <6 g/day (sodium 2 g). Those with concomitant chronic kidney disease (CKD) should limit protein intake, especially those with CKD stages 3–5 (daily protein of 0.6–0.8 g/kg with adequate energy intake of 30–35 kcal/kg/day).

Recommendation 8. Lifestyle modification focusing on the reduction of saturated fat (<7% of total calories) and cholesterol (<200 mg/day), as well as the avoidance of trans-fat, is recommended for patients with T2D and concomitant dyslipidemia.

Recommendation 9. The use of meal replacements should be based on clinical judgment and individual assessment. For patients who are overweight, meal and/or snack replacements are recommended as part of meal plans to reduce total calorie intake (Table 3). For patients of normal weight with uncontrolled T2D, 1-2 servings of a GTSN formula per day, incorporated into a meal plan as meal or snack replacement, are recommended. For underweight individuals, 1–3 servings of a GTSN formula per day are recommended as supplementation based on the clinical judgment and individual assessment of desired rate of weight gain and clinical tolerance.

Recommendation 10. To provide support and motivate patients to comply with MNT, monthly follow-ups are recommended for patients with poorly-controlled T2D and for those who are at high risk of complications. For patients with well-controlled T2D, regular follow-up every 3 months is recommended.

Disclosures

Zanariah Hussein has received consulting fees from Abbott Nutrition, Novo Nordisk, AstraZeneca, and Boehringer Ingelheim. Osama Hamdy has served as a consultant for Abbott Nutrition and a speaker for Amylin/Eli Lilly. Yook Chin Chia has received honorarium for lectures from Pfizer, Servier,

AstraZeneca, Sanofi-Aventis, Reckitt Benckiser, GlaxoSmith-Kline, and Sandoz. Shueh Lin Lim has received honorarium for lectures from Merck Sharp Dohme, Eli Lilly, Abbott, Novo Nordisk, Novartis, AstraZeneca, Merck Serono, and Sanofi-Aventis. Santha Kumari has no conflict of interests to declare. Husni Hussain has received honorarium for lectures from Merck Serono, Sanofi-Aventis, and ASP Medical Clinic Sdn Bhd. Ming Yeong Tan has received consulting fee from Abbott Nutrition and honorarium for lectures from Roche Diagnostics, Abbott Nutrition, Merck Sharp Dohme, and Merck Serono. Ridzoni Sulaiman, Barakatun Nisak, and Winnie Siew Swee Chee have received consulting fee or honorarium from Abbott Nutrition. Refaat A. Hegazi is employed by Abbott Nutrition; the material presented in this paper is based on the best-known clinical evidence and is not affected by this financial relationship. Albert Marchetti has received financial support for research and the development of educational materials from Eli Lilly, Takeda, GlaxoSmithKline, Bristol-Myers Squibb, and Abbott Nutrition. Jeffrey Mechanick has received financial support for the development of educational presentations from Abbott Nutrition. He has received financial support for consultancy and for writing and reviewing the paper from Abbott Nutrition. He has received fees for participation in review activities such as data monitoring boards, statistical analysis, and endpoint committees from Abbott Nutrition International. He has received funding for travel and accommodations from Abbott Nutrition.

Acknowledgments

The content of this paper was created and enriched solely by the authors, tDNA task force members, through a process of the ongoing literature searches, independent contributions and reviews, and group interactions for consensus. Financial support was provided by Abbott Nutrition International through an educational grant. Editorial support was provided by Mediconnexions Consulting Sdn Bhd.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2013, Article ID 203610, 7 pages
http://dx.doi.org/10.1155/2013/203610

Clinical Study

B-Flow Twinkling Sign in Preoperative Evaluation of Cervical Lymph Nodes in Patients with Papillary Thyroid Carcinoma

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Received 20 December 2012; Accepted 26 April 2013

Academic Editor: Annabel E. Barber

Papillary thyroid cancer (PTC) is the most common histologic type of differentiated thyroid cancer. The first site of metastasis is the cervical lymph nodes (LNs). The ultrasonography (US) is the best diagnostic method for the detection of cervical metastatic LNs. We use a new technique, B-flow imaging (BFI), recently used for evaluation of thyroid nodules, to estimate the presence of BFI twinkling signs (BFI-TS), within metastatic LNs in patients with PTC. Two hundred and fifty-two patients with known PTC were examined for preoperative evaluation with conventional US and BFI. Only 83 with at least one metastatic LN were included. All patients included underwent surgery; the final diagnosis was based on the results of histology. The following LN characteristics were evaluated: shape, abnormal echogenicity, absent hilum, calcifications, cystic appearance, peripheral vascularization, and BFI-TS. A total of 604 LNs were analyzed. Of these, 298 were metastatic, according to histopathology. The BFI-TS showed high values of specificity (99.7%) and sensitivity (80.9%). The combination of each conventional US sign with the BF-TS increases the specificity. Our findings suggest that BFI can be helpful in the selection of suspicious neck LNs that should be examined at cytologic examination for accurate preoperative staging and individual therapy selection.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common histologic type of differentiated thyroid cancer and accounts for 80% of all thyroid cancers [1, 2]. The disease-specific survival rate of PTC is excellent but its recurrence rate is high [2–4]. PTC and the follicular variant of PTC have a propensity for cervical lymphatic spread that occurs in 20% to 50% of patients on standard review of surgical pathologic specimens and in 90% of those examined for micrometastases [3–7]. The spread of tumor cells occurs in a predictable pattern that initiates in the perithyroidal lymph nodes (LNs) of the central neck and progresses to the LNs of the lateral cervical compartments and the superior mediastinum [8, 9]. Skip metastases to the lateral compartment without central neck nodal involvement are rare but do occur [8, 9]. Patients with nodal metastasis have higher rates of persistent and recurrent disease during postoperative surveillance [10]. Furthermore, lymph node metastasis has also been identified as a risk factor for distant metastasis.

Several studies have shown that ultrasonography has higher sensitivity than palpation and the other diagnostic methods for the detection of cervical metastatic LNs in patients with PTC [11]. Ultrasound is easily repeatable and has been shown to change the surgical procedure performed in 39% of thyroid cancer patients. [12, 13]. Metastatic LNs tend to be large, round, hypoechoic, and hypervascularized with a loss of hilar architecture [14, 15]. In differentiated thyroid cancer, metastatic LNs may also have specific features such as hyperechoic punctuations or microcalcifications and cystic appearance [16–18].

B-flow imaging (BFI) is a non-Doppler technique widely used to evaluate carotid artery stenosis and other vascular diseases [19]. The BFI technique has recently been used to evaluate thyroid nodules [20, 21]. BFI can identify a new sign (the twinkling sign; BFI-TS) in "suspect" PTC nodules, which

appeared to be generated by microcalcifications and increase the US accuracy in identification of malignant nodules [20, 21]. The BFI-TS is a rapidly flashing white light behind such stationary objects as microcalcifications, which gives the appearance of movement.

When an incidental sonographic beam impinges a rough interface composed of sparse reflectors, the sign is generated by the phase shift, thereby causing a faint variation of the sonographic beam at the interface. The sign is also caused by the increase of pulse duration, which results in multiple reflections in the medium. In thyroid nodules, these rough interfaces were the microcalcifications formed from aggregates of primary psammoma bodies (PBs); they consist mainly of highly reflecting crystalline aggregates of calcium [22]. The same features described in thyroid nodules, represented by microcalcifications and colloid crystals, are also present in lymph node metastases. The aim of this study was to determine the presence of BFI-TS in metastatic LNs and to compare it with the other ultrasound features in relation to the results obtained from the surgical specimen.

2. Materials and Methods

2.1. Patients. Between September 2006 and December 2011, 252 patients with known PTC were examined at our institution for preoperative sonographic evaluation with grayscale ultrasonography (US), color Doppler US, and BFI-TS. Moreover, 121 patients with suspicious metastatic cervical LN at US examination underwent FNAB for cytology and thyroglobulin determination in the aspirate fluid. Only 83 patients (19 men, 64 women; mean age 52 years range, 26–79 years) with at least one metastatic LN were included in our study. All these patients underwent surgery, and the final diagnosis was based on the results of histologic examination of the resected specimens. The mean interval between sonographic examination and surgery was 5.3 days (range 1–17 days). The study was conducted at the Department of Radiology and Endocrinology of the University of Naples Federico II and at the Department of Endocrinology of the Second University of Naples, according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of the University of Molise. Written informed consent was obtained from all subjects.

2.2. US and Cytological Examinations. US, color Doppler, and BFI examinations were performed with LOGIQ 9 GE Healthcare (Chalfont St Giles, UK), a commercially available real-time US system, equipped with a 5 to 14 MHz (M12L) and 2.5 to 7 MHz (7L) linear array transducer. All examinations were performed by two blinded radiologists with 8 and 10 years of neck sonography experience separately, and all data analysis was performed by another investigator. When results of the examiners were discordant, agreement was found by conjoint review of clips of the US examinations. At grayscale US, the following six sonographic characteristics were evaluated for all LNs examined: a round shape (ratio of short axis to long axis > 0.5), absence of echogenic hilum, abnormal echogenicity of LN, calcification, cystic change, and a peripheral color Doppler pattern. The shape, size, and location (levels I–VI) of all cervical LNs were recorded, based on the American Joint Committee on Cancer and the American Academy of Otolaryngology-Head and Neck Surgery nodal classification [23–25].

BFI was performed at 10 MHz (M12L) and 7 MHz (7L) with the BFI capability at the level of the LNs. PRI was set at 3. BFI gain was not fixed and was adjusted to allow a better visualization of the signs. This technique focuses on high flow, with suppression of the tissue signal. BFI images were used to evaluate the presence or the absence of the signs. The BFI-TS is a rapidly flashing white light behind such stationary objects as microcalcifications and colloidal crystals. The sign was considered positive when at least a twinkling was present in the LNs examined and repeatable over time.

After the US features were assessed, patients underwent a cytological evaluation. US-guided FNA was simultaneously performed by an endocrinologist, a radiologist, and pathologist. Physicians were highly experienced in carrying out US-guided FNA using 27- and 22-gauge needles; the technique used is described elsewhere [26, 27]. Three or four smears were prepared; the first was air dried and immediately stained with Diff Quick stain. Inadequate smears were immediately repeated. After collection of the cytology samples, each FNAB needle was washed with 0.1–0.5 mL of normal saline; the washes from all needles were pooled (final volume 0.5–1 mL) and sent to the laboratory. Thyroglobulin was measured in fine needle washouts using an immunoradiometric assay (IRMA—DYNOtest Tg-plus, BRAHMS Diagnostica GmbH, Berlin, Germany).

When the measured FNAB-Tg level was greater than the serum Tg level, we deemed the LN positive for metastasis from PTC.

2.3. Surgery and Histologic Examination. All patients underwent thyroidectomy and ipsi- or bilateral modified radical neck dissection to include levels II–V. All possible measurements were taken to ensure an accurate one-to-one comparison between the LNs that were imaged and those that were removed during surgery. After US examination, the location of each lymph node was mapped with respect to the surrounding anatomic structures (i.e., trachea, main vessels, and sternocleidomastoid muscle) and plotted on the sketched diagram of the neck. Surgeons were assisted by a radiologist for correlation of the LN location seen on the US images with the LNs seen in the lymphadenectomy specimens. After being resected, each LN specimen was fixed in 10% formalin, embedded in paraffin, cut into thin slices, and stained with standard hematoxylin-eosin. During histologic examination, two or three histologic slices per LN were examined. The final diagnosis of metastatic lymph node involvement was made by a pathologist who had 15-year experience in diagnosing histologic cervical LN. Complete versus incomplete metastatic involvement and the presence of necrosis and/or calcifications were also investigated.

2.4. US and Pathology Correlation. To match each LN found at pathological examination to the corresponding node on US, we took into account its location, shape, and size. Only LNs that were unequivocally matched between US and

Table 1: The diagnostic performance of sonographic criteria for metastatic lymph nodes in 83 patients with papillary thyroid cancer.

US features	Total lymph nodes (604)	Metastatic lymph nodes (298)	Sensitivity (%)	Specificity (%)	P	PPV	NPV
Round shape Short to long axis (diameter ratio > 0.5)	183	155	52	90.8	χ^2 131.3 P 0.0000	84.7	66
Abnormal echogenicity	290	244	81.9	85	χ^2 270.3 P 0.0000	84.1	82.8
Absence of the hilum	400	274	91.9	58.8	χ^2 174 P 0.0000	68.5	88.2
Calcification	94	93	31.2	99.7	χ^2 109.5 P 0.0000	98.9	59.8
Cystic change	63	63	21.1	100	χ^2 72.2 P 0.0000	100	56.6
Peripheral vascularity	238	142	47.6	68.6	χ^2 16.7 P 0.0000	59.7	57.4
BFI-TS	242	241	80.9	99.7	χ^2 407.9 P 0.0000	99.6	84.2

US: Ultrasound; LNs: lymph nodes; PPV: positive predictive value; NPV: negative predictive value; BFI-TS: B-flow imaging twinkling sign.

pathology were taken into account. Multiple LNs at a given neck level on US were taken into account only if all LNs of the compartment were either benign or malignant.

2.5. Statistical Analyses. Qualitative variables were compared by using the χ^2 test. The BFI characteristics of each LN were recorded separately and processed blindly for statistical evaluation. The unit of analysis was each LN rather than each patient. The value of each visual and qualitative criterion that showed the highest diagnostic accuracy in the distinction between benign and metastatic lymph nodes was selected as the cutoff value. For each criterion examined, the sensitivity, specificity, positive and negative predictive values, and overall accuracy in the differentiation between benign and metastatic LNs were calculated. Quantitative data are reported as means ±1 standard deviation. Statistical significance was assumed when the P value was less than 0.05. The same analysis has been performed on the association between the BFI and each ultrasound parameter.

3. Results

A total of 604 LNs were analyzed. Of these, 298 were metastatic while the remaining 306 were benign, as evaluated by histopathology. The minimum diameters of LNs on sonography ranged from 2.3 to 13 mm; the mean diameter of metastatic LNs was 5.8 mm, and the mean diameter of nonmetastatic LNs was 4.6 mm; the difference was not significant ($P > 0.05$). The diagnostic performance of each ultrasound finding evaluated in this study is shown in Table 1. Most ultrasound features had high specificity and positive predictive value (PPV) but low sensitivity and negative predictive value (NPV). The only sonographic characteristic with high specificity and sensitivity was the BFI-TS. The BFI-TS was positive in all LNs with microcalcifications at US examination (93 LNs) and in 148 LNs (all metastatic) in which microcalcifications were not evident at US. One LN positive at the BFI-TS and with calcifications at US was found to be a tuberculous node after treatment with intranodal macrocalcifications at histological examination.

The diagnostic performance of the combination of each conventional ultrasound sign with the BFI-TS is shown in Table 2. This combination allowed to increase the specificity and the PPV related to different ultrasound signs. The association of the absence hilum with BFI-TS presented the highest values of sensitivity, specificity, and PPV.

4. Discussion

Neck US is highly sensitive for the diagnosis of metastatic LNs in patients with PTC. The specificity reported varies from 85% to 90% [28]. A variety of diagnostic criteria have been reported to be useful for the distinction between benign and metastatic LNs (Figure 1).

Lymph node shape has been used as a diagnostic criterion of metastatic LNs. Metastatic lymph nodes often appeared as round lesions, whereas benign nodes are usually flat or oval [29]. In the present study, LN shape had an excellent specificity (90.8%) but low sensitivity (52%). Initial or partial metastatic LN involvement does not result in an alteration of the shape. Of note, LNs of the parotid and submandibular regions are often round in normal individuals [30].

The presence of a hyperechoic hilum of the nodes is usually considered a strong diagnostic criterion for benign LNs [31]. It has been reported that 84%–92% of benign nodes but less than 5% of metastatic nodes have a hyperechoic hilum [32]. The absence of a fatty hilum is often seen in normal individuals, especially in young subjects and in LNs located in level V [33]. In our study, metastatic LNs with visible hilum and partial involvement were at I-II level, whereas the LN metastases at low level showed in 99.5% the absence of hyperechoic hilum. The absence of the hilum had high sensitivity

Table 2: The diagnostic performance of the combination of each conventional ultrasound signs with the BFI-TS.

Combined US features	Total lymph nodes (604)	Metastatic lymph nodes (298)	Sensitivity (%)	Specificity (%)	P	PPV	NPV
Round shape Short to long axis (diameter ratio > 0.5) + BFI-TS	126	125	41.9	99.7	χ^2 158.4 P 0.0000	99.2	63.8
Abnormal echogenicity + BFI-TS	200	200	67.1	100	χ^2 307 P 0.0000	100	75.7
Absence of the hilum + BFI-TS	221	221	74.2	100	χ^2 357.9 P 0.0000	100	78.9
Calcification + BFI-TS	92	92	30.9	100	χ^2 111.4 P 0.0000	100	59.8
Cystic change + BFI-TS	61	61	20.5	100	χ^2 69.7 P 0.0000	100	56.4
Peripheral vascularity + BFI-TS	117	116	39.9	99.7	χ^2 144 P 0.0000	99.1	62.6

US: ultrasound; LNs: lymph nodes; PPV: positive predictive value; NPV: negative predictive value; BFI-TS: B-flow imaging twinkling sign.

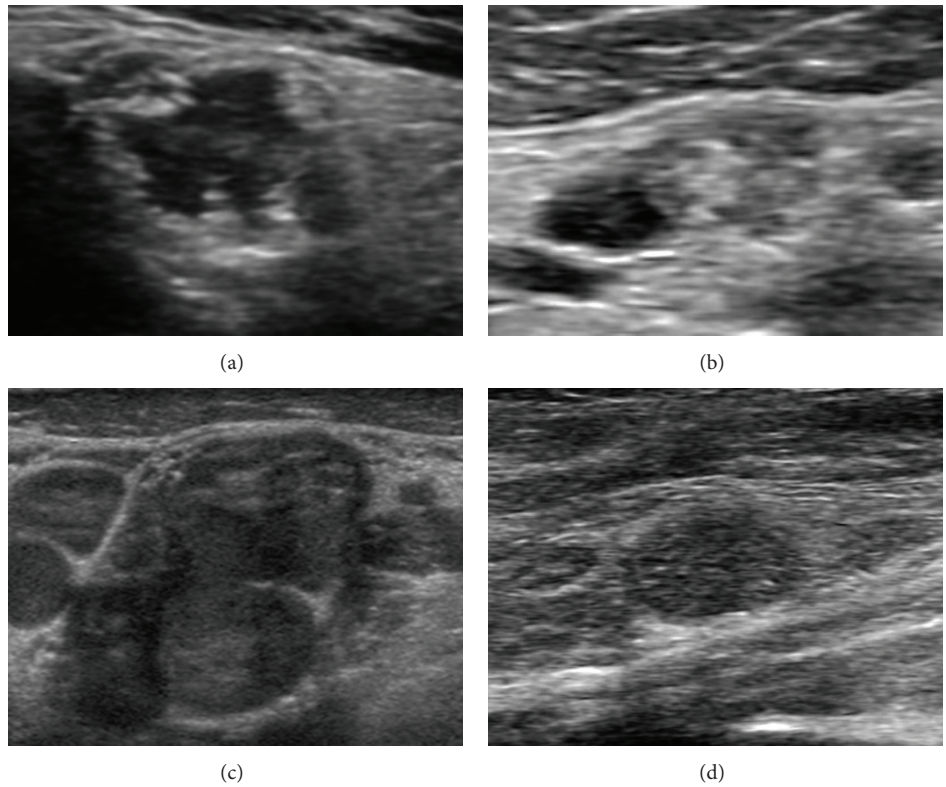
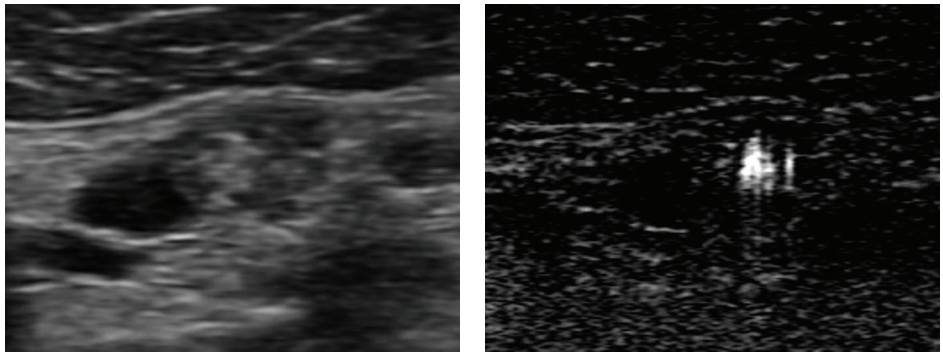


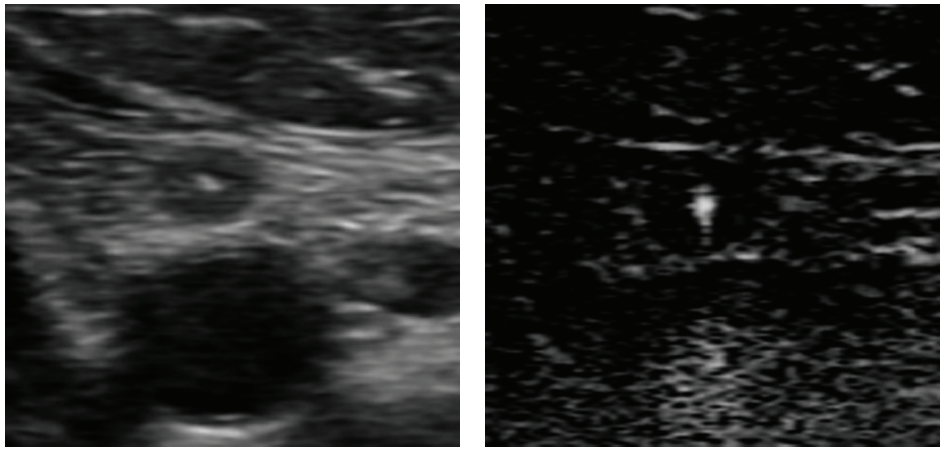
Figure 1: Metastatic lymph nodes at grayscale examination in patients with papillary thyroid cancer. Absence of echogenic hilum ((a), (b), (c), (d)), abnormal echogenicity ((a), (b), (c)), calcifications (b), cystic change ((a), (b)), and round shape ((c), (d)).

(91.9%) but low specificity (58.8%). Differently, *abnormal LN echogenicity* had both high sensitivity and specificity (resp., 81.9% and 85%). In our experience, echogenicity was normal in 54 metastatic LNs (18%). *Calcification* was a specific sign but not sensitive criterion. Calcification in metastatic LNs is characteristic of PTC but generally rare. In our study, nodal calcifications were detected in only 93 of the 298 metastatic LNs. Similarly, *cystic appearance* had a very high specificity (100%) and a low sensitivity (21.1%). All LNs with hyperechoic punctuations or a cystic appearance in a patient w *i*th PTC should be considered as malignant. *Assessment of nodal vascularity* at color Doppler US is another diagnostic criterion for metastatic LNs. It has been noted that benign LNs tend to show hilar vascularity or to appear avascular [34]. In contrast, metastatic nodes tend to have peripheral or mixed (both peripheral and hilar) vascularity [35]. In our study, color Doppler US vascularity had intermediate specificity (68.6%) but low sensitivity (47.6%). These findings



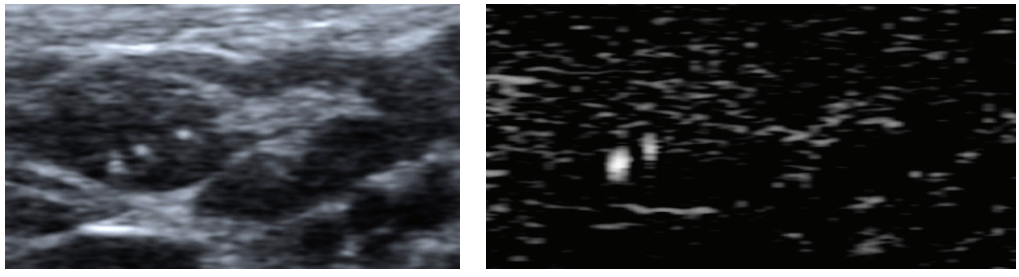
(a) (b)

Figure 2: Metastatic lymph nodes at B-mode and BFI examination in patients with papillary thyroid cancer. The lymph node presents microcalcifications and multiple BFI-TS in the same place.



(a) (b)

Figure 3: Small metastatic lymph node at B-mode and BFI examination in patients with papillary thyroid cancer. The lymph node presents BFI-TS without any suspect US features.



(a) (b)

Figure 4: Focal metastasis in upper pole of lymph node at B-mode and BFI examination in patients with papillary thyroid cancer. The lymph node presents BFI-TS in the metastatic pole.

could reflect the high differentiation of PTC and the reduced tendency to neoangiogenesis.

The BFI-TS had a higher specificity and sensitivity (resp., 99.7% and 80.9%) than conventional US features (Figure 2). The BFI-TS was positive in all LNs with calcification on US (93 LNs) and in 148 LNs (all metastatic) in which calcifications were not identified on US. The BFI-TS identified significantly more microcalcifications than B-mode US, and it also identified highly reflective and noncalcified structures such as colloidal crystals. This is confirmed by the histological findings of microcalcifications and colloidal crystals in the sites of BFI-TS. We detected BFI-TS in 6 metastatic LNs that were negative to the other conventional US features (Figure 3). Given its high specificity (99.7%), BFI-TS identifies better suspicious LNs that should be re-evaluated by surgery or US-guided FNAC (Figure 4). Therefore, the presence

of BFI in addition to conventional US increases the diagnostic specificity for suspicious LNs (Table 2). As an example, the association of BFI-TS and absence of the hilum shows the best value of specificity, PPV, and diagnostic accuracy.

The BFI is an ultrasound technique that integrates conventional ultrasound but it does not replace it. When an LN presents at the least suspect ultrasound signs, it has to be studied also with the BFI since the positivity to BFI-TS gives evidence of its metastatic involvement with high diagnostic accuracy.

The techniques have several limits; namely, they can be affected by the pulsatility of the main neck vessel and by the deep places of examined LNs. These limits could explain the missed detection of 57 LNs (19%) that were metastatic at histological examination. The other limit is the presence of nonmetastatic LN calcifications; in fact, the BFI-TS was false-positive only in one LN with calcifications deriving from tuberculosis [36].

Overall, our results indicate that this technique can be applied to studies of cervical nodes in patients with PTC and that its sensitivity and specificity is higher than those of traditional US diagnostic techniques.

5. Conclusions

BFI is a promising imaging technique that can help in the differentiation of benign and metastatic neck LNs in patients with PTC. Our findings suggest that BFI can be helpful in the selection of suspicious neck LNs that should be examined cytologically or with open biopsy for accurate preoperative staging and individual therapy selection. A dedicated cervical US that includes nodal levels II–VI should be performed to detect nonpalpable LN metastases in patients undergoing surgical evaluation. However, longitudinal studies on a large population are required to verify the efficacy of BFI in the diagnosis of metastatic LNs.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2013, Article ID 285680, 9 pages
http://dx.doi.org/10.1155/2013/285680

Clinical Study

How to Estimate Fat Mass in Overweight and Obese Subjects

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Received 20 February 2013; Accepted 18 March 2013

Academic Editor: Felice Strollo

Background. The prevalence of overweight and obesity is increasing and represents a primary health concern. Body composition evaluation is rarely performed in overweight/obese subjects, and the diagnosis is almost always achieved just considering body mass index (BMI). In fact, whereas BMI can be considered an important tool in epidemiological surveys, different papers stated the limitations of the use of BMI in single individuals. *Aim*. To assess the determinants of body composition in overweight and obese subjects. *Methods*. In 103 overweight or obese subjects (74 women, aged 41.5 ± 10 years, and 29 men, aged 43.8 ± 8 years), a multidimensional evaluation was performed including the assessment of body composition using Dual Energy X-Ray Absorptiometry (DXA), anthropometry, bioimpedance analysis (BIA), and biochemical parameters (total cholesterol, triacylglycerol, HDL- and LDL-cholesterol, free fatty acids and glycerol, glucose, insulin, C-reactive protein, plasma acylated and unacylated ghrelin, adiponectin, and leptin serum levels). *Results*. BMI does not represent the main predictor of FM estimated by DXA; FM from BIA and hip circumference showed a better association with FM from DXA. Moreover, models omitting BMI explained a greater part of variance. These data are confirmed by the predictive value analysis where BMI showed a performance similar to a "coin flip."

1. Introduction

The prevalence of individuals who are classified as overweight or obese is increasing all over the world, representing a primary health concern due to the relationship between obesity and a number of diseases, disabilities, comorbidities, and mortality [1, 2].

The definition of obesity should consider not only the increase of body weight but more precisely the increase in body fat mass [3–5]. However, body composition evaluation is rarely performed in overweight and obese subjects, and the diagnosis is often achieved just considering body mass index (BMI = kg/m^2). Even important Government Institutions suggest to use BMI to determine the presence of overweight and obesity [6].

The widespread use of BMI depends on its safety and minimal costs, and also on a rash and uncritical use of an epidemiological tool in clinical practice, conflicting with the advice of the inventor of BMI who first applied it to epidemiology. In 1972, the physiology professor and obesity researcher Ancel Keys published a landmark study encompassing more than 7,400 men in five countries [7]. Keys examined which of the height-weight formulas matched up best with each subject's directly measured fat mass (FM). It turned out that the best predictor was Quételet's index: body weight divided by height squared. Keys renamed this number as the *body mass index*. But BMI was explicitly cited by Keys as being appropriate for *population* studies and inappropriate for individual diagnosis. Nevertheless, due to its simplicity, it came to be widely used for individual diagnosis, despite its inappropriateness.

In fact, while BMI can be considered an important tool in epidemiological surveys, different papers stated the limitations of the use of BMI in single individuals [8–11] because of its incapacity to distinguish body components (fat mass and lean body mass in particular).

On the contrary, it is pivotal to have a reliable estimation of FM both at the initial as well as at the outcome evaluation of obese subjects.

The purpose of this study is to verify the determinants of body composition in a population of overweight and obese subjects and to propose a different model of estimation of FM of these subjects when reliable equipments for the evaluation of body composition are not available.

2. Methods

2.1. Participants. This study was based on the baseline data from a randomised controlled trial aimed at the evaluation of the effects of 2-month consumption of a combination of bioactive food ingredients on changes in body composition, satiety control, thermogenesis, and serum markers of lipolysis [12].

The study was performed under the approval of the Ethics Committee of the Department of Internal Medicine and Medical Therapy at University of Pavia and registered at ClinicalTrials.gov (Clinical Trial Registration no. NCT01806493). The informed consent to the study was obtained by all the participants or their legal representatives. Healthy males and females aged from 25 to 45 years, with a BMI greater than 25 kg/m^2 and less than 35 kg/m^2, were eligible for the study. All subjects underwent physical examination, anthropometric assessment, and routine laboratory tests. The complete medical history was collected for all the subjects. Individuals who were pregnant or lactating or had any disease potentially affecting body composition and laboratory evaluation were excluded from the study; especially, severe hepatic or renal disease, unstable cardiovascular disease, uncontrolled hypertension, active cancer, and surgery for weight loss were the main exclusion criteria.

2.2. Multidimensional Evaluation. After a 12-hour fasting, and abstinence from water since midnight, the subjects arrived at around 8:00 AM, using motorised transportation, at the Endocrinology and Clinical Nutrition Unit of Azienda di Servizi alla Persona di Pavia, University of Pavia (Italy) and at the Dietetic and Metabolic Unit, "Villa delle Querce" Clinical Rehabilitation Institute in Rome (Italy).

Blood sampling for routine blood analysis and for the measurements of leptin, adiponectin, ghrelin, insulin, glycerol, and free fatty acid levels, as well as the assessment of body composition by dual energy X-ray absorptiometry (DXA) and anthropometry, was performed in the fasting state at baseline.

2.2.1. Body Composition Measurements. Body composition was measured using DXA (Lunar Prodigy DEXA, GE Medical Systems, Waukesha, WI). The *in vivo* coefficients of variation were 4.2% and 0.48% for fat and lean mass, respectively. Central fat, defined as the approximation of the visceral fat, was assessed with DXA, measuring the fat percentage corresponding to an ideal rectangle defined from the upper edge of the second lumbar vertebra to the lower edge of the fourth lumbar vertebra. The vertical sides of this area were the continuation of the lateral sides of the rib cage [13]. All measurements for each parameter were gathered by the same investigator.

Anthropometry. The following anthropometric measurements were performed in all subjects:

(i) body weight and height;

(ii) biceps (BSF), triceps (TSF), suprailiac (SISF), and subscapular (SSSF) skinfold thicknesses;

(iii) waist circumference (W), hip circumference (H), arm circumference (AC), and calf circumference (CC).

In order to avoid the interassessor variability, anthropometric variables were measured by a unique investigator following a standardized technique [14]

Using the aforementioned anthropometric parameters, the following variables were calculated:

(i) body mass index (BMI): weight (kg)/height^2 (m^2);

(ii) waist to hip ratio (WHR);

(iii) arm muscle area (AMA) (cm^2) = AC $-$ $(\pi * \text{TSF})^2/4\pi$;

(iv) arm fat area (AFA) (cm^2) = $(\text{AC}^2/4\pi)$ $-$ AMA;

(v) muscle arm circumference (MAC) (cm) = AC $-$ $(\pi *$ TSF).

Bioimpedance Analysis (BIA). Whole-body impedance vector components, resistance (R), reactance (X_c), and phase angle (pA), were measured with a single-frequency 50 kHz analyzer STA-BIA (AKERN Bioresearch SRL, Pontassieve, Florence, Italy). Other parameters like Body Cell Mass (BCM: the protein rich compartment which is affected in catabolic states) and hydration status (total body (TBW), extracellular (ECW), and intracellular water (ICW)) were derived from electrical data. Measurements were obtained following standardized procedures [15]. The external calibration of the instrument was checked with a calibration circuit of known impedance value. Estimations of FFM and FM by BIA were obtained using gender-specific, BIA prediction equations recently developed by Sun et al. [16] in a large population that included extremes of BMI values. The fat mass index (FMI) was calculated through the normalisation of FM, obtained by the BIA, for height: FMI = FM (kg)/height (m)^2.

2.3. Biochemical Analyses. Subjects were instructed to fast over 12 hours and to refrain from any form of exercise for 48 hours, before blood collection. Female subjects were tested during the early follicular phase of their menstrual cycles (days 3–10). Fasting venous blood samples were drawn between 08.00 and 10.00 AM. Blood collection and handling were carried out under strictly standardized conditions, and clinical chemistry parameters were detected with dedicated

Table 1: Body composition and biochemical parameters of subjects studied[1].

	F	M
N	74	29
Age (y)	41.6 ± 10.2	43.8 ± 8.1
DXA		
Fat tissue (kg)	35.0 ± 6.2	31 ± 7.2*
Android fat (%)	51.5 ± 5.2	45.1 ± 5.2*
Gynoid fat (%)	51.5 ± 5.0	34.6 ± 6.1*
Android/gynoid ratio	1.0 ± 0.1	1.3 ± 0.1*
Lean tissue (kg)	40.5 ± 5.4	59.3 ± 5.3*
Anthropometry		
BMI (kg/m^2)	29.9 ± 3.2	31.0 ± 3.2
Waist (cm)	95.6 ± 9.3	104.6 ± 7.2*
Hips (cm)	109.1 ± 7.1	106.0 ± 6.3
WHR	0.88 ± 0.07	0.98 ± 0.03*
TSF (mm)	28.8 ± 7.1	17.4 ± 5*
BSF (mm)	19.2 ± 8.1	9.7 ± 5.2*
SISF (mm)	31.0 ± 9.2	27.8 ± 10.1
SSSF (mm)	31.9 ± 8.2	30.8 ± 9.4
AFA (cm^2)	5.2 ± 1.0	4.9 ± 1.1
AC (cm)	33.2 ± 3.1	34.2 ± 2.3
CC (cm)	38.6 ± 2.2	39.7 ± 2.2*
AMA (cm^2)	40.6 ± 11.2	56.2 ± 10.2*
MAC (cm)	24.2 ± 2.3	28.7 ± 2.2*
Bioimpedance analysis		
R (Ω)	554.7 ± 58.1	454.6 ± 50.1*
X_c (Ω)	57.1 ± 7.1	54.4 ± 7.3
pA (°)	5.9 ± 0.7	6.8 ± 0.9*
TBW (L)	35.5 ± 3	49.2 ± 4.2*
ECW (L)	16.4 ± 1.1	20.8 ± 2.2*
ICW (L)	19.1 ± 2.2	28.4 ± 3.3*
FM-BIA (kg)	30.5 ± 6.2	26.6 ± 6.3*
FMI	11.6 ± 2.1	8.8 ± 2.4*
FFM-BIA (kg)	48.3 ± 4.2	67.3 ± 5.3*
BCM (kg)	24.5 ± 4.2	34.4 ± 7.1*
Laboratory parameters		
CT (mg/dL)	200.3 ± 38.2	212.3 ± 35.1*
HDL cholesterol (mg/dL)	56.4 ± 12.1	43 ± 8.1
LDL cholesterol (mg/dL)	125.0 ± 30.1	137.3 ± 33.1
CT/HDL ratio	3.6 ±0.71	5.1 ± 1.3*
TG (mg/dL)	94.4 ± 42.2	160.0 ± 103.3*
Free fatty acids (mM/L)	0.42 ± 0.2	0.39 ± 0.1
Glycerol (mM/L)	0.14 ± 0.04	0.14 ± 0.04
Glycaemia (mg/dL)	88.6 ± 9.2	93.5 ± 9.0*
Insulin (IU/mL)	9.4 ± 4.2	11.7 ± 5.3*
HOMA	2.1 ± 1.2	2.7 ± 1.0*
QUICKI	0.35 ± 0.02	0.34 ± 0.02*
CRP (mg/L)	0.4 ± 0.6	0.3 ± 0.4
Adiponectin (ng/mL)	93.9 ± 52.1	57.4 ± 28.2*
Leptin (pg/mL)	272.7 ± 163.3	80.3 ± 51.3*
Leptin/adiponectin ratio	3.8 ± 3.4	2.3 ± 3.2*
Ghrelin (pg/mL)	442.4 ± 260.4	240.3 ± 131.3*

[1]Values are means ± SD.
*$P < 0.05$.
Legend: BMI: body mass index; WHR: waist hip ratio; BSF: biceps skinfold thickness; TSF: triceps skinfold thickness; SISF: suprailiac skinfold thickness; SSSF: subscapular skinfold thickness; AC: arm circumference; CC: calf circumference; AMA: arm muscle area; AFA: arm fat area; MAC: muscle arm circumference; R: resistance; X_c: reactance; pA: phase angle; TBW: total body water; ECW: extracellular water; ICW: intracellular water; FM-BIA: fat mass estimate through bioimpedance analysis; FMI: fat mass index; FFM-BIA: fat free mass estimate through bioimpedance analysis; BCM: body cell mass; CT: cholesterol total; TG: triglycerides; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; CRP: C-reactive protein.

commercial kits. In particular, total cholesterol, triacylglycerol, HDL- and LDL-cholesterol, free fatty acid (FFA), glycerol, glucose, insulin, C-reactive protein (CRP), plasma acylated and unacylated ghrelin, adiponectin, and leptin serum levels were measured. Leptin/adiponectin ratio (LAR) was calculated. Insulin resistance was evaluated using the Homeostasis Model Assessment (HOMA) [17] and Quantitative Insulin sensitivity Check Index (QUICKI) [18] using the following formulas:

$$\text{HOMA-IR} = [(\text{fasting insulin}, \mu\text{U/mL}) \times (\text{plasma glucose, mmol/L})]/22.5,$$

$$\text{QUICKI} = 1/[\log(\text{glucose, mg/dL}) + \log(\text{insulin}, \mu\text{U/mL})].$$

2.4. Statistical Analysis. Data were described as mean and standard deviation (SD) if continuous and as percentage if categorical.

We considered FM from DXA as the outcome variable and all the anthropometric, bioimpedance, and laboratory data as potential explicative variables.

The predictive values of BMI and FM from BIA were compared to the FM from DEXA (overall predictive value, sensitivity, specificity, positive, and negative predictive values). Therefore, we considered the following cut-off values for the definition of obesity:

(i) FM ≥ 25% for men and ≥35% for women (at DXA and BIA) [3];

(ii) BMI ≥ 30 kg/m^2 [6].

The variance analysis and the Student t-test was used to assess the significance of differences in the averages; the χ^2 to compare the frequencies observed with those expected; Pearson's to evaluate the correlation existing between two continuous variables.

Variables univariately proven to correlate with the outcome variable were entered a pool of potential contributors in multiple regression analysis.

Table 2: Predictive value of BIA and BMI towards DXA.

		DXA		
		Nonobese (FM < 25% M, < 35% F)	Obese (FM ≥ 25% M, ≥ 35% F)	
BMI	<30 kg/m^2	2	53	Overall predictive value: 48.5% Sensitivity: 47.5% Specificity: 100% Positive predictive value: 100% Negative predictive value: 3.6%
	≥30 kg/m^2	0	48	
BIA	Non-obese (FM < 25% M, 35% F)	2	15	Overall predictive value: 85.3% Sensitivity: 85% Specificity: 100% Positive predictive value: 100% Negative predictive value: 11.8%
	Obese (FM ≥ 25% M, 35% F)	0	85	

We estimated models using a forward likelihood stepwise method (cut-off probability for entry: 0.05). With each added variable, the discriminant function was recalculated, and any variable that no longer met the significance level was removed from the equation (cut-off probability for removal: 0.1).

Some variables with similar biological significance were excluded from the logistic analysis, in order to avoid the confounding effect of collinearity (verified with Pearson's r, t-test, or χ^2). The best fitting model was chosen according to the value of the correlation coefficients R^2 (comparing the explained variance of the model's predictions with the total variance of the data) and the adjusted R^2 (R^2 adj), considering a correction for inclusion of variables.

We considered a significance level equal to a 5% probability of error.

Data were analysed using the SPSS for Windows 10.0 (SPSS Inc. 1989–1999) and the Win Episcope 2.0 (Facultad de Veterinaria di Saragozza (E), Wageningen University (N), and University of Edinburgh (GB)) statistical software packages.

3. Results

One hundred and three overweight or obese subjects were included in the study: 74 women (aged 41.5 ± 10.2 years) and 29 men (aged 43.8 ± 8.1 years); baseline characteristics are summarized in Table 1.

BIA showed a good predictive value in classifying subjects as obese when compared to DXA (overall predictive value 85.3%, sensitivity 85%), while BMI exhibited a very bad performance (overall predictive value 48.5%, sensitivity 47.5%) (Table 2).

The results of the univariate analysis considering the correlation between FM from DXA and all anthropometric, bioimpedance, and laboratory parameters (Table 3) showed that

(1) a good correlation was found between FM from DXA and BMI (r = 0.74), AFA (r = 0.59), waist and hip circumferences (r = 0.75). Although it is slightly lower, a statistically significant correlation was also observed between FM from DXA and skinfold thicknesses, waist, arm, and calf circumferences;

(2) a good correlation was present between FM from DXA and FM from BIA (r = 0.91) and FMI (r = 0.86);

(3) a good correlation was shown between FM from DXA and CRP (r = 0.43) and leptin levels (r = 0.57), and leptin/adiponectin ratio (r = 0.42). Although it is slightly lower, a statistically significant correlation was observed between FM from DXA and insulinemia, HOMA, and QUICKI indexes.

The multivariate regression analysis was performed using only the independent variables significantly correlated with the outcome variable in the univariate analysis: BMI, AFA, H, and FM from BIA, FMI, CRP, leptin, and LAR.

In the block model of the regression analysis, all the selected variables were included and R^2 and R^2 adj of the model were, respectively, 0.88 and 0.87. The strength of association between fat mass from DXA and independent variables was, in descending order, greater for FM from BIA (r = 0.91; r = 0.75), BMI (r = 0.73), AFA (r = 0.59), leptin (r = 0.57), FMI (r = 0.42), CRP (r = 0.42), and LAR (r = 0.41).

With the forward stepwise, three variables (FMI, CRP, and LAR) were omitted; R^2, R^2 adj, and the strength of association between fat mass from DXA and independent variables remained unchanged.

When BMI entered the regression equation (at the third step), it accounted for 1.6% to the variance of the model (sig F change = 0.001).

Different models considering alternatively BMI or FM from BIA together with leptin and CRP levels were verified. The model including FM from BIA showed a better correlation (greater R^2 and R^2 adj) than the model using BMI (Tables 4 and 5). The inclusion in the model of the FMI instead of the FM from BIA did not result in any improvement of the model.

The results and models identified have maintained their substantial validity for both genders and for different classes of BMI (less than or greater than 30 kg/m^2) or age (less than or greater than 30 years) (data not shown).

4. Discussion

The results of the study showed that the BMI did not represent the main predictor of FM from DXA. FM from BIA and

Table 3: Univariate analysis: correlation between FM from DXA and anthropometry, bioimpedance, and laboratory parameters.

	r
Anthropometry	
BMI (kg/m^2)	0.74*
Waist (cm)	0.4*
Hips (cm)	0.75*
WHR	0.16
TSF (mm)	0.52*
BSF (mm)	0.5*
SISF (mm)	0.48*
SSSF (mm)	0.32*
AFA (cm^2)	0.59*
AC (cm)	0.51*
CC (cm)	0.5*
AMA (cm^2)	0.06
MAC (cm)	0.04
Bioimpedance analysis	
R (Ω)	0.05
X_c (Ω)	0.14
pA (°)	0.2*
TBW (L)	0.06
ECW (L)	0.07
ICW (L)	0.12
FM-BIA (kg)	0.91*
FMI	0.86*
FFM-BIA (kg)	0.06
BCM (kg)	0.2*
Laboratory parameters	
CT (mg/dL)	0.08
HDL cholesterol (mg/dL)	0.07
LDL cholesterol (mg/dL)	0.08
CT/HDL ratio	0.19
TG (mg/dL)	0.09
Free fatty acids (mM/L)	0.03
Glycerol (mM/L)	0.02
Glycaemia (mg/dL)	0.1
Insulin (IU/mL)	0.24*
HOMA	0.2*
QUICKI	0.18
CRP (mg/L)	0.43*
Adiponectin (ng/mL)	0.1
Leptin (pg/mL)	0.57*
Leptin/adiponectin ratio	0.42*
Ghrelin (pg/mL)	0.2

*$P < 0.05$.

Legend: BMI: body mass index; WHR: waist hip ratio; BSF: biceps skinfold thickness; TSF: triceps skinfold thickness; SISF: suprailiac skinfold thickness; SSSF: subscapular skinfold thickness; AC: arm circumference; CC: calf circumference; AMA: arm muscle area; AFA: arm fat area; MAC: muscle arm circumference; R: resistance; X_c: reactance; pA: phase angle; TBW: total body water; ECW: extracellular water; ICW: intracellular water; FM-BIA: fat mass estimate through bioimpedance analysis; FMI: fat mass index; FFM-BIA: fat free mass estimate through bioimpedance analysis; BCM: body cell mass; CT: cholesterol total; TG: triglycerides; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; CRP: C-reactive protein.

hip circumference showed a better association with FM from DXA than BMI. Moreover, models omitting BMI explained a greater part of the variance. These data were confirmed by the predictive value analysis where BMI showed a performance similar to a "coin flip."

The boundary between health and disease in malnutrition (over- and undernutrition) in terms of body composition is crucial to accurately define criteria for intervention, and in particular methods and intensity of nutritional intervention, but it still represents a clinical challenge to be addressed.

The BMI formula was developed nearly 200 years ago by Adolphe Quételet. The index appeared for the first time in an article published on Proceedings of the Academy of Sciences [7] titled "*Recherches sur le poids de l'homme aux différens âges*" in 1833. A. Quételet devised the equation in 1832 in his quest to define the "normal man" taking into account a number of aspects, from his average arm strength to the age at which he marries. The equation was used to describe the standard proportions of the human build—the ratio between body weight and height in the average adult. Using data collected from several hundred countrymen, he found that body weight varied not in direct proportion to height but in proportion to the square of height (people 10% taller than average tended to be about 21% heavier). It is therefore not a measurement of adiposity, but merely an imprecise mathematical estimation, as shown in many papers [19–23].

Even if BMI represents an important epidemiological tool, as evidenced by the study by Ancel Keys [8], when considering the single individual, it cannot be considered a reliable diagnostic tool to define the degree of obesity that is necessary to define the intensity of the clinical interventions (nutritional, psychological, rehabilitation, surgical, and pharmacological interventions) that can be applied to the overweight or obese patient. The reason is that the BMI is not able to accurately assess the body composition, especially in terms of FM, FFM, and water content, whereas it is useful in defining the severity of obesity. It means that the predictive ability of BMI to identify obese subjects (FM > 25% for men and >35% for women) [3] is very poor, as shown in our study. In addition, the BMI is not able to discriminate two broad categories of subjects that deserve special attention in their therapeutic and rehabilitative pathway: patients suffering from "sarcopenic obesity", who have a more marked disability, due to their reduced FFM, and the "normal weight-obese" subjects whose FM is increased despite a normal BMI, having a higher risk of comorbidities such as hyperlipidemia, coronary artery disease, hypertension, and diabetes [24]. Furthermore, change in BMI predicts neither change in FM nor in FFM, as demonstrated in different categories of patients [25, 26]. Finally, different studies show that BMI/FM relation is curvilinear especially at higher BMIs with a different association at different levels of BMI [27].

BMI significantly underestimates prevalence of obesity when compared to DXA direct measurement of body fat percentage. In our study, the predictive capacity of BMI to correctly classify subjects as obese is very low. In our sample, despite considering only overweight or obese subjects, BMI explained just 74% of the variance of FM. In other studies,

Table 4: Fat mass prediction (FM from DXA)—multivariate regression analysis.

		Variables in the model	B	Sig. t changes	R^2	R^2 adj
Model 1	Block model	Constant	−10.55	0.032	0.879	0.868
		BMI	0.285	0.042		
		AFA	0.628	0.034		
		H	0.117	0.028		
		FM-BIA	0.739	0.000		
		FMI	0.288	0.345		
		CRP	0.0036	0.995		
		Leptin	0.00714	0.01		
		LAR	0.0594	0.599		
	Forward stepwise selection	Constant	−11.021	0.02	0.877	0.871
		FM-BIA	0.645	0.000		
		Leptin	0.00545	0.004		
		BMI	0.245	0.058		
		H	0.131	0.11		
		AFA	0.627	0.32		
Model 2	Block model	Constant	6.818	0.000	0.852	0.847
		FM-BIA	0.868	0.000		
		Leptin	0.00629	0.002		
		CRP	0.477	0.41		
	Forward stepwise selection	Constant	6.642	0.000	0.851	0.848
		FM-BIA	0.876	0.000		
		Leptin	0.00681	0.001		
Model 3	Block model	Constant	−10.21	0.011	0.68	0.67
		BMI	1.338	0.000		
		Leptin	0.0153	0.000		
		CRP	0.842	0.321		
	Forward stepwise selection	Constant	−11.025	0.005	0.677	0.67
		BMI	1.369	0.000		
		Leptin	0.01638	0.000		

Legend: BMI: body mass index; AFA: arm fat area; H: hips circumference; FM-BIA: fat mass estimate through bioimpedance analysis; CRP: C-reactive protein; LAR: leptin-adiponectin ratio.

based on the general population, the results are even worst [28].

On the other hand, despite representing the reference method in clinical practice to define body composition, DXA presents some critical aspects related to the fact that it is not available in all facilities treating obese subjects, to the necessity to use the same DXA device and analysis software for longitudinal evaluation and studies, and to its structural limitations that do not allow, in most cases, an effective assessment in particular of patients with a BMI > 40 mg/m^2 [29].

Hence, we still need to measure and estimate body composition, reflecting nutritional intakes, losses, and expenses over time. Therefore, practical tools for this purpose and clinically useful biomarkers remain to be identified, in order to better characterize obese subjects and target their therapeutic and rehabilitative approaches.

In contrast with body weight and BMI, techniques for body composition measurement allow the measurement of tissue losses, by analyzing separately FFM and FM [30].

Moreover, different authors suggest that FFM and FM should be better normalized for body height (FFMI = FFM (kg)/height (m)^2); FMI = FM (kg)/height (m)^2, similarly to normalization of body weight for height through BMI calculation, to express the results of body composition [28, 31, 32]. In our study, this normalization did not improve the predictive value of the multivariate regression models.

The validity of anthropometric variables and bioimpedance analysis has been questioned [33–35]. If anthropometry has not indifferent limits linked to the principles and clinical applications of BIA have been described in different studies since many years and reviewed in two position papers of the ESPEN [36, 37]. BIA is based on the ability of hydrated tissues to conduct electricity. The measurement of total body impedance allows the estimation of total body water by assuming that hydration status is constant. From total body water (60% is the proportion of body weight attributable to water in healthy adult), assuming that in muscle there is about 73% of water, and using validated equations and reference values, it is possible to estimate FFM and, by

Table 5: Forward stepwise multivariate regression analysis (FM from DXA as dependent variable).

	Step	Variables entered	R^2	R^2 change	Sig. F change	R^2 adj
Model 1	1	Constant FM-BIA	0.828		0.000	0.826
	2	Leptin	0.847	0.02	0.001	0.844
	3	BMI	0.863	0.016	0.001	0.859
	4	H	0.871	0.008	0.019	0.866
	5	AFA	0.877	0.006	0.032	0.871
Model 2	1	Constant FM-BIA	0.831		0.000	0.829
	2	Leptin	0.851	0.019	0.001	0.848
Model 3	1	Constant BMI	0.541		0.000	0.537
	2	Leptin	0.677	0.135	0.000	0.67

Legend: BMI: body mass index; AFA: arm fat area; H: hips circumference; FM-BIA: fat mass estimate through bioimpedance analysis.

the difference between body weight and FFM, body fat, indirectly [38, 39]. Because of its simplicity, noninvasiveness, low-cost, quickness of use at bedside, and high interoperator reproducibility, BIA has emerged as the technique of choice for the systematic and repeated evaluation of FFM (and FM) in clinical practice [40].

As already stated by Deurenberg, however, several factors limit the valid application of BIA in the severely obese state: the assumption of a constant hydration status, body geometry, and body water distribution [41].

Different attempts were made to improve the predictive capacity of anthropometric parameters and bioimpedance analysis implementing their results with different biochemistry parameters (leptin, adiponectin, insulin levels, etc.) [20, 42]. In our study, models considering FM from BIA together with leptin concentrations seem to be better correlated with FM from DXA.

In other studies, the use of leptin levels improved the precision of BMI adjustment, whereas, as verified in our study, adiponectin to leptin/adiponectin ratio, insulin, and ghrelin levels did not. This effect was attributed to hyperleptinemia among obese subjects (in particular in women) [20]. It was previously suggested to incorporate leptin adjustments into a more accurate diagnosis of obesity considering also that a significant decrease of leptin affects long-term weight control [43, 44]. Moreover, increased leptin levels are associated with the inflammatory process and potentially the entire increased morbidity of obesity [45, 46].

Our study had several limitations. First of all, it was a cross-sectional study; longitudinal data would allow the quantification of outcomes related to adiposity in particular in "normal" BMI population and in sarcopenic obese subjects. Furthermore, our study was based on a convenience sample of small size considering only subjects with BMI between 25 and 40 kg/m^2 and aged between 18 and 57 years. Therefore, the results that we found must be verified in other age classes and for BMI groups below and above this range.

Finally, an accurate definition of fat mass is necessary as one pivotal criterion for clinical interventions, in particular in tailoring nutritional intervention and to document its effectiveness. Considering that the BMI cannot be a reliable predictor of FM, we can hypothesize that the use of BIA in combination with other biomarkers (leptin levels in particular) could be very useful in defining the clinical features of the obese patient in order to better address the therapeutic and rehabilitative approaches, as long as the cost/effectiveness of DXA will not be favorable.

Conflict of Interests

All the authors have no conflict of interests to declare.

Acknowledgment

This work was under Clinical Trial Registration no.: NCT01806493, registered at ClinicalTrials.gov.

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Hindawi Publishing Corporation
International Journal of Endocrinology
Volume 2013, Article ID 394934, 9 pages
http://dx.doi.org/10.1155/2013/394934

Clinical Study

Peripheral Arterial Tonometry to Measure the Effects of Vardenafil on Sympathetic Tone in Men with Lifelong Premature Ejaculation

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Received 29 January 2013; Accepted 20 February 2013

Academic Editor: Felice Strollo

To elucidate whether adrenergic overtone is involved in the pathophysiology of men with lifelong (LL) premature ejaculation (PE), we investigated differences in reactive hyperemia index (RHI) responses by using peripheral arterial tonometry (PAT). 20 men with LL-PE (18–40 years) were enrolled in an 8-week, double-blind, placebo-controlled, crossover study and compared with 10 age-matched controls without LL-PE. Primary endpoints were PAT modifications induced by vardenafil 10 mg on demand. Secondary endpoints were the improvement in intravaginal ejaculatory latency time (IELT) as measured by the stopwatch technique and variations in anxiety scores at Stai-X1 for state-anxiety and Stai-X2 for trait-anxiety. At baseline, men with LL-PE showed higher RHI variation ($P < 0.001$), Stai-X1 and Stai X2 scores ($P < 0.0001$, resp.), and prolactin levels ($P < 0.05$) compared with controls. Vardenafil treatment markedly reduced RHI variation in men with LL-PE ($P < 0.01$) when compared with placebo. Mean changes in geometric IELT were higher after taking vardenafil (0.6 ± 0.3 versus 4.5 ± 1.1 min, $P < 0.01$) when compared with placebo. STAI-X1 and STAI-X2 scores fell within the normal range after treatment with vardenafil ($P < 0.01$). Vardenafil was an effective treatment in men with LL-PE; improvements of IELT may be due to increased NO production which is able to reduce adrenergic overactivity and anxiety levels.

1. Introduction

Lifelong premature ejaculation (LL-PE) is defined as a "male sexual dysfunction" characterized by ejaculation which always or nearly always occurs before or within about one minute of vaginal penetration and the inability to delay ejaculation on all or nearly all vaginal penetrations and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [1]. The organs involved in the emission phase comprise the epididymis, vas deferens, seminal vesicles, prostate gland, prostatic urethra, and bladder neck. The organs participating in the expulsion phase include the bladder neck and urethra, as well as the pelvic striated muscles. The central ejaculatory neural circuit comprises spinal and cerebral areas that form a highly interconnected network. The sympathetic, parasympathetic, and somatic spinal centers, under the influence of sensory genital and cerebral stimuli integrated and processed at the spinal cord level, act in synergy to command physiologic events occurring during ejaculation. A wide number of neurotransmitters, including serotonin (5-HT), dopamine, oxytocin, gamma-aminobutyric acid (GABA), adrenaline, acetylcholine, and nitric oxide (NO), have been shown to be involved in the regulation of ejaculation. Since 1984, the nonselective alpha-blocker phenoxybenzamine was demonstrated to be able to improve premature ejaculation in humans [2]. Subsequent animal studies demonstrated that the effect of selective alpha blockade is obtained by inhibiting the contractile response of the rat seminal vesicle to electrical nerve stimulation [3]. Further evidence indicates that the

contractility of the human seminal vesicle is under the control of the NO-cGMP pathway, thus giving a rationale for the use of NO donors in the pharmacotherapy of PE [4].

The baseline pulse amplitude at fingertip level is highly dependent on digital blood flow and sympathetic tone, as is evidenced by a marked reduction in digital pulse amplitude after the administration of phenylephrine, an alpha-adrenergic vasoconstrictor agent [5]. Measurement of peripheral vasodilator response with a fingertip pulse amplitude tonometry (PAT) device is emerging as a useful method for assessing vascular function [6, 7]. In response to hyperemic flow, digital pulse amplitude increases, a response that has been shown to depend in part on NO synthesis [5]. Augmentation of pulse amplitude in the finger with hyperemia is a complex response to ischemia and reflects both changes in digital flow and digital microvessels dilation and is blunted by the presence of increased sympathetic tone.

In this study, we investigated the pulse amplitude hyperemic response within the first 60 seconds in men with lifelong PE without vascular risk factors as a possible marker of sympathetic overtone and compared it with age-matched normal subjects. Then, in a randomized, double-blind, placebo-controlled crossover study, we investigated the effects of vardenafil fixed dose on reactive hyperemia index (RHI) variations and on intravaginal ejaculatory latency time (IELT).

2. Methods

2.1. Inclusion Criteria. Vardenafil naïve men aged 18–40 years were included if they met the ESSM definition of LL-PE, as a "persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before the subject wishes it." Patients were included if they had a score of ≥11 of the premature ejaculation diagnostic tool, a 5-item questionnaire (scored from 0 to 4 according to progressive severity of ejaculatory dysfunction) to identify men who may have a problem with ejaculating too soon during sexual activity [8]. They were entered into a 4-week run-in period, during which a diary of all sexual activity was filled. Subjects who reported at least one intercourse episode per week and IELT ≤1 minute at stopwatch in 90% of intercourse attempts during the run-in period were enrolled and randomized to receive vardenafil or placebo for 8 weeks in the double-blind, placebo-controlled crossover trial (Figure 1). IELT was defined as the time elapsed between penetration and ejaculation, and an ejaculation occurred before penetration was assigned an IELT of 0 min. Patients had to remain in a stable, single-partner relationship and have at least one sexual intercourse episode per week throughout the treatment period.

2.2. Exclusion Criteria. Patients were excluded if they always experienced ejaculation prior to penetration or had IELT ≥1 minute in 90% of intercourse attempts. Patients were further excluded if they had a history of ED (score of <22 on erectile function domain of the IIEF) or other ejaculatory dysfunctions to limit the possibility of a response to vardenafil as a result of treating comorbid moderate-to-severe ED. The erectile function domain of IIEF is a 5-item questionnaire (IIEF5) that investigates the presence of erectile disturbances (scored from 1 to 5 for each item) according to the capacity to obtain and maintain an erection successful for sexual intercourse along with the evaluation of confidence and satisfaction with sexual life [9]. Patients were also excluded if they used condoms or masturbated before sexual intercourse for purposes of decreasing penile sensitivity or used any other treatment for PE. Patients were excluded if they had a history of vascular disease including stroke, myocardial infarction, unstable angina, or life-threatening arrhythmias within the past 6 months or were using organic nitrates or cytochrome P450 inhibitors. Moreover, screening for hyperthyroidism (TSH, FT3, and FT4), hypogonadism (total testosterone), prolactin disorders (PRL), and prostate smears for detecting acute or subacute prostatitis were carried out before the study entry. PRL and T were measured with chemiluminescent microparticle immunoassay (CMIA, Architect System) (Abbott Laboratories, IL, USA), with detection limits of 0.05 U/L 0.07 U/L and 0.6 ng/mL and 0.28 nmol/L, respectively; intra- and interassay coefficients of variation for our laboratory were 3.5 and 4.2% at 5.8 ng/mL (PRL) and 2.3 and 3.8% at 13.7 nmol/L (T). Serum concentrations of TSH, FT3, and FT4 were determined by chemiluminescent microparticle immunoassay (CMIA, Architect System) (Abbott Laboratories, IL, USA), with limits of detection of 0.0025 mIU/L, 1.536 pmol/L, and 5.148 pmol/L, respectively.

2.3. Procedures. Couples were instructed to attempt sexual intercourse four or more times during the 4-week baseline period and six or more times per month during the 8-week treatment period (minimum of 24 h between doses of medication) and to record IELT for the first event after each dose in the event log by the stopwatch technique. Patients were randomly assigned within each stratum 1 : 1 to receive placebo or fixed-dose phosphodiesterase type-5 inhibitor (PDE5-i) vardenafil (10 mg) and were given 15 doses of study medication (one dose was one tablet; tablets in all groups were identical in appearance since the active principle was encapsulated) each four weeks; one dose was to be taken 30 min before anticipated sexual intercourse, and no more than one dose was allowed to be taken in a single day. Ejaculation-delaying techniques and behavioral therapy were to be avoided. Also, couples were instructed not to use condoms or topical anesthetic cream, not to pause during intercourse, or to have interrupted intromission. Furthermore, they were requested not to increase their intercourse frequency, and if intercourse took place more than once in a single session, only the first intercourse IELT was measured. Patients agreed not to change the type of treatment during the study period. Treatment efficacy was assessed at 8 weeks.

2.4. Psychological Evaluation. In order to identify anxiety in the psychological context of the examined subjects, the State-Trait Anxiety Inventory (STAI) test, a self-administered questionnaire, was used [10, 11]. It consists of two different scales (STAI-X1 and STAI-X2) of 20 items each, with multiple

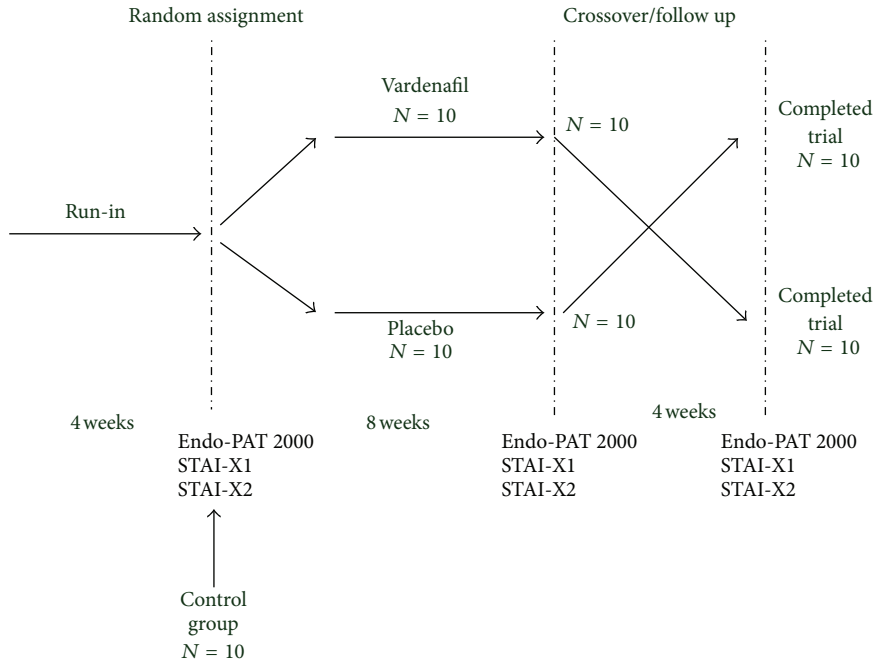

Figure 1: Study Design.

choice answers (never, sometimes, often, and always). Stai-X1 is directed at investigating the state anxiety and gives a transitory estimation of the emotional state, which varies in intensity and fluctuates in time as a function of the stressors impinging on the individual at the moment of starting the procedure. Stai-X2 is directed at relatively stable individual differences in subjects who become anxious in different circumstances [12]. Psychometric tests were performed to identify the presence of state anxiety (Stai-Xl) and trait anxiety (Stai-X2) before and after each treatment. The threshold scores for STAI questionnaires were chosen according to previously published methods [13] (normal range = 28–44 and 28–48 for the X1 and X2 form, resp.).

2.5. Main Outcome Measures. The primary endpoint of the study was to evaluate differences in RHI responses between men with LL-PE and controls and to evaluate differences in RHI responses after vardenafil or placebo in men with LL-PE. In addition, differences between anxiety scores at baseline and after different treatments were evaluated. Secondary endpoint was IELT at week 8. IELT was defined as the mean duration of intercourse attempts since the last clinic visit (past 4 weeks) for which intravaginal ejaculation was reported; ejaculation occurring before penetration was assigned an IELT of 0 minutes. During the screening visit, participants and partners received instructions on the IELT measurement technique, in which partners were to activate the supplied stopwatch on vaginal penetration during sexual intercourse and to stop the stopwatch on either intravaginal ejaculation or withdrawal without ejaculation. The time noted on the stopwatch at this point was recorded as the duration of sexual intercourse until ejaculation or withdrawal. This technique has been validated elsewhere [14].

2.6. Determination of Peripheral Arterial Tonometry (PAT). Each patient underwent peripheral arterial tonometry (PAT), a newly developed proprietary technology for noninvasively measuring the magnitude and dynamics of arterial tone changes in peripheral arterial beds. Digital pulse amplitude was measured, with a PAT device (Endo-PAT2000, Itamar Medical, Caesarea, Israel), in the fasting state in the supine position and both hands on the same level in a comfortable, thermoneutral environment, comprising a pneumatic plethysmograph that applies uniform pressure to the surface of the distal finger (fingers II, III, or IV) of each hand (same finger on both hands), allowing measurement of pulse volume changes in the finger. Baseline pulse amplitude was measured from each fingertip for 5 min. Arterial flow was interrupted for 5 min by a cuff placed on a proximal forearm at whichever occlusion pressure would be higher: 200 mmHg or 60 mmHg plus systolic blood pressure. Pulse amplitude was recorded electronically in both fingers and analyzed by a computerized, automated algorithm (owned by Itamar Medical) that provided the average pulse amplitude for each 30-second interval after forearm cuff deflation up to 4 min. The hyperemic response (called the PAT ratio) was expressed as the natural logarithm of the ratio of after deflation to baseline pulse amplitude in the hyperemic finger divided by the same ratio in the contralateral finger that served as control and expressed in percentage [15].

2.7. Statistics. We tested for differences between treatment groups by using ANCOVA. For each 30-second interval, PAT response to hyperemia is calculated as the natural logarithm transformation of PAT ratio at 90- to 120-second postdeflation time period as follows: ln[(Xh90–120/Xh120–150)/(Xc90–120/Xc120–150)]; for our study, the PAT ratio

was modified, and calculated at 30- to 60-second postdeflation time period as follows: ln[(Xh30−60/Xh60−90)/(Xc30−60/Xc60−90)] with h denoting hyperemic finger, X being the pulse amplitude, and with c denoting the control finger. A multiple regression analysis was performed for STAI-X1 and STAI-X2 against the variation of PAT ratio. A P value $< 0.05 \pm$ SD was considered statistically significant. Statistical analysis was performed using the computer statistical package SPSS/10.0 (SPSS, Chicago, IL, USA) and SAS/6.4 (SAS Institute Cary, NC, USA).

3. Results

All patients were seen with their partners and interviewed about their sexual activity and patient's ejaculation function. In total, 20 patients completed the whole randomized trial study. No patient was lost at followup. There were no statistical differences in patients' characteristics at baseline at the time of randomization (Table 1) excepting for PEDT scores and prolactin levels (Table 1).

At baseline, no differences in RHI values were found between groups (Figure 2(a)) when calculated as the natural logarithm transformation of PAT ratio at 90- to 120-second after deflation; when we calculate the differences in RHI, as the natural logarithm transformation of PAT ratio at 30- to 60-second after deflation (Figure 2(b)), a significant difference in the variation of RHI was found as suggested by delta_RHI calculation ($P < 0.001$, Figure 2(c)).

All patients underwent PAT evaluation either after one tablet assumption (Figure 3) or after 8-week on-demand treatment (Figure 4). No differences in RHI values were found between groups (Figure 3(a)) when calculated as the natural logarithm transformation of PAT ratio at 90- to 120-second after deflation; when we calculate the differences in RHI, as the natural logarithm transformation of PAT ratio at 30- to 60-second after deflation (Figure 3(b)), a significant difference in the variation of RHI was found as suggested by delta_RHI calculation ($P < 0.01$, Figure 3(c)).

Also, after 8-weeks on-demand treatment, no differences in RHI values were found between groups (data not shown); when calculated as the natural logarithm transformation of PAT ratio at 30- to 60-second after deflation, a significant difference in the variation of RHI was found as suggested by delta_RHI calculation in the treatment group only ($P < 0.01$, Figure 4(a)); when delta_RHI was compared with placebo at the end of treatment, a significant difference between the two groups was found ($P < 0.01$, Figure 4(b)). Interestingly, patients with higher delta_RHI at baseline showed greater decrease after vardenafil 8-week treatment ($P < 0.01$, Figure 4(c)).

At baseline, Stai-X1 scores were different between groups ($P < 0.0001$, Figure 5(a)). Accordingly, also Stai-X2 scores showed significant differences between groups ($P < 0.0001$, Figure 5(b)). After 8 weeks of treatment with vardenafil on-demand, a significant decrease in both Stai-X1 and Stai-X2 scores were found ($P < 0.001$) which remained significant when compared with controls.

Table 1: Demographic characteristics at baseline.

	LL-PE ($n = 20$)	CTRL ($n = 10$)
Age (ys)	31 ± 9	34 ± 9
SBP (mmHg)	115 ± 15	117 ± 17
DBP (mmHg)	79 ± 13	81 ± 14
BMI	22.5 ± 1	22 ± 0.9
AI (%)	−10 ± 14	−9 ± 15
AI@75 (%)	−16 ± 12	−16 ± 11
Cigarette smoking (%)	40	40
PEDT score	18 ± 0.8**	7 ± 0.6
IELT (minutes)	0.6 ± 0.3	11 ± 3***
TSH (mUI/mL)	2.1 ± 0.4	2.4 ± 0.3
Testosterone (ng/mL)	5.9 ± 1.4	5.8 ± 1.6
Prolactin (ng/mL)	12.2 ± 2.4	9.1 ± 2.8*

LL-PE: lifelong premature ejaculation. CTRL: controls. SBP: systolic blood pressure. DBP: diastolic blood pressure. BMI: body mass index. AI: augmentation index. AI@75: augmentation index corrected by heart rate. PEDT: premature ejaculation diagnostic tool. IELT: intravaginal ejaculatory latency time. TSH: thyroid stimulating hormone. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Interestingly, a direct relationship between delta_RHI and Stai-X1 ($r2 = 0.55$, $P < 0.001$; Figure 6(a)) and Stai-X2 ($r2 = 0.59$, $P < 0.001$; Figure 6(b)) was found.

Baseline (geometric mean ± SD) IELT for patients randomized to vardenafil or placebo was 0.6 ± 0.3 minutes and 0.7 ± 0.3 minutes, respectively (data not shown). At the end of treatment, IELT time increased from 0.6 ± 0.3 to 4.5 ± 1.1 ($P < 0.01$, data not shown) and from 0.7 ± 0.3 to 0.9 ± 1.0 (ns), respectively. At the time of followup, patients who crossed over from placebo to vardenafil reported significant improvements in IELT (from 0.9 ± 1.0 to 2.0 ± 0.9 min, $P < 0.05$, data not shown), while on the other arm, a significant reduction in IELT was found compared with the end of study (from 4.5 ± 1.1 to 3.2 ± 1.2, $P < 0.05$, data not shown); however, this latter IELT was still superior to baseline ($P < 0.01$, data not shown). This represents a mean change per patient of 3.8 ± 1.3 minutes for patients taking vardenafil and 0.2 ± 0.3 minutes for patients taking placebo. Thus, the magnitude of the increase in IELT compared with baseline was statistically significant ($P < 0.01$, data not shown). Adverse events were significantly superior ($P < 0.01$) with vardenafil (versus placebo) after 4 weeks of treatment and were headache (10% versus 1%), flushing (12% versus 0%), and dyspepsia (10% versus 1%), which tended to disappear at the end of the study (data not shown).

4. Discussion

As far as we are aware, this is the first controlled study providing a possible explanation regarding the possible action of vardenafil on ejaculatory latency time. At baseline, different PAT responses were found between men with lifelong PE and controls. The finding that men with LL-PE have late vasodilator response at PAT hyperemic response is very new. In fact, when we evaluate mean RHI scores, no difference between groups was found. Indeed, a deeper evaluation of

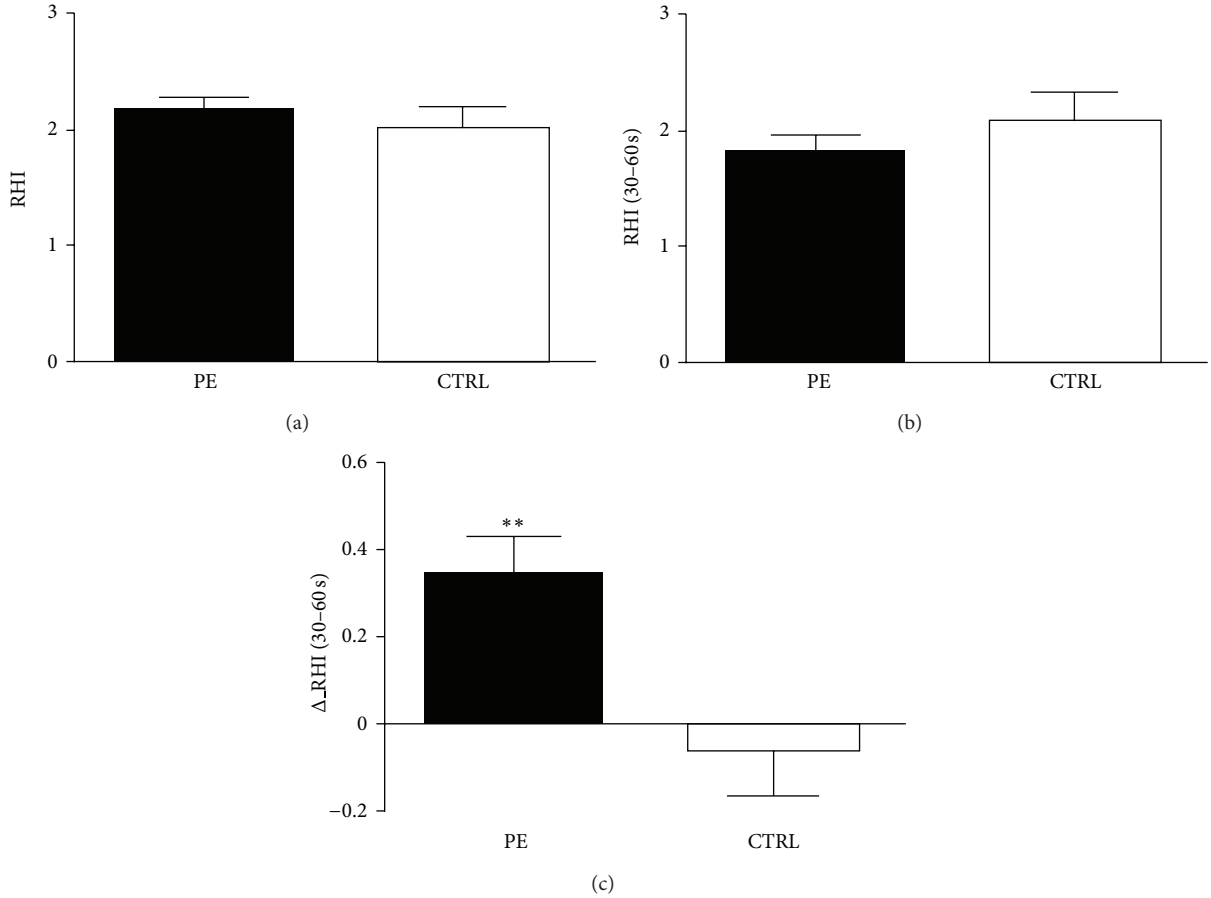

Figure 2: RHI values at baseline in different groups. The difference between groups is significant only when calculated as a linear variation of increment from baseline (delta RHI). PE = premature ejaculation. CTRL = controls.

PAT response within the first 60 seconds after induced shear-stress represents a new possible application of this technique. At the outset, we demonstrate a positive relationship between PAT hyperemic response obtained within 60 seconds after vardenafil, treatment period and anxiety levels; remarkably, no PAT response to vardenafil was found in healthy controls. Interestingly, IELT improved in men treated with vardenafil while no changes were found after placebo, as previously reported in a larger study by our group [13].

Sympathetic activation causes attenuation of the PAT signal, indicative of vasoconstriction, coupled with pulse rate acceleration in addition to the typical changes reported by oximetry [16]. This technique is widely used for the diagnostic approach to sleep apneas, by giving additional information on changes of sympathetic and parasympathetic tone during sleep. Based on this knowledge, we applied this technique to men with LL-PE in order to identify differences in the autonomic control of peripheral vessels and to correlate them with the presence of anxiety. PAT software employs algorithms based on weighting two features of the PAT signal, each of which indicates sympathetic surge: amplitude attenuation (reflecting vasoconstriction) and pulse rate increase (comparable to heart rate increase) [17]. The results presented in this paper, even if obtained in a small population, are consistent with the presence of sympathetic overtone as one of the possible causes of PE in this subset of young men. The significant modification of RHI (expressed as delta RHI) implies that vardenafil treatment was able to improve vasodilatation through a nitric-oxide-(NO) mediated pathway. Given the improvements in ejaculatory function that have meaning for men with PE and their partners, the paucity of side-effects, and the fast onset of action, vardenafil may be offered as a treatment option in many men in which PE is associated with substantial psychological effects—for example, interpersonal distress, decreased self-confidence, and relationship difficulties that play a major role in the pathogenesis of the disorder. Indeed, psychological causes of PE, that is, increased performance anxiety, are well-known causes of PE and are usually treated with psychosexual therapies [18]. Furthermore, there is a real possibility for the motivated couple that the combination of pharmacotherapy with a PDE5-i and behavioral techniques may yield greater improvements in IELT.

The thoracolumbar sympathetic and the sacral parasympathetic and somatic spinal ejaculatory center (Onuf's nucleus) play a pivotal role in ejaculation because they integrate peripheral and central signals and send coordinated outputs to pelviperineal anatomic structures that allow

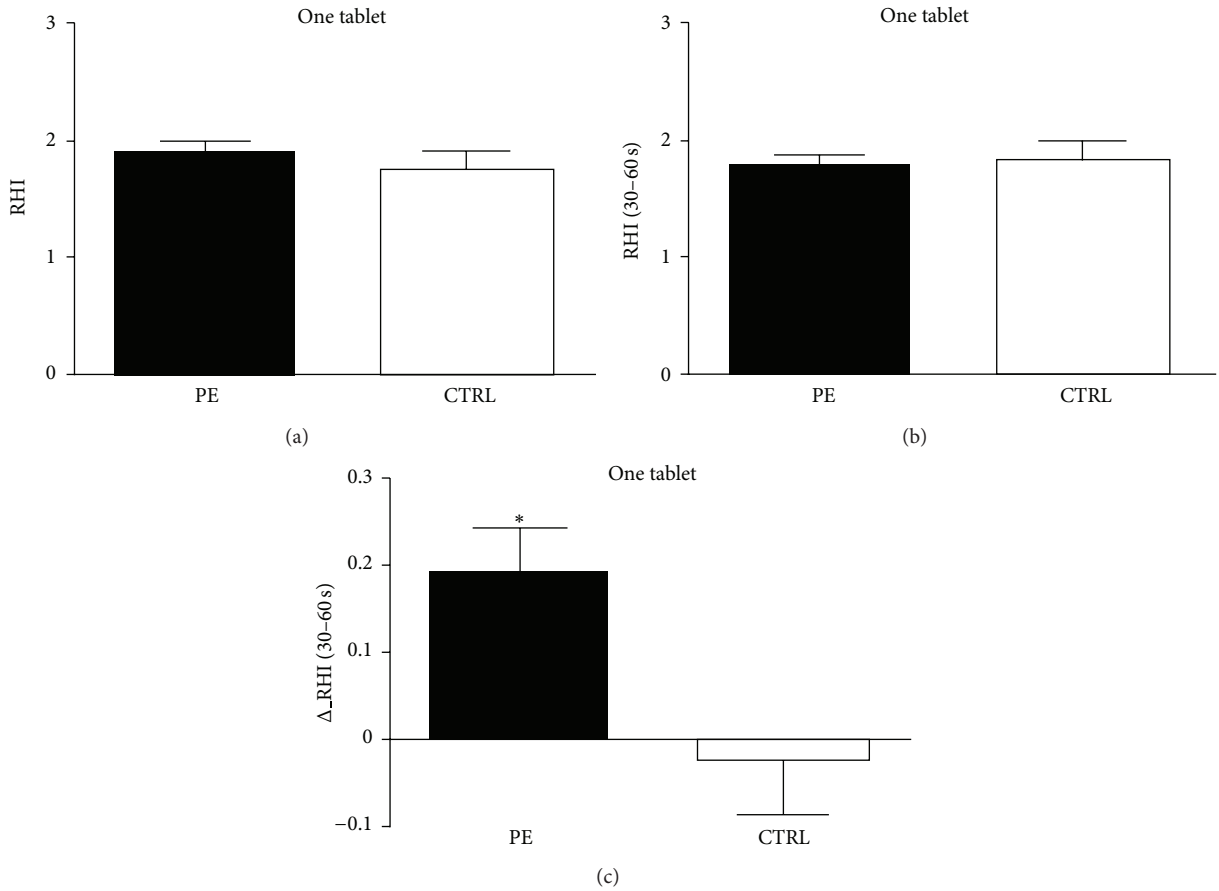

Figure 3: Variations in RHI values after assumption of one tablet of vardenafil 10 mg. The difference between groups is significant only when calculated as a linear variation of increment from baseline (delta RHI). PE = premature ejaculation. CTRL = controls.

a normal ejaculatory process to occur [19]. PDE5i may exert their influence both centrally and peripherally. The NO/cGMP pathway seems to play a role in sexual behavior via a central effect [20, 21]. Some authors have demonstrated that NO decreases central sympathetic output to the periphery via a cGMP-dependent mechanism or through interactions with other neurotransmitters. Specifically, a decrease of sympathetic tone by NO activity in the MPOA is related to inhibition of ejaculation [22]. Moreover, PDE5i may increase sexual arousal by acting in the central nervous system, in part mediated by the activation of mesolimbic dopaminergic neurons [23]. Many lines of evidence support the presence and activity of the NO/cGMP and NO/cAMP signaling pathways in the vas deferens (VD), smooth muscles, prostate, and urethra. Thus, those pathways may be responsible for the peripheral effect of PDE5i in the relaxation of penile corporal smooth muscles and could also affect smooth muscle in the VD, seminal vesicles (SVs), prostate, and urethra. A recent study demonstrated that the phasic contractile activity induced by means of electrical field stimulation of the SV tissue was most effectively inhibited by the PDE4 inhibitor rolipram and the PDE5 inhibitors sildenafil and vardenafil [24]. These observations were consistent with the findings from the studies mentioned earlier, indicating that PDE5 inhibitors can abolish the contractility of isolated human SV. Overall, these findings are in agreement with both central and peripheral actions of vardenafil on sexual behavior and on ejaculation.

The hormonal control of ejaculation and the pathophysiology of PE are still not fully understood. Corona et al. reported that testosterone, PRL, and TSH, significantly and independently contribute to the reported IELT variation in a large population of males complaining of sexual dysfunction [25]. In particular, low PRL and high testosterone levels were associated with a higher risk of PE, even after adjusting for confounding factors that include age, body mass index, medicaments, and smoking habit. Prolactin levels have also been found to be positively correlated with reported ejaculatory latency (from severe premature ejaculation to anejaculation), after excluding men with pathological hyperprolactinaemia and adjusting for SSRI use [26]. It must be emphasized that these associations were found in a population of patients without the specific use of the stopwatch method for the quantification of IELT, as it is evaluated in the present study where PRL levels were higher in LL-PE group, but within the normal range. Additionally, we can speculate

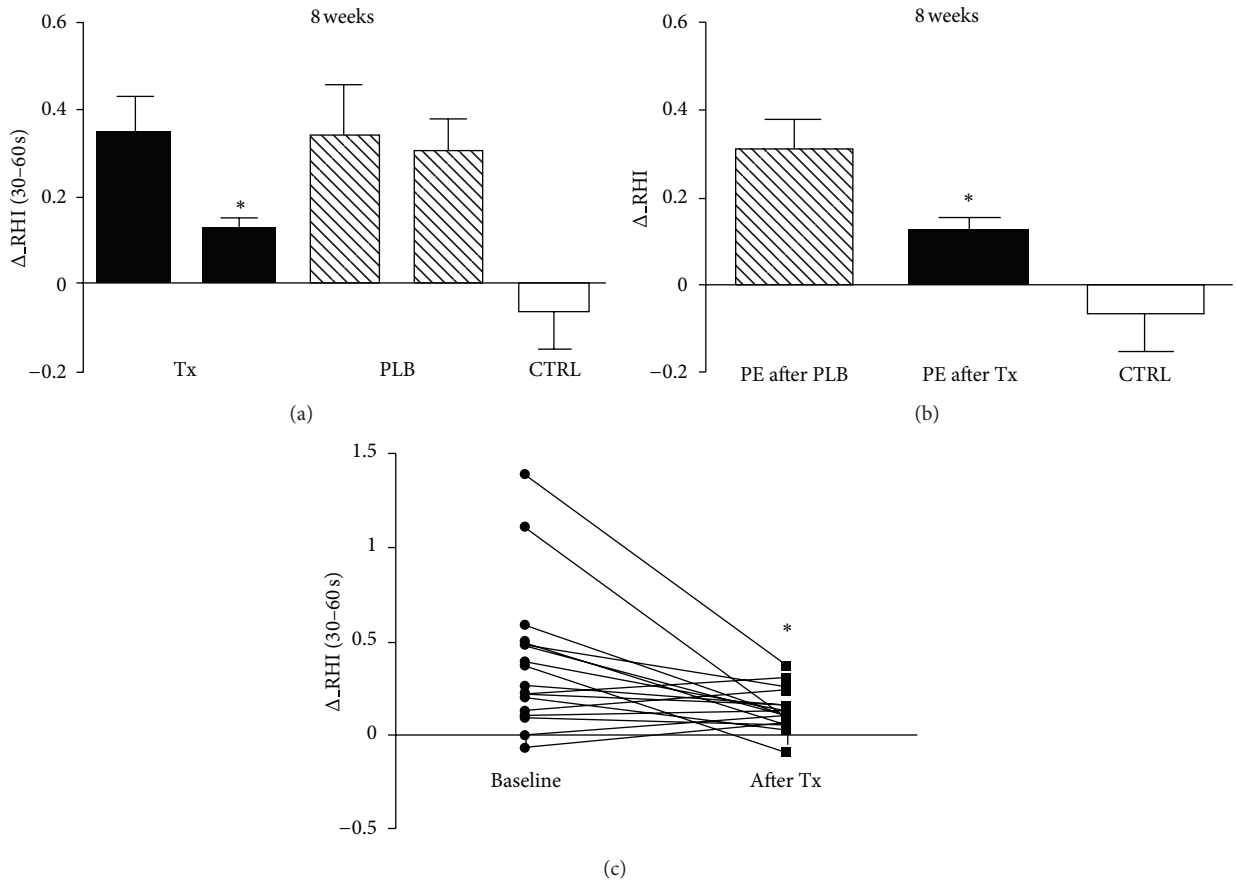

Figure 4: Variations in delta_RHI values after 8-week double-blind controlled trial. Tx = active treatment. PLB = placebo treatment. CTRL = controls.

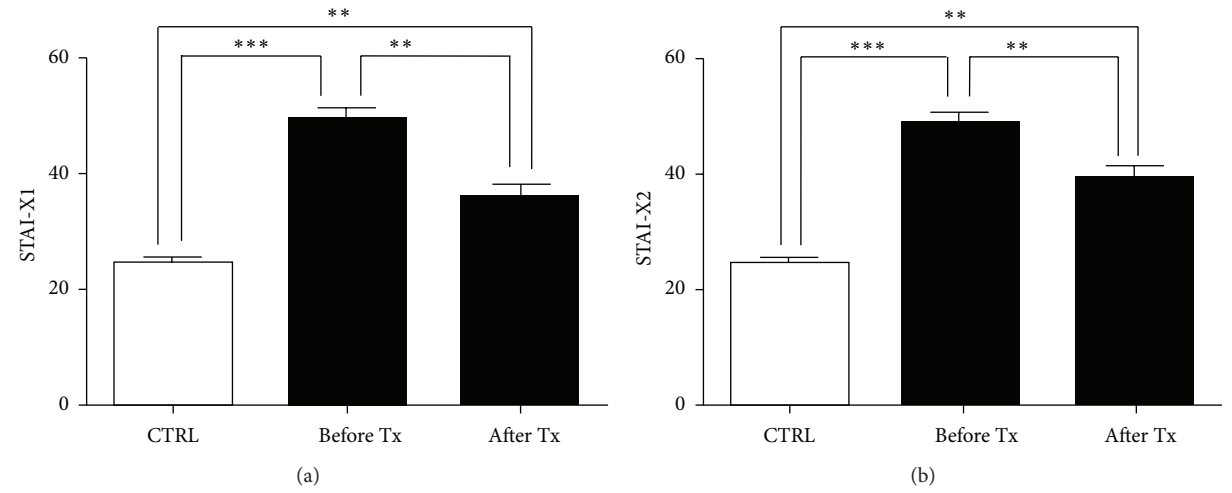

Figure 5: State anxiety (Stai-Xl) and trait anxiety (Stai-X2) questionnaire score changes after 8-week period treatment. Before Tx = before active treatment. Post Tx = after active treatment. CTRL = controls.

that higher PRL levels might be the result, not the cause, of the loss of ejaculatory control in our study population because of the presence of an elevated anxiety trait.

There is suggestive evidence that men with PE are more likely to endorse questionnaire items indicating anxiety. Given that PE may be psychogenic, at least in part, and possibly related to anxiety, while part of its definition is feelings of lack of ejaculatory control, bother, and distress; there is considerable room for a placebo effect in all studies on the management of PE. In the present study, we observed

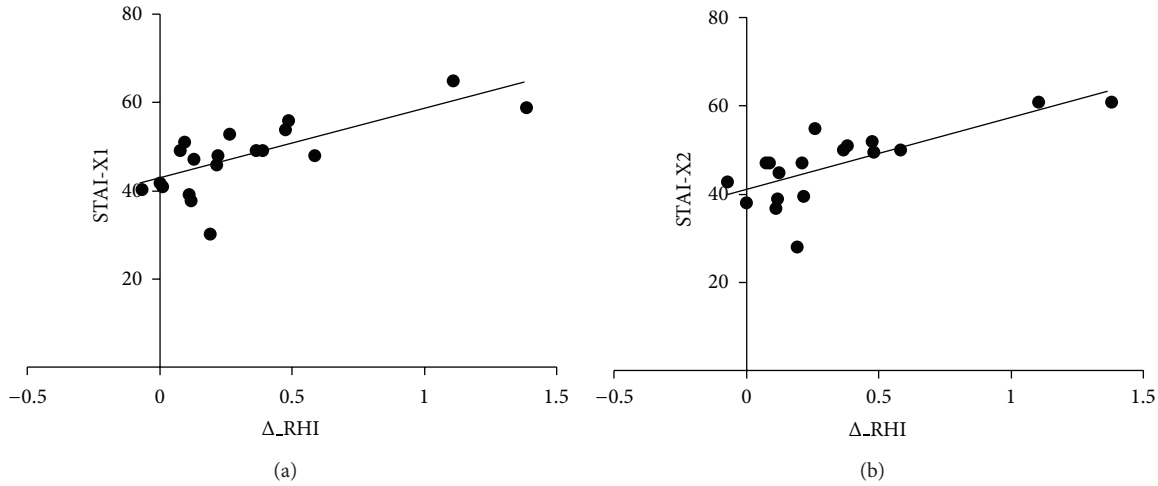

Figure 6: Linear ralationship between state anxiety (Stai-Xl) and trait anxiety (Stai-X2) questionnaire scores and delta_RHI variations.

an inconsistent placebo effect probably due to the design that considered an extension crossover period of time. We firstly demonstrated that PAT hyperemic response was strongest in the 30- to 60-second interval after fingertip flow was restored. The logarithmic transformation of the PAT ratio and selection of the 30- to 60-second time interval increased the overall association with the presence of a baseline constricted arterial tone, suggesting that this may be the optimal method for assessing the presence of sympathetic overactivity. The selected time period includes the portion of hyperemic response that has been previously shown to depend in part on NO production. Further studies in larger populations are needed to validate the possibility that the PAT hyperemic response is decreased in men with LL-PE and to validate the use of PAT as a diagnostic tool to identify possible responders to PDE5-I in the clinical setting.

In conclusion, fixed-dose vardenafil 10 mg is a safe and effective treatment in the absence of ED in young men with LL-PE and high anxiety scores. Vardenafil effects on IELT and PAT responses are encouraging; even if this is a pilot study, this represents indirect evidence that neurobiological patterns of PE still need to be investigated. Further larger population controlled studies to confirm the beneficial effects of vardenafil are warranted.

Conflict of Interests

The authors declare that they have no conflict of interests.

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