AMERICAN JOURNAL OF DIABETES

All articles peer-reviewed

Vol. 1, No. 1, February 2004

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Premier issue for diabetes educators and physicians who care for patients with diabetes

AMERICAN JOURNAL OF DIABETES

Vol. 1, No. 1, February 2004

American Journal of Diabetes is a professional clinical journal focussing on the diagnosis, management and treatment of diabetes. Each issue includes articles that physicians and diabetes educators can apply in daily practice.

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Original articles

INFORMATION FOR AUTHORS

We provide up-to-date information about diabetes research, FDA-approved devices and therapies to healthcare professionals so that they have the information they need to enable persons with diabetes to lead long and productive lives. Our articles are targeted at the physician in clinical practice and the diabetes educator, and our goal is to build bridges between our target audience and academic scientists so that laboratory and clinical findings can be rapidly disseminated in a form that can be applied in the daily practice of medicine. Towards this aim, we have assembled an editorial board of scientists, physicians, and diabetes educators to assess current research and therapies. Some of the members of the Board are themselves living with diabetes. The editorial board is charged with reviewing every word of every article that we print and to ensure the separation of advertising and editorial.

Each article is reviewed by at least 2 members of the editorial board and the Editor-in-Chief, and outside reviewers as the need arises. We adhere to the requirement of the National Library of Medicine for inclusion of journals in their database is that "neither the advertising content nor commercial sponsorship should raise questions about the objectivity of the published material."

Publication of the journal is supported by advertising FDA-approved diabetes medications and devices, events, meetings of interest to healthcare professionals working with patients with diabetes. The articles are selected for review by the Editor-in-Chief, working independently of the Publishers, who select the advertisers.

All articles published are required to meet the standards of the National Library of Medicine. Our major criteria for selecting each article are scientific merit, relevance to our target audience and quality of writing. We invite submission of articles reporting clinicaland preclinical studies, reviews of current clinical and pre-clinical studies, discussion of devices and medications, case reports on treating adults and children with type 1 and type 2 diabetes, case reports on preventing diabetes in patients at risk. Submissions of review articles and case reports must be preceded by communication with the Editor-in-Chief. We also invite submission of letters to the Editor, which should address observations in clinical practice, early results of studies, discussion of applications of basic research to clinical practice or discussion of clinical guidelines.

For consideration by the editorial board, all manuscripts must be written according to the uniform requirements for manuscripts submitted to biomedical journals, which are posted on www.icmje.org and in summary on www.nejm.org/hfa/subinstr.asp.

The preferred form for submission is by attaching articles prepared electronically to e-mails. First send an e-mail with a cover letter, then send a second e-mail with the article attached. For us to lay out the article, it needs to be in MS Word or another commonly used word-processing program. When we accept the article for review, we will e-mail or fax you a form which you need to sign, stating that you are the senior author of the article under review and that all tables and figures are either original or you have proof that you are permitted to reproduce them and that you have named all persons involved in preparing the manuscript.

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PRESS RELEASES

Prescription and OTC Drugs

Received from American Diabetes Association, 18 Dec 2003: report of a paper addressing the dual problems of obesity in patients with type 2 diabetes and additional weight gain when these patients are started on insulin. The paper can be downloaded free from clinical.diabetesjournals.org: ***D Thomas-Dobersen. Case Study: a 64-year man with a history of type 2 diabetes in whom insulin therapy led to inproved control but no weight gain after 6 months. Clinical Diabetes. 2003; 21(4):190-2.***

Received from NovoNordisk, 15 Dec 2003: Will Cross is being sponsored by the manufacturer to be the first person with diabetes and the first American to successfully climb the highest mountains in each of the Earth's 7 continents and also to trek to the North and South Poles. Mr Cross is 36, is a high school principal in Pennsylvania, is the father of 5 children and he has type 1 diabetes. Mr Cross was quoted as saying, "Using NovoLog® insulin with the FlexPen® helps me not only manage my diabetes in my everyday life but also while I am climbing some of the highest peaks in the world."

Received from Paddock Laboratories, 14 Nov 2003: Information about their prescription drug, LAClotion™ 12% (ammonium lactate) Lotion for the treatment of dry skin conditions that can be associated with diabetes foot care. Free physician LAClotion™ samples and "Rule of 15®" patient education pamphlets in English and Spanish are available"; and an over-the-counter drug: "Paddock Laboratories manufactures Glutose 15™ (oral glucose gel) for hypoglycemia. Visit www.Paddock.labs.com or contact us at 1-800-328-5113 for more information."

Received from Novo Nordisk, 11 Nov 2003: discussion of a study of 140 patients with type 2 diabetes whose inadequate glucose control on oral hypoglycemic agents necessitated starting insulin injections. The study was published: ***C Kilo, N Mezitis, R Jain, J Mersey, J McGill, P Raskin. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. J Diabetes Complications. 2003; 17(6):307-13.*** The lead investigator, Dr Kilo, was quoted "Our findings show that a single dinnertime injection of NovoLog® Mix 70/30 in combination with metformin appears to be at least as effective, safe and convenient as comparable combination therapy with NPH insulin or biphasic human insulin".

Received from Novartis, 23 Oct 2003: The FDA has approved nateglinide for combination therapy with thiazolidinedione in patients with type 2 diabetes who are not adequately controlled by thiazolidinedione monotherapy.

Prevention

Received from the National Institutes of Health, 16 Dec 2003: discussion of a study reporting that "cardiorespiratory fitness in early adulthood significantly decreases the chance of developing high blood pressure and diabetes... in middle age...Further, improving fitness in healthy young adults can cut as much as 50% the risk for diabetes and the metabolic syndrome." The patient population was from the Coronary Artery Risk Development in Young Adults (CARDIA) Study which began in January 1984 and ended in December 2001 and is published: ***MR Carnethon, SS Gidding, R Nehgme, S Sidney, DR Jacobs jr, K Liu. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA. 2003; 290(23):3092-100.***

Received from the Centers for Disease Control, 15 Dec 2003: the CDC has launched a peer-reviewed electronic journal, ***Preventing Chronic Disease.*** Download full articles freely from **www.cdc.gov/pcd.**

The American Journal of Diabetes neither has financial interest in nor endorses any products mentioned.

PRACTICE GUIDELINES SUMMARY

The Prevention or Delay of Type 2 Diabetes

American Journal of Diabetes Summary of 2003 Practice Guidelines

As type 2 diabetes reaches epidemic proportions, the costs in human and economic terms are increasing, which are of great concern to the United States Department of Health and Human Services.(1) The American Diabetes Association and the National Institute of Diabetes, Digestive and Kidney Diseases produced a Position Paper in 2003 discussing the prevention or delay of type 2 diabetes. The Position Paper can be fully and freely downloaded from care.diabetesjournals.org/ content/vol26/ suppl_1/. This article, prepared by the American Journal of Diabetes, is a summary of the Position Paper, and all references cited are those cited in the Position Paper. *American Journal of Diabetes Summary. The prevention or delay of type 2 diabetes. Amer J Diabetes. 2003; 1(1):31-34.*

The Prevention or Delay of Type 2 Diabetes

Four studies in which data indicated that changes in lifestyle can prevent diabetes are described at length: 2 lifestyle studies, the Finnish Study and the Diabetes Prevention Program Study (DPP) and 2 pharmacological prophylaxis studies, Troglitazone in Prevention of Diabetes (TRIPOD) and the STOP-NIDDM trial.(2-7)

In the Finnish Study, 522 subjects (mean age 55 years, mean BMI 31 kg.m^{-2}) with impaired glucose tolerance (IGT) were randomly assigned to either:

1. brief diet and exercise counseling: Control Group
2. intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity: Intervention Group

After an average follow-up of 3.2 years, the incidence of diabetes was reduced 58% in the Intervention group compared with the Control group. The progression to diabetes was strongly negatively related to subjects being able to achieve at least 1 of the following goals:

1. lose weight (goal of 5.0% weight reduction)
2. reduce fat intake (goal of <30% of calories)
3. reduce saturated fat intake (goal of <10% of calories)
4. increase fiber intake (goal of >15 g.1,000 kcal^{-1})
5. exercise (goal of >150 minutes.week^{-1}).

The 3,234 subjects in the DPP Study (mean age 51 years, mean BMI 34 kg.m^{-2}) had nearly identical IGT as those in the Finnish study.(5-7) DPP subjects were randomly assigned to either:

1. intensive nutrition and exercise counseling: Lifestyle Group

2. biguanide metformin therapy plus standard diet and exercise recommendations: Metformin Group

3. placebo therapy plus standard diet and exercise recommendations: Placebo Group

After an average follow- up of 2.8 years (range 1.8-4.6 years), a 58% relative reduction in the progression to diabetes was observed in the Lifestyle Group (absolute incidence 4.8%), and a 31% relative reduction in the progression of diabetes was observed in the Metformin Group (absolute incidence 7.8%) compared with the Placebo Group (absolute incidence 11.0%). On average, 50% of the Lifestyle Group had >7% weight reduction, and 74% maintained at least 150 min.week^{-1} of moderately intense activity. No serious side effects were seen in any group.

In the Troglitazone in Prevention of Diabetes (TRIPOD) study, 235 Hispanic women with previous gestational diabetes were randomly assigned to either

1. a thiazolidinedione (troglitazone)

2. placebo

After a median followup of 30 months, the annual incidence of type 2 diabetes in the two groups was 12.3 and 5.4%, respectively.(8) Thus, troglitazone treatment was associated with a 56% relative reduction in progression to diabetes. After a washout period of >8 months, the preventive effects of the drug were still observed.

In the double-blind placebo-controlled STOP-NIDDM trial.(9,10) 429 subjects (mean age of 55 years, mean BMI of 31 kg.m^{-2}) with IGT were randomly assigned to either

1. an alpha-glucosidase inhibitor (acarbose)

2. placebo

After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on one OGTT, was observed in the acarbose treated group compared with the placebo group. If this diagnosis was confirmed by a second OGTT, a 36% relative risk reduction was observed in the acarbose group compared with the placebo group. The absolute risk reduction in the acarbose-treated group was 9%. The effect of acarbose was consistent among all age groups, BMI values and between both sexes.

The current evidence suggests that opportunistic screening to detect prediabetes (IFG or IGT) should be considered in persons >45 years of age, particularly in those with a BMI >25 kg.m^{-2}. Screening should also be considered for persons >45 years of age who are overweight if they have another risk factor for diabetes. Asian-Americans should be considered for screening at lower BMI (eg, 23 kg.m^{-2}). Patients should be screened with the FPG test or 2-h OGTT. The FPG test is preferably given in the morning because afternoon values tend to be lower.(11)

The authors suggest that normoglycemic middle-aged subjects should be tested every 3 years.

The strategies shown to be effective in preventing diabetes relied on lifestyle modification or glucose-lowering drugs that have been approved for treating diabetes. In both the Finnish and the DPP studies, diabetes was delayed or prevented with only modest changes in weight and activity, however, considerable effort from well-trained staff was needed to achieve these behavioral changes and some weight was regained despite the continuation of intensive strategies. Although many other weight loss strategies have been described, all have been difficult to accomplish and maintain.(12-16) Without question, howev-

er, many individuals have achieved and maintained appropriate lifestyle changes, and some have done so without health care system interventions. Even so, better strategies are needed to help people lose weight and keep it off and exercise more often. Moreover, the U.S. healthcare system is not structured to provide or reimburse for regular lifestyle counseling.(13,14)

The greater benefit of weight loss and physical activity strongly suggests that lifestyle modification should be the first choice to prevent or delay diabetes. Modest weight loss (5-10% of body weight) and modest physical activity (30 minutes daily) are the recommended goals. Health care providers should urge all overweight or sedentary individuals to adopt these changes, and such recommendations should be made at every opportunity.

Drug therapy to prevent or delay diabetes appears to be much less beneficial. The Position Statement does not recommend the routine use of hypoglycemic agents to prevent diabetes, for the following 4 reasons.

1. All glucose-lowering drugs require monitoring, have been associated with significant adverse side effects, and are contraindicated in some individuals.

2. No glucose lowering agents tested or commercially available have been studied with regard to protection against cardiovascular disease or have any other clinical benefit to nondiabetic individuals.

3. For patients with diabetes, metformin is the only glucose-lowering agent for which outcome data suggests possible effectiveness in reducing the incidence of macrovascular disease.(17,18)

4. Prescribing a medication to delay the onset of diabetes, which is also used to treat diabetes, will increase a patient's total years of drug exposure and may increase the likelihood of untoward drug effects.

How do strategies to prevent diabetes differ from those to treat diabetes?

The answers given in the Position Statement:

1. Patients with diabetes receive tests and procedures that are not relevant to patients with prediabetes. Such tests include foot examination, dilated eye examination, HbA1C measurement, urine protein.

2. Patients with diabetes are at risk for some acute complications such as hypoglycemia, increased infections and microvascular complications that have not been documented in patients with prediabetes. Both patient self-monitoring and careful monitoring by a provider for some diabetes-related conditions are not as important in patients with prediabetes as in patients with diabetes.

3. The goals for blood pressure and lipid management for patients with diabetes are more rigorous than for patients with prediabetes.

4.Patients labeled "diabetic" are more likely to be subject to possible social and economic discrimination.

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Answers to puzzle, page 38: *Acarbose, ACE, Acidosis, Aerobic, Albuminuria, ARB, Beta, BMI, BP, Carbohydrate, Cardiovascular, Counting, DASH, Diet, Endocrine, Exercise, Eye, Fast, Fat, Fibrate, Fit, Foot, Flu, Gastroparesis, GDM, Glargine, Glucometer, Glycohemoglobin, Grams, Hyperglycemia, Hypo, ICU, Insulin resistance, Ketones, Lancet, Lean, Lente, Lipids, Lispro, Meglitinide, Men, Metabolic, Metformin, Nerve, Neuropathy, Niacin, Obese, One, PCOS, Pen, Protein, Pump, PVD, Renal, Retina, Statin, Steroid, Sulfonylurea, Syringe, Test, Trig, Two, Types, TZD, Unit*

BOOK REVIEWS

Where Does Diabetes Come From?

Microcompetition with Foreign DNA and the Origin of Chronic Disease. Hanan Polansky. CBCD Publishing, Rochester NY. 2003, ISBN 0-9740463-0-2. 543 pp $73.00.

In the first book we review, the author believes he knows the answer. Dr Hanan Polansky was a Professor of Marketing at the University of Rochester who left his job to read through the literature to see if he could determine the causes of obesity, and in the process believes he has uncovered the causes of all chronic diseases.

According to the preface, Dr Polansky moved into an office which he described as a cave, and stayed there until he had produced his theory of the origin of chronic disease. ***The American Journal of Diabetes*** asked him how he prevented himself from starving to death. His answer was that his family lived off his savings for 2 years, and his savings ran out exactly when he believed he had the answer to the causes of obesity. At that time, investors in Rochester stepped in and were convinced that Dr Polansky not only knew the answer to the cause of obesity, but that he also knew the cause of all chronic diseases, including type 1 diabetes and type 2 diabetes. This relationship with the investors led to his producing this book and filing for patent protection for any treatments that are based on his theories.

Dr Polansky defines chronic disease as a disruption, and describes exogenous events as those that move biological systems from "good health" to chronic disease" are disruptions. He describes a chronic disease as a stable body system after a disturbance has altered the stable system associated with good health, and claims to have identified the single disruption responsible for many chronic diseases: foreign DNA competing with human DNA and binding onto GABP. He discusses his theory in the context of the development of type 1 diabetes, type 2 diabetes, atherosclerosis, stroke, autoimmune disease and obesity as well as other chronic diseases, and then discusses treatments.

Dr Polansky's theory is interesting and is backed up by 1224 references, and if he is right, perhaps a target for curing chronic disease should not be the symptoms of the disease but the carriers of the foreign DNA that is competing with the patient's own genetic material.

The patent application filed with the US Patent and Trademark Office (#20030069199, dated April 10, 2003) is for treatment methods based on this theory. In his patent application he describes his theory as microcompetition for a limiting GABP complex.

American Journal of Diabetes Editorial Board member Raymond T. Pekala, MD, is an ophthalmologist in clinical practice who majored in Chemistry in his baccalaureate from Yale University. We asked Dr Pekala to review the book. He reported that he skimmed through the book for 2 hours and saw no immediate clinical application of the theories discussed.

Help For Patients With Type 2 Diabetes

Type 2. A Book of Support for Type 2 Diabetics. Miryam Ehrlich Williamson. Walker Publishing Company, Inc. 2003, ISBN 0-8027-7666-3. 236 pp $12.00.

The second book we review this month is a small support book for patients who are living with type 2 diabetes. It was written by Miryam Ehrlich Williamson, a medical journalist with an adult daughter who has type 2 diabetes.

In 7 chapters Ms Williamson explains the different etiologies of type 1 and type 2 diabetes, explains why some patients with type 2 diabetes need to inject insulin and explains why some patients have a mix of both types of diabetes.

Ms Williamson has had a long career in explaining complex medical issues to a non-clinically trained public, and this book continues in this tradition. She includes a comprehensive bibliography, internet sites including list serves that patients can join for support from other patients, and appendices explaining in easily understandable terms antidiabetic oral medications and blood glucose monitors.

ORIGINAL ARTICLE

Insulin Pumps: Current Features and Technology

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Abstract

Insulin pumps offer safety and convenience and have built-in features which make them possible insulin-delivery systems for all patients dependent on exogenous insulin. *Sparrow-Bodenmiller J. Current features and technology of insulin pumps. Amer J Diabetes. 2004; 1(1):20-22.*

Introduction

The effectiveness of continuous subcutaneous insulin infusion (CSII) in treating type 1, and type 2 diabetes has been extensively reported.(1-4) Since the first portable insulin pumps used for CSII by John Pickup and his colleagues at Guys Hospital in London (6), and then by William Tamborlane and his colleagues at Yale (7), insulin pump technology has advanced considerably to the point where we are today, with smaller, easier to use, safer and more durable pumps.

Features of New Insulin Pumps

Weighing as little as 3.3 ounces, insulin delivery by CSII is precise to 0.05 units. The newer insulin pumps have data download capability and can wirelessly interface with a blood glucose monitor. Various improved features include square/extended bolus, dual/combination bolus, insulin to carbohydrate ratio calculator, high blood glucose correction ratio calculator, and the "insulin on board" calculator. These features are all "menu" driven and very user friendly. While a pump can be found for every patient needing exogenous insulin, the key to successful insulin pump therapy is the patient learning how to use the pump.

Temporarily Adjusting the Basal Rate of Insulin Delivery

The temporary basal rate adjuster is not a new feature of the insulin pump, but is perhaps the most underused. This feature permits a short-term change in basal rate for up to 24 hours so that the patient can participate in active exercise such as running (lower the basal rate) or adjust to illness, stress or a dawn phenomenon (raise the

basal rate).

Insulin Bolus Calculation

Current insulin pumps can automatically calculate the insulin bolus required to cover the carbohydrates about to be consumed. When the grams or exchanges of carbohydrates are entered, the pump calculates the amount of insulin that metabolism of the foods require, based upon the preset carbohydrate ratio. Different carbohydrate ratios may be programmed for varying times of the day. Furthermore, newer pump features permit different ways of delivering a bolus.

Square/extended bolus delivers a bolus evenly over a specified period of time, 30 minutes to several hours. This is helpful for drawn out meals, extended snacking, or for meals with a high fat content. It is also helpful for those patients who have delayed gastric emptying from gastroparesis. If regular bolus delivery drops the blood sugar too rapidly, using the square/extended wave bolus better matches insulin to the patient's needs.

Dual/combination bolus delivers a normal bolus, followed by an extended bolus. This feature is useful for meals that include both rapidly and more slowly absorbed carbohydrates. A meal of fresh fruit and white bread followed by pasta with cream sauce, pizza or Chinese food is better handled by the combination bolus, providing insulin immediately and continued.

High blood sugar correction can be handled with ease by modern pump. Once the blood glucose is entered into the pump, the correction bolus required to reduce the glucose to a preset target is automatically calculated using the pre-determined insulin sensitivity factor.

Pump Safety Features

Pump safety features include the "insulin on board" program. Utilizing the pharmaco/dynamic profiles of the rapid-acting insulin analogues, the pump calculates the amount of active insulin remaining in the body, at any given time following a prior bolus. If another bolus is given, the amount of active insulin remaining will be deducted from the current bolus, thus preventing "stacking" of insulin doses. This algorithm will also deduct insulin from a bolus being given, when the blood glucose value is below the preset target. These features contribute towards making CSII a much safer and easier to manage therapy, while limiting the need for a calculator to determining total grams of carbohydrates.

Improved alarms incorporated into current pumps give the user a greater sense of security and made CSII safer and more acceptable. One feature, used with children and other patients incapable of comprehending their treatment, permits pump button activation only by code. Other features of modern pumps include alarms warning insufficient insulin in a cartridge, low delivery or occlusion, low battery charge, and of motor error. Safeguards are an important requirement for FDA approval of insulin pumps.

Bolus Delivery For the Visually Impaired

Other features available include an "audible" bolus, allowing a bolus to be programmed without needing to see the pump screen. This function is helpful for the partially sighted, or blind individual or, simply the wearer who prefers to leave the pump in a pocket, rather than have it visible.

The bolus is programmed using beeps that have been set for a pre-determined amount, i.e. 0.5 unit. Each press of the touch bolus button is registered with a beep, and the total dose confirmed by a series of beeps. A small remote control device available by one manufacturer works in the same manner as the audio bolus, however it is a separate unit the size of a car door remote.)

Interfacing Insulin Pumps with Glucose Monitors

Utilizing radio frequency technology, some insulin pumps can automatically receive blood glucose readings from a specific glucose meter. The computer download capabilities of these pumps enable the healthcare team to analyze more integrated data and facilitate the management of pump patients.

Up to 4 different basal programs or patterns are possible with today's pumps. Days prior to the menstrual cycle when often the blood glucose levels rise, night shift workers with differing sleep and working hours, and days with markedly different activity levels: these days are better managed using multiple basal patterns. Once the basal rates are set for each pattern, it is simple to program the pump to deliver the required pattern for that day.

Catheter Sets

In pace with CSII, the catheter sets have also evolved. Finer catheters with flatter profile insertion sites that can be disconnected at the skin level now are available. Catheter set introducers, make it possible for the younger patient, or those needle phobic, to easily insert the catheter by themselves.

Generic tubing sets have cut the cost of maintaining CSII therapy, and make it more available to those with no insurance and limited insurance resources.

Pump Upgrades

In my experience, patients may be eligible for a pump upgrade by their insurance carrier after four years. However, with the new microchip technology, pumps can now be upgraded just by reprogramming. Patients will have the choice of paying for only those programs that they can use. The problem of insurance paying for these upgrades may be complicated by other factors.

Conclusions

The insulin-dependent patient has had increasingly more options in the past decade. Insulin pumps have improved and perhaps in the next decade will become fully automatic by incorporating glucose monitors so that together they mimic a functioning pancreas.

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ORIGINAL ARTICLE

Whole Blood Viscosity and Diabetes

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Abstract

Whole blood viscosity (WBV) is a major determinant of the work of the heart and the perfusion status of every cell in the body, and is an important factor in the care of patients with types 1 and 2 diabetes and in preventing type 2 diabetes. WBV measurement has been neglected in clinical practice. The literature and preliminary studies support the hypothesis that optimizing WBV delays development of cardiovascular disease. *Kensey, KR. Whole blood viscosity and diabetes. Amer J Diabetes. 2004; 1(1):24, 26-28.*

Introduction

I am a cardiologist, and over the past 15 years I have been involved in research to try and prevent cardiovascular disease developing.(1-6) Drugs that keep blood fluid are known to reduce the likelihood of cardiovascular events, such drugs are lipid lowering drugs and anticoagulants. A major lack in the tools for caring for patients at high risk for cardiovascular events, such as everyone with diabetes, is the lack of an easy way to determine blood fluidity. Commercially available viscometers are unwieldy and are not in the hands of the practicing physician. My colleagues and I have developed a viscometer that measures viscosity easily, over a range of shear stresses, which we call the Rheolog™.(7,8)

Atherosclerosis and Diabetes

The most prevalent complication of diabetes is cardiovascular disease; indeed, diabetes has been called a cardiovascular disease. The American Diabetes Association and the American College of Cardiology have started a program called "Make the Link! Diabetes, Heart Disease and Stroke" which is aimed at increasing awareness of the link between diabetes and heart disease. The introduction to "Make the Link" states that 2 out of 3 patients with diabetes die from heart disease and stroke and stresses the need for diabetes management to include management of blood pressure and cholesterol, both of which are risk factors for cardiovascular disease associated with elevated blood viscosity.(9)

WBV and Diabetes

Adults with diabetes have increased high shear WBV which results from decreased erythrocyte deformability, elevated lipids, glucose, fibrinogen and globulin.(10,11) Decreased low shear blood viscosity is also oberved in patients with diabetes because of the lack of rouleaux formation and anemia. The following reports indicate that elevated high shear WBV contributes to cardiovascular disease in patients with diabetes.

In a 1987 study, 22 patients with overt nephropathy had higher WBV and plasma viscosity and lower erythrocyte deformability than 24 patients with normal functioning kidneys (all $P<0.05$).(12) These same rheologic abnormlaities were related to impairments in glomerular filtration rate and renal plasma flow in patients with overt nephropathy (all $P<0.01$).

In a 1999 study, WBV and hematocrits were higher and erythrocyte deformability lower (all $P<0.05$) in children with diabetes.(13) Children with diabetes were studied before and after 4 to 6 weeks treatment with insulin or after being treated with insulin for 5 to 8 years.

WBV and hematocrit were negatively related to the insulin sensitivity index ($P=0.01$ for both) in 14 hypertensive and 12 normotensive premenopausal women.(14) Risk markers for metabolic syndrome, ie, blood HDL-c, triglycerides, glucose, and diastolic blood pressure were measured in 561 nonsmoking men.(15) As the number of risk markers increased from 0 to 3, plasma viscosity increased ($P=0.0005$). When 4 risk markers indicated the metabolic syndrome, plasma viscosity was significantly higher.($P<0.001$)

Determinants of Whole Blood Viscosity

The major determinants of WBV are:

1. *Hematocrit*. The most important determinant of WBV. Higher hematocrits in men and postmenopausal women than in premenopausal women may be linked to greater frequencies of cardiovascular events.

2. *Erythrocyte deformability.* In large vessels, at low shear rates, erythrocytes are in the shape of biconcave disks; at high shear rates they are ellipsoid. At low shear rates, healthy erythrocytes aggregate into rouleaux, and have high WBV. At high shear rates, these aggregates separate, decreasing the WBV. When erythrocytes become rigid, they do not aggregate easily, and rouleaux do not form.(16)

3. *Plasma viscosity.* Independent of age, sex and shear rate, the viscosity of plasma is dependent on fibrinogen and other plasma proteins such as immunoglobulins and LDL-cholesterol. However, the interaction of these plasma proteins greatly influences WBV.(17,18)

4. *Lipids, carbohydrates, leukocytes and platelets and other blood constituents.* These directly affect WBV, which increases with increasing total cholesterol, serum triglyceride, LDL-cholesterol, and apolipoprotein A2 and B levels, and decreasing HDL-cholesterol.(19,20)

WBV and the Work of the Heart

When WBV increases at a constant systolic blood pressure, peripheral resistance increases and blood flow is reduced. As WBV increases, systolic pressure must also increase if cardiac output is to be maintained. However, when WBV decreases, blood flows more easily, resulting in increased perfusion, which is particularly important in micro vessels. WBV is, therefore, a major determinant of heart work and tissue perfusion. As an increased WBV requires a higher blood pressure to ensure the same circulating volume, both the burden on the heart and the forces acting on the vessel wall are directly influenced by

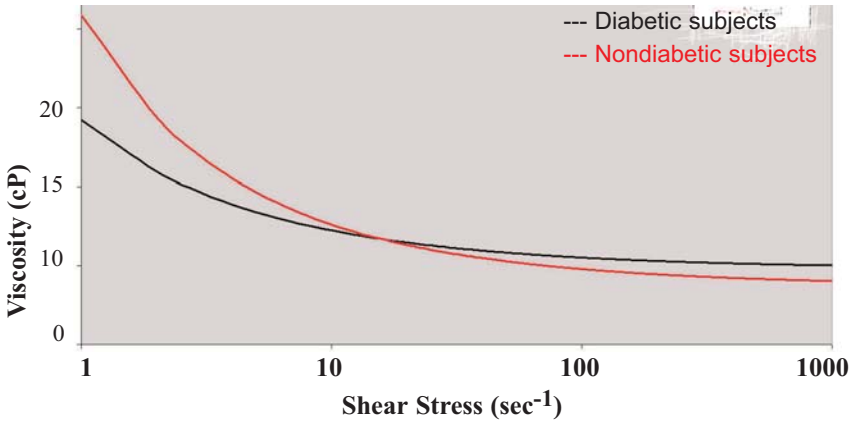

Figure 1. Plot of representative viscosity versus shear rate profiles in 2 populations of adults: those with diabetes (n=30) and healthy non-diabetic control subjects (n=121). These data are taken from unpublished results of Kensey and Hogenauer.

changes in WBV.

Measuring WBV

We propose that WBV determinations should be included in routine cardiovascular risk profiling. Monitoring WBV could play an important role in reducing the incidence of various diseases and their associated morbidity and mortality as do monitoring and control of blood pressure and plasma lipids. Real-time blood viscosity measurements markedly enhance the feasbility of analysing blood viscosity, thus facilitating clinical decisions and improving therapeutic strategies for disease. Because of logistic complications associated with conventional viscometry, both major types of viscometers (rotational and capillary tube) can be complicated and technically demanding, especially when measuring WBV across a range of physiological shear rates, a clinically important profile.

We have designed and built a novel device to measure WBV using 3 mL samples of whole blood under physiological conditions. This device, the Rheolog™, has been described.(8) Examples of viscosity-shear rate curves for 2 populations, non-diabetic control subjects and diabetic subjects, are given in Figure 1. These curves were obtained with whole blood withdrawn from the antecubital veins. Both curves are presented as means for the populations. In each population the curves in individuals varied greatly, as did, we believe, their risks of having major cardiovascular events.

In a future paper in this journal we will be presenting the raw data and describing the studies in which these data were obtained.

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Ongoing Clinical Trial

Action to Control Cardiovascular Risk in Diabetes (ACCORD)

This large randomized multicenter clinical trial is sponsored by the NIH. The study design is to enrol 10,000 patients. The 7 ACCORD Principal Investigators oversee 7 clinical networks in which patients are treated at 69 clinical sites in the US and Canada. These sites are identified at www.accordtrial.org/public/pi.cfm. Subjects are being recruited, treated and followed for 4 to 8.4 years. Subjects must be over 54 years of age or over 39 years of age with a history of cardiovascular disease, have stable type 2 diabetes, have HbA1c 7.5-11%.

From www.accord-ne.org, the overall goal for ACCORD is “to test 3 complementary medical treatment strategies for type 2 diabetes to enhance options for reducing the very high rate of major CVD morbidity and mortality.” These 3 medical strategies are:

1. Intensive glycemic control with goals of HbA1c less than 6% versus HbA1c from 7-7.9%
2. Treatment to increase HDL-C and lower triglycerides by treating with fenofibrate + simvastatin versus simvastatin alone
3. Intensive blood pressure control with systolic blood pressure goals being less than 120 mmHg versus less than 140 mmHg

CLINICAL TRIALS

US Ongoing Trials

Clinical trials aimed at diabetes prevention, diabetes care or diabetes cure are listed at ***clinicaltrials.gov.*** The total number of clinical trials listed for patients with diabetes:

Diabetes	Number of Trials
Type 1	62
Type 2	54

On this page we have summarized some of these clinical trials. A large trial, ACCORD, in which 10,000 subjects with diabetes is described on page 28.

Ingested interferon alpha: prolongation or permanence of the "Honeymoon" phase in newly diagnosed diabetes mellitus type 1

This clinical trial (01-DK-0249) is sponsored by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and aims to determine whether interferon alpha can prevent or minimize the risk of complications from diabetes type 1, by stopping or slowing the immune attack on insulin-producing cells. Patients between 3 and 25 years of age who were diagnosed within 42 days of study entry are being recruited for this randomized, double-blind, placebo-controlled phase II trial. Contact Dr Kristina Rother, 301-402-3905.

Urinary vitamin C loss in diabetics

This NIDDK study (04-DK-0021), of vitamin C in plasma, neutrophils and 24-hour urine, is aimed at determining whether urinary vitamin C loss is increased by type 1 and type 2 diabetes type 1 and type 2. The investiagtors are recruiting 150 adults between 18 and 65 years of age, do not smoke and in general have good health and do not have neuropathy affecting the internal organs.To enrol in this trial, telephone 1-800-411-1222.

Evaluation of a diabetes vaccine in newly diagnosed diabetics

This clinical trial is sponsored by the National Institute of Allergy and Infectious Disease (NIAID). Patients are treated in Boston, Massachusetts in the Children's Hospital and the Joslin Diabetes Center. It is discussed by the Principal Investigator on pages 31-34.

Inhibition of intestinal glucose absorption by the bioflavonoid quercetin in the obese and in obese type 2 diabetes

This NIDDK multi-site double-blind placebo-controlled phase II trial (03-DK-0256) aims to test the hypothesis that quercetin blunts intestinal glucose absorption in humans and attenuates postprandial hyperglycemia. Study subjects are between 19 and 65 years of age with a body mass index of 30 or more, and they must have none of the severe complications of diabetes. To enrol in the trial, contact Anita Stuck, 301-402-5588. The Principal Investigator is Dr Sebastian Padayatty, phone 301-496-1069.

Pilot study of Vedic medicine for type 2 diabetes

Maharishi Vedic Medicine (MVM) is being tested on up to 60 subjects in a randomized, open-label, active control, phase II clinical trial (R21 AT001324-01) sponsored by the National Center for Complementary and Alternative Medicine (NCCAM). Subjects are 25 to 80 years of age, are in Portland, Orgeon and have newly diagnosed type 2 diabetes. Principal investigator is Charles Elder, MD MPH. This study was estimated to be completed by January, 2004. ***American Journal of Diabetes*** notes that MVM is an ancient system of natural medicine with a strong interest in prevention.

Evaluation of a Diabetes Vaccine in Patients Newly Diagnosed with Type 1 Diabetes

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Abstract

The National Institute of Allergy and Infectious Diseases (NIAID) and the Immune Tolerance Network (ITN) is sponsoring this phase I clinical trial. The vaccine is IBC-VSO1, a synthetic, metabolically inactive form of insulin which does not alter blood sugar. Our aim is to evaluate the vaccine's ability to protect against autoimmune attack at the clinical onset of type 1 diabetes mellitus. Enrollment is limited to a total of 12 subjects whose pancreatic function has not yet deteriorated. *Orban T. Autoantigen vaccination in human type 1 newly diagnosed diabetes mellitus. Amer J Diabetes. 2004; 1(1):49-54.*

Introduction

With funds granted from the National Institutes of Health, my colleagues and I are undertaking a pilot study to investigate the safety and immunologic mechanisms of human insulin B-chain in incomplete Freund's adjuvant (IFA) in humans. The ultimate goal of this intervention is to prevent or delay further loss of beta cell mass after clinical onset of type 1 diabetes mellitus.

Immunization with autoantigens in different autoimmune diseases is a new, effective approach to treatment in humans and animals. The endpoint of the study is 24 months, by December 2003, 2 patients have been enrolled and we are continuing to screen patients until we have a total of 12.

Background

Type 1 diabetes mellitus is an autoimmune disease. The process by which the pancreatic beta cell is destroyed is not well understood, however, several risk factors and immune-related markers are known that accurately identify many first-degree relatives of patients with type 1 diabetes who will develop the disease. Because we can predict the development of type 1 diabetes in some patients, investigators have begun to explore the use of intervention therapy to halt or prevent beta cell destruction in these

patients.(1,2)

The current vaccine trials that my team is running are based on the autoimmunogenicity of insulin in autoimmune diabetes. Reintroduction of autoantigen in a patient with autoimmune disease can generate protective antigen-specific cell mediated immunity. We first knew this because of animal data showing that the Th1/Th2 balance plays a crucial role in the pathogenesis of the disease. Additionally, insulin B-chain in incomplete Freund's adjuvant (IFA) has been shown to reduce IFN-gamma (Th1) expression and reduce insulitis. Preliminary animal data from my laboratory and others have shown that insulin B-chain in IFA reduces the diabetes incidence in NOD scid/scid model and prevents insulitis. Our preliminary human studies show extreme Th1 bias in invariant V alpha 24 Jalpha Q+ T-cells of patients with Type 1 diabetes, which further supports the Th1/Th2 paradigm in human diabetes. This cellular marker can be used along with humoral (IAA, GAD65Ab and IA2Ab and heterophile AB) and metabolic markers (FFIR) to predict development of diabetes in humans, an existing prerequisite for prevention.(3-6)

This adjuvant-enhanced autoantigen vaccine is aimed at stopping or slowing the ongoing autoimmunity against pancreatic beta cells at the clinical onset of the disease by immune modulation. At the clinical onset, 15-40% of the beta cells are still intact. Arrest of autoimmune destruction of these beta cells would lead to prolonged or lifelong remission, which is characterized by little or no exogenous insulin requirement. Even only prolongation of the remission time would result in major reduction of insulin therapy and better control; also in delaying the late complications of diabetes it would significantly ameliorate the invasive treatments involved. If successful, this vaccine could prevent the onset of type 1 diabetes in persons who would otherwise develop it.(7-11)

Subject Involvement

The protocol being followed in the vaccine trial which is underway is to:

1. identify possible subjects who have been diagnosed with type 1 diabetes within the previous 30 days.

2. determine whether possible subject has insulin autoantibodies

3. inject subject with human insulin B-chain in IFA once

4. assess beta cell functions by repeated measurements of the mixed meal (Sustacal) stimulated C-peptide levels throughout the study as a primary surrogate marker for preservation of beta cell function.

5. monitoring humoral and cellular markers as secondary markers for effect of vaccine:

   a. Humoral studies include measurements of insulin autoantibodies (IAA), insulin antibody isotyping (IAA isotypes), insulin B-chain antibodies (IBCAb), GAD65 autoantibodies (GAD65Ab), GAD65Ab isotyping, IA2 autoantibodies (IA2-icAb) and heterophile antibodies. The changes in insulin and GAD65 antibody isotype profile could indicate a shift in Th1/Th2 balance with increase in IgG1, IgG4 and IgE would support Th2 predominance.

   b. Cellular studies include measurements of CD4- CD8- Va24JaQ+ T cells cloned from the peripheral blood and stimulated with antiCD3 to analyze their IL-4 and INF-gamma secretion profile. The change, if any, in the cytokine secretion profile of these T

cells will indicate the change of Th1/Th2 balance over time.

Additional goals

SNP/DNA: We are part of the Immune Tolerance Network (ITN, see page x). A project of the ITN is to collect DNA from all patients enrolled in ITN-supported studies so that we can find unique single nucleotide polymorphisms (SNPs) associated with diseases. Thus, DNA collected from all subjects in the vaccine trial will be collected and analyzed for this purpose.

A panel of geneticists is working with the ITN to determine the best strategy for defining disease-associated SNP's and SNP's that are related to therapeutic responses. One approach is to collect DNA from approximately 20 diverse healthy persons and approximately 50 patients, sequence across approximately 2000 immune response genes and identify novel SNPs that may contribute to the disease process. When any novel disease-associated SNPs are identified, these will be analyzed in all patient samples collected in ITN-supported clinical trials or retrospective studies using ITN archived materials.

Trial enrolment

Your patients is eligible for inclusion in the vaccine trial if he or she:

1. is between 18 and 35 years of age

2. has had clinical onset of type 1 diabetes within the last 30 days

3. is either living close to Boston or is willing to travel to Boston for the duration of the trial

Your patient is not eligigible if she or he has had:

1. a history of treatment with oral hypoglycemic agents or ongoing use of medications known to influence glucose tolerance

2. complications related to routine vaccinations

3. pregnancy or planned pregnancy within the time frame of the study

4. prior participation in a trial for prevention of type 1 diabetes (unless the individual is known to have been in the placebo arm of a completed prior prevention trial)

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Adults between 18 and 35 years who were diagnosed with type 1 diabetes within 30 days of study entry are being recruited by Heyam Jalahej, MD, who may be contacted by e-mail: heyam.jalahej@joslin.harvard.edu and by phone: 617-713-3463.

Immune Tolerance Network (ITN)

From their website, www.immunetolerance.org:

"The Immune Tolerance Network is a collaborative research effort that solicits, develops, implements and assesses clinical strategies and biological assays for the purposes of inducing, maintaining and monitoring tolerance in humans for kidney, liver and islet transplantation, autoimmune diseases and allergy and asthma."

Funded by the NIH and the Juvenile Diabetes Research Foundation, the ITN has 70 clinical and preclinical collaborators supervising clinical trials and tolerance assay studies.

TrialNet

From their website, www.diabetestrialnet.org:

TrialNet originated after the USPHS publication Healthy People 2010 spelled out the dangers of increasing numbers of American living with diabetes. Congress mandate resulted in formation of the Diabetes Reasearch Working Group, which recommended increasing the number of clinical trials investigating type 1 diabetes prevention. TrialNet provides the infrastructure to organize and support these trials, which are funded by the NIH and are conducted in 18 sites: 13 in the US and 5 in other countries.

JOURNAL CLUB

Clinical Trials in Subjects with Type 2 Diabetes and Diabetic Nephropathy

The first article describes a large randomized study that is in progress, and has the aim of determining whether diabetic nephropathy can be prevented by timely interventions. The second article investigates the effect of lowering blood pressure on the progression of diabetic nephropathy.

The BErgamo NEphrologic DIabetes Complications Trial is a prospective, randomized, double-blind parallel-group study primarily aimed at evaluating the possibility of preventing the progression to microalbuminuria (urinary albumin excretion rate 20-200 microg.min^{-1}) in 1,209 hypertensive, type 2 diabetic patients with a normal UAE rate (<20 microg.min^{-1}).

BENEDICT Group. The BErgamo NEphrologic DIabetes Complications Trial (BENEDICT): design and baseline characteristics. Control Clin Trials. 2003; 24(4):442-61.

During phase A of the study, patients were randomized to a 3-year treatment with either (1) a nondihydropyridine CCB (verapamil SR 240 mg/day); (2) an ACE inhibitor (trandolapril 2 mg/day); (3) the combination of the above study drugs (verapamil SR 180 mg.day^{-1} plus trandolapril 2 mg.day^{-1}); or (4) placebo. Phase B of the study evaluates the progression to macroalbuminuria (UAE> or =200 microg.min^{-1}) in patients who progress to microalbuminuria in phase A or are found with microalbuminuria during the screening phase; these patients are randomized to a 2-year treatment with either trandolapril (2 mg.day^{-1}) alone or verapamil SR (180 mg.day^{-1}) plus trandolapril (2 mg.day^{-1}). BENEDICT final results are expected to be available by the end of 2003 for phase A and 2 years later for phase B. The BENEDICT study aims to determine whether primary prevention of diabetic nephropathy is an achievable goal, and aims to examine prospectively risk factors of nephropathy and other chronic complications of type 2 diabetes.

Results of the RENAAL study was reported from the Department of Preventive Medicine, Rush Presbyterian/St Luke's Medical Center, Rush Medical College, Chicago, Illinois.

Bakris GL, Weir MR, Shanifar S, Zhang Z, Douglas J, van Dijk DJ, Brenner BM; RENAAL Study Group. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med. 2003; 163(13):1555-65.

A total of 1,513 subjects with established nephropathy and hypertension associated with type 2 diabetes were evaluated. The RENAAL study was a randomized, placebo-controlled study of losartan versus placebo. Its goal was a BP below 140/90 mm Hg immediately before the next dosing. Patients were followed after the study for a mean of 3.4 years.

A baseline SBP range of 140 to 159 mm Hg increased the risk for endstage renal disease (ESRD) or death by 38% (P =.05) compared with those below 130 mm Hg. In a multivariate model, every 10-mm Hg rise in baseline SBP increased the risk for ESRD or death by 6.7% (P =.007); the same rise in DBP decreased the risk by 10.9% (P =.01) when adjusting for urinary albumin-creatinine ratio, serum creatinine, serum

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albumin, hemoglobin, and hemoglobin A1c.

Subjects randomized to losartan with a baseline PP above 90 mm Hg had a 53.5% risk reduction for ESRD alone (P =.003) and a 35.5% risk reduction for ESRD or death (P =.02) compared with the placebo group. The conclusions were that baseline SBP is a stronger predictor than DBP of renal outcomes in patients with diabetic nephropathy. Those with the highest baseline PP have the highest risk for nephropathy progression but also have the greatest risk reduction with SBP lowered to under 140 mm Hg.

Pancreas Transplants

The following paper reports a large, NIH study investigating the efficacy of pancreas transplant as a treatment for diabetes in patients who have functional kidneys. The authors concluded that conventional therapy is better for survival than pancreas transplants.

This retrospective observational and cohort study was reported from the Transplantation and

Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival After Pancreas Transplantation in Patients With Diabetes and Preserved Kidney Function. JAMA. 2003 Dec 3;290(21):2817-2823.

Autoimmunity Branch, NIDDK, NIH, Department of Health and Human Services, Bethesda, Maryland.

The study aimed to determine the association between solitary pancreas transplantation and survival in patients with diabetes and preserved kidney function in 124 US transplant centers in 11,572 patients with diabetes mellitus on the waiting list for pancreas transplantation (pancreas alone, pancreas-after-kidney, or simultaneous pancreas-kidney) at the United Network for Organ Sharing/Organ Procurement and Transplantation Network between January 1, 1995, and December 31, 2000.

Patients were excluded if they received other multiorgan transplants, were listed for solitary pancreas transplantation with serum creatinine greater than 2 $mg.dL^{-1}$, or if they ultimately received a simultaneous pancreas-kidney transplant.

The study determined that the overall relative risk of all-cause mortality for transplant recipients over 4 years of follow-up was 1.57 (95% confidence interval [CI], 0.98-2.53; P =.06) for pancreas transplant alone, 1.42 (95% CI, 1.03-1.94; P =.03) for pancreas-after-kidney transplant, and 0.43 (95% CI, 0.39-0.48) for simultaneous pancreas-kidney transplant.

Pancreas transplantation has been controversial since it was first used as a treatment for patients lacking insulin production. We will investigate all aspects of pancreas transplantation in the September 2004 issue of American Journal of Diabetes: case reports, immunosuppressant drugs, review of clinical trials, what is being done now, how surgical techniques have evolved, the effectiveness of pancreas transplantation on halting and reversing some of the severe complications of diabetes. We invite manuscript submissions, we ask authors to contact the Editor-in-Chief before submitting review articles.

JOURNAL CLUB

Transplant patient 1- and 4-year survival rates were 96.5% and 85.2% for pancreas transplant alone, respectively, and 95.3% and 84.5% for pancreas-after-kidney transplant, while 1- and 4-year survival rates for patients on the waiting list were 97.6% and 92.1% for pancreas transplant alone, respectively, and 97.1% and 88.1% for pancreas-after-kidney transplant.

They concluded that from 1995-2000, survival for patients with diabetes and preserved kidney function who received a solitary pancreas transplant was significantly worse than the survival of patients who received conventional therapy while they remained on the waiting list.

PUZZLE CORNER

Find the Words

Elizabeth A Pector, MD, family physician with Spectrum Family Medicine, Napierville, Illinois. www.synspectrum.com.

Dr Pector challenges you to find 65 words or acronyms related to diabetes care. The answers are upside-down on page 16.

P B I T A E D I N I T I L G E M R E T I N A A
I L S M L T A N G G N I T N U O C V S N R A I
L A T E B S S S R L I P I D S A P R E B C C M
U H A N U A H T A F Y E E B R U L E T S U A S
T Y T I M F T O M D G C N B M M O N N I K R Y
I P I M I L E O S N O I O P Y H D I M S E B R
N E N R N D C F L U E H O H L Z I G E O T O I
U R I O U V N D Z T Y P E S E B E R T D O S N
E G C F R P A O O D E L E A N M T A A I N E G
T L A T I C L R R D I O R E T S O L B C E E E
A Y I E A O P A E R O B I C E C A G O A S X L
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B E E T I E N D O C R I N E G I R T I O C R N
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F I T W O E C N A T S I S E R N I L U S N I R
A A E R U L Y N O F L U S N A E E S E B O S N
G A S T R O P A R E S I S Y H T A P O R U E N

ORIGINAL ARTICLE

Physiologic Insulin Replacement: Insulin Pump Therapy (CSII) vs Multiple Daily Insulin Injections (MDI)

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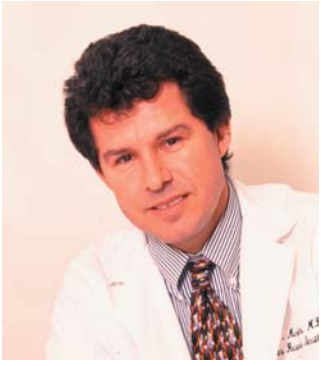

Abstract

A 28-year-old woman had been diagnosed with type 1 diabetes 12 years previously. At diagnosis she was taught how to inject herself with insulin, but, 12 years later, was unsure of the relationship between blood glucose and carbohydrate ingestion. She reported recent hypoglycemic episodes involving loss of consciousness. After sessions with a dietician and a diabetes educator, the woman achieved glycemic control on MDI and was prescribed CSII. *Meneghini L. Physiologic Insulin Replacement: Insulin Pump Therapy (CSII) vs Multiple Daily Insulin Injections (MDI). Amer J Diabetes. 2004; 1(1):40-45.*

Case Report

A 28 year-old legal secretary with type 1 diabetes refers herself to the clinic to check her diabetes status. She was initially diagnosed 12 years previously after presenting with diabetic ketoacidosis (DKA) and at that time was placed on 1 injection of 35 units of NPH insulin, which she continues to take. She is satisfied with her current diabetes control, although she admits to testing only once a day, especially if she is "feeling" a low blood sugar reaction. She has passed out on several occasions because of hypoglycemia and has often had to leave work following a hypoglycemic episode.

She received education on insulin injections when she was initially diagnosed. She was once prescribed 15 units of regular insulin before dinner, but refused to take it following a moderate episode of hypoglycemia during the night 1 week after starting it. She has never been given a fast-acting insulin corrective scale. She is not sure of the relationship between blood glucose and carbohydrate ingestion.

The patient is active, preferring to spend her weekends doing outdoors activities. She is concerned that she often gets fatigued during physical activity from around midday to early afternoon. At that time she occasionally tests her blood sugars; they are below 60 mg.dL^{-1}.

On examination she is 64 inches tall and weighs 60 kg with blood pressure of 120/74 mmHg and heart rate of 82.min^{-1}. She has some background retinopathy, but no other microvascular complications. A random urine sample is negative for albumin. Her last HbA1c 2 weeks ago was 10.2%.

The patient is evaluated at the diabetes center and after a discussion of the benefits and challenges of physiologic insulin replacement she is started on a basal/bolus schedule with insulin glargine 15 units at bedtime and insulin aspart 5 units before meals with a correction ratio of 1 unit of insulin aspart per 60 mg.dL^{-1} of blood glucose above pre-meal target (150 mg.dL^{-1}). She is referred to the dietitian to learn and reinforce carbohydrate counting and matching to insulin and to the nurse educator to reinforce the concepts of physiologic insulin replacement.

She is reevaluated by the endocrinologist 2 months later. By that time she is adjusting her insulin aspart dose to her planned carbohydrate intake based on a ratio of 1 unit per 15 grams of carbohydrate. She is injecting insulin 4 or more times daily. Her HbA1c has fallen to 7.5% and she has lost 8 pounds without any substantial changes in her activity level or food intake. The 2 issues she wants to discuss are control of her nighttime glycemic excursions and correcting the elevation in blood glucose in the evening when dinner is delayed.

From the above presentation, is this patient a candidate for CSII?

Continuous subcutaneous insulin infusion (CSII), or insulin pump therapy, which began in the mid 1970's, was initially intended as a research procedure.(1) However, by the early 1980's CSII evolved as an alternative form of insulin replacement therapy in clinical practice. Whereas Medtronic Minimed and Disetronic still dominate the market share of insulin pump users in this country, a number of competitors have introduced excellent products in the past few years (Animas IR 1200, Deltec Cozmo™, and Nipro Amigo) forcing a rapid evolution of hardware and software for continuous insulin delivery. One such advance are the bolus calculators (or wizards) available on virtually all new pumps and discussed elsewhere in this issue of the American Journal of Diabetes.

The Diabetes Control and Complications Trial (DCCT) emphasized the importance of intensive insulin therapy in improving blood glucose control and reducing the microvascular complications of diabetes.(2) Of note is that the participants using CSII in the DCCT obtained a lower HbA1c (~ 0.3%; $p<0.001$) than those using multiple daily insulin injections (MDI).(2) A number of recent reviews of the literature have attempted to compare and contrast MDI and CSII to determine effectiveness of therapy, impact on psychosocial issues and challenges.

The majority of published studies demonstrate better blood glucose control when CSII is compared to MDI, although comparisons using glargine as the basal insulin are just now emerging.(4) In many cases the differences in HbA1c are modest (approximately 0.5%) though statistically significant, and often associated with a reduction in the total daily insulin dose (approximately 14% dose reduction).(5) The most significant reductions in HbA1c were documented in patients using CSII for at least 1 year.(6) There is increasing evidence regarding the safety and effectiveness of CSII use in children, even when compared with MDI using insulin glargine, with almost universal preference by study participants for CSII rather than MDI.(7-9) In addition, preliminary results in a small trial comparing CSII to MDI at diagnosis of type 1 diabetes

showed lower insulin requirements at 6 months in the CSII group.(10)

The effects of insulin pump therapy on body weight vary and probably result from improved blood glucose control and greater dietary freedom. Likewise, the overall risk of hypoglycemic events are comparable between intensive therapies.(6) Severe episodes of hypoglycemia with CSII are described as occurring between 0.1 and 0.4 episodes per patient per year, however in the hands of medical professionals experienced in CSII management significant reductions in both frequency and severity of hypoglycemia are reported.(11,12)

Insufficient data is available to clearly define the impact of intensive insulin therapy on psychosocial parameters, examples of which include quality of life, anxiety, and self-esteem. Patients who start and continue CSII as the preferred method of insulin administration report that the insulin pump affords them better glycemic control with greater flexibility in terms of lifestyle, including ease of scheduling and timing of meals and daily activities.(6) Health professionals with type 1 diabetes were asked their preferred method of insulin administration; in general, they chose CSII over other methods.(13)

CSII may have several advantages over MDI for intensive insulin management. Overnight hypoglycemia or the early morning blood glucose rise in response to counterregulatory hormones can more effectively be addressed and corrected by CSII through modification of basal rates at any time over a 24-hour day. The ability to distribute an insulin bolus over a prolonged time period (dual wave bolus) is a unique feature of CSII that can facilitate coverage of high fat meals such as pizza and Chinese food, with improvement in late postprandial blood glucose.(14,15) Patients with exquisite insulin sensitivity (young children) can benefit from the pump being able to deliver insulin in smaller increments of 0.05 to 0.1 units compared with 0.5 to 1.0 units with insulin syringes or pens.(7) Individuals with active lifestyles requiring greater flexibility to achieve optimal blood glucose levels can benefit from the ability to easily adjust and modify both basal and bolus insulin delivery. Some investigators report reductions in hypoglycemia frequency and the reacquisition of hypoglycemia unawareness in patients switched to CSII who had experienced frequent hypoglycemia with MDI or conventional therapies.

Concerns with using CSII include especially the frequency of DKA and the risk of skin infections at the site of CSII catheter insertion. The risk of DKA is potentially more worrisome in CSII since the insulin depot is considerably smaller than with MDI and any interruption in insulin delivery can rapidly result in insulin deficiency.(16) Although early studies indicated a higher rate of DKA with CSII, data available after the release of the DCCT are inconclusive, and often show no greater risk than for patients using MDI.(4,8) With proper patient education and medical management the frequency of DKA in CSII is similar to that seen in MDI.

Technologic difficulties with CSII can also impact the ability to control glycemia by patients using insulin pumps. Pump malfunctions (pump failure, battery failure, alarm malfunctions, over and under dosage) are relatively rare in the technologically advanced devices available today. Of note, however, is the recent increase in technical problems that have plagued some of the newer pumps on the market, possibly due to the pressures of getting hardware and software updates to market. In general, most pump companies have excellent customer service and back-up in the event of a pump failure.

Interruption of insulin delivery to subcutaneous tissues can result from catheter occlusion because of insulin precipitation or catheter bending. These problems should be easily detected by the pressure alarms built into the pump's computer circuitry. Occasionally a pump catheter may dislodge from the skin and if undetected delivery of insulin is interrupted with consequent loss of glycemic control. Frequent blood glucose monitoring and appropriate self-management techniques can prevent more serious deterioration in diabetes control. Skin infections at the site of catheter insertion are mostly prevented by keeping the site clean and changing the site of insertion as prescribed in the pump literature (every 2 to 3 days). Some patients have skin irritation, some are hypersensitive to the occlusive dressings keeping the catheter in place. The rate of skin infection has been reported to be around 0.06 to 0.27 events per patient per year.(6)

Not every patient is a candidate for CSII. Meticulous screening of potential candidates as well as careful discussions of the pros and cons of insulin pump therapy is essential. Patients who are unable to master the technical aspects of pump therapy (button pushing, catheter insertion) or are not able to follow a basal/bolus approach to diabetes management will probably not do as well on CSII (the exception is a very young child whose parents can manage the pump). Patients with psychological or social issues, those with eating disorders, and those with poor social support do not generally benefit from switching to insulin pump therapy.(18)

Another potential barrier to CSII is physician resistance either because of unfamiliarity with insulin pump therapy and/or do not have access to proper insulin pump training for patients. Although insulin management, pattern recognition and algorithm adjustments to basal/bolus insulin therapy are essentially identical whether using CSII or MDI, many endocrinologists are still uncomfortable using this technology. In addition, to properly start an individual on insulin pump therapy often requires a significant amount of patient education and reinforcement and can only be achieved with the support of qualified diabetes educators and nutritionists. Not having this level of patient education support severely limits a physician's ability to prescribe and implement insulin pump therapy, even when the benefits are clearly evident. One solution to this problem could be to designate and train specific patient education centers on insulin pump therapy and encourage access to these centers from any physician that may not have adequate patient self-management education support.

Another barrier to the use of CSII is cost. Although most insurance plans will cover most insulin pump therapy costs, these costs are a considerable economic burden when compared to the traditional use of insulin syringes. The insulin pump itself can cost anywhere from $4,000-$6,000 with related supplies usually running about $100-$150 monthly. Once purchased, pump therapy costs are similar to the annual costs of using pen-injected insulin and considerably higher than syringe-injected insulin.(19)

The algorithms used to initiate and manage insulin pump therapy are very similar to those for MDI, the main differences being the delivery system and the mode of basal insulin replacement. Five simple steps are needed to calculate initial algorithms for CSII therapy. Modifications to these initial algorithms will be based on blood glucose monitoring results and glycemic responses to various conditions.

The 1st step involves the calculation of the estimated total daily dose (TDD) for each patient. Although some physicians prefer to start set carbohydrate and corrective ratios for all their

SENSITIVITY TO INSULIN	CONDITION	ESTIMATED SENSITIVITY INDEX
Very sensitive	Children & thin elderly	0.2-0.3 units.kg^{-1}.day^{-1}
Normal sensitivity	Ideal weight adults	0.4-0.7 units.kg^{-1}.day^{-1}
Moderate resistance	Puberty, pregnancy, illness or other stress	1.0-1.5units.kg^{-1}.day^{-1}
High resistance	Puberty or severe stress	2.0-3.0 units.kg^{-1}.day^{-1}

Table 1. Estimation of index of sensitivity to insulin.

patients, using the TDD to personalize these ratios is a more rational approach. Deciding on the starting TDD can be done by either using the patient's current total daily insulin dose or recalculating a TDD based on the patient's weight in kilograms and perceived insulin sensitivity index. If using the patient's current TDD, reduce this amount by 25% to obtain the TDD for CSII. If recalculating the TDD based on patient weight, multiply the weight in kilograms by the estimated insulin sensitivity index, Table 1.

The 2nd step involves estimating the patient's basal insulin requirements for 24 hours. Since, usually the daily basal insulin requirement constitutes 40-60% of the daily insulin needs, the basal dose per day is calculated by simply halving the TDD. The daily basal dose is divided by 24 to obtain the hourly basal rate for the pump.

The 3rd and 4th steps are essential in determining the insulin bolus, which requires the calculation of the carbohydrate and correction ratios. These calculations make use of simple formulae originally introduced with insulin pump therapy. The carbohydrate ratio is calculated by dividing either 450 (for regular insulin) or 500 (for insulin aspart or lispro) by the TDD. The result represents the grams of carbohydrate ingested covered by 1 unit of rapid-acting insulin. The correction ratio is calculated by dividing either 1500 (for regular insulin) or 1800 (for insulin aspart or lispro) by the TDD. The result gives the expected fall in blood glucose (mg.dL^{-1}) for each unit of rapid acting insulin.

The last step entails establishing glycemic targets for the patient to use to guide premeal, and if appropriate postmeal, corrective insulin administration. Understand that these algorithms represent a starting point that will most probably require adjustments based on a number of factors, including a patient's variable insulin sensitivity from early morning to night.

The following is an example of the calculations described above for the individual discussed in the case presentation. At the time of her last visit her TDD was 30 units and she had appropriate hypoglycemia awareness. Assuming you will be using insulin aspart with the pump:

1. starting TDD for CSII is 30 units x 0.75 = approx. 23 units.day^{-1}

2. basal rate is 23 / 2 units per day = approx. 12 units.day^{-1} divided by 24 hours = 0.5 units.h^{-1}

3. Carbohydrate ratio = 500 / 23 = approx. 22 (22 grams per unit of insulin aspart)

4. Correction ratio = 1800 / 23 = approx. 80 mg.dL^{-1} fall in blood glucose per unit of aspart

5. Premeal glycemic target = 120 mg.dL^{-1}

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RESOURCES

The National Diabetes Education Program, www.ndep.nih.gov, is a partnership of the National Institutes of Health, the Centers for Disease Control and Prevention, and more than 200 public and private organizations.

Cardiovascular Complications of Diabetes

The NDEP has the following statement on the index page of its large website dedicated to its campaign to educate patients about cardiovascular health, **www.ndep.nih.gov/campaigns/BeSmart/ BeSmart_index.htm:**

"About 65% of people with diabetes will die from a heart attack or stroke, yet 2 out of 3 people with diabetes are unaware of their increased risk. ***Be Smart About Your Heart, Control the ABCs of Diabetes*** encourages people with diabetes to control not only their blood glucose (sugar), but also their blood pressure and cholesterol. By keeping all 3 levels as close to normal as possible, people with diabetes can live long, healthy lives."

This statement follows with links to diabetes education materials, fact sheets, press releases, articles and public service announcements.

Diabetes Prevention

A second NDEP campaign is ***Small Steps. Big Rewards. Prevent type 2 Diabetes*** accessed at **www.ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm** from which can be downloaded publications aimed at educating patients in prevention strategies. From the index page of this site: "Diabetes is a serious disease, affecting millions of Americans and growing at epidemic rates, with 1 million new cases each year. But, there is Good News: Diabetes can be prevented. By losing a modest amount of weight, getting 30 minutes of physical activity 5 days a week, and eating healthier, people with prediabetes can delay or prevent the onset of the disease. The ***Small Steps. Big Rewards. Prevent type 2 Diabetes.*** campaign, the first ever national diabetes prevention campaign, spreads this message of hope to the 16 million Americans with prediabetes."

Diabetes Prevalence

Prevalence of Diabetes and Impaired Fasting Glucose in Adults --- United States, 1999-2000. MMWR. 2003; 52(35):833-837.

National Health and Nutrition Examination (NHANES) 1999-2000 indicated that 29 million persons (14.4% of the population who are over 19 years of age) had either diagnosed diabetes, undiagnosed diabetes, or impaired fasting glucose; 29% of persons with diabetes were undiagnosed. The report includes an Editorial Note directing the reader to the messages of alleviating the symptoms of diabetes by diet and exercise. These messages are communicated through education and outreach programs such as ***Steps to a Healthier US*** by the Department of Health and Human Services (**www.healthierus.gov/steps**) and ***Control the ABCs of Diabetes*** (**www.ndep.nih.gov/control/control.htm**).

Amputation

Lower extremity amputation episodes among persons with diabetes --- New Mexico, 2000. MMWR. 2003; 52(4):66-68.

The New Mexico Diabetes Prevention and Control Program analyzed data from the Hospital Inpatient Discharge Database and the Santa Fe Indian Hospital from 2000 and calculated that the rate of lower extremity amputation in non-Hispanic whites was 3.3 per 1,000 persons and in Native Americans was 11.4 per 1,000 persons.

MEETINGS CALENDAR

February 21-27, 2004. **Pediatric Potpourri: State of the Art 2004, Maui, Hawaii. Website: www.ucmg.org/cme/pp04/pp04.pdf**

February 22-27, 2004. **Advances in Internal Medicine 2004, Park City, Utah. Website: www.int.med.utah.edu/advances**

February 26-29, 2004. **3rd National Symposium on Pituitary Disorders: New Surgical and Medical Approaches in Childhood Through Adulthood. Belleview Biltmore Resort & Spa, Clearwater, Florida. Website: www.cme.hsc.usf.edu**

February 28 - March 2, 2004. **5th Pan Arab Congress On Endocrinology and Diabetes, Riyadh, Saudi Arabia. Contact: panarab-congress5@hotmail.com**

February 29 - March 5, 2004. **7th Mayo Clinic Endocrine Course, Big Island of Hawaii, Hawaii. Contact: cme@mayo.edu**

March 3-10, 2004. **American College of Cardiology 53rd Annual Scientific Sessions, Orlando, Florida. Website: www.acc.org**

March 4-5, 2004. **AACE Pediatrics Practice Management Grand Hyatt Washington, Washington, DC. Website: www.aace.com**

March 5-7, 2004. **AACE Practice Management Course Grand Hyatt Washington, Washington, DC. Website: www.aace.com**

March 2, 2004. **Endocrinology for Non-endocrinologists & Neurology for Non-neurologists Glasgow, Scotland, UK. Contact: mgt.cooper@rcpsglasg.ac.uk**

March 5, 2004. **29th Annual UC Davis Diabetes Symposium, Sacramento, California. Website: som.ucdavis.edu**

March 11-14, 2004. **4th National Symposium Bioethical Considerations in Human Subject Research, Clearwater, Florida, Website: www.cme.hsc. usf.edu**

March 26-30, 2004. **American Pharmacists Association. Seattle, Ashington. Website: www.aphameeting.org.**

March 28-31 2004. **Immunology of Diabetes Society IDS-7. Cambridge, UK. Website: www.idsoc.org/doc/IDS7Program.pdf**

April 3-6, 2004. **American Association of Endocrinology Surgeons 25th Annual Meeting, Charlottesville, Virginia. Website: www.endocrinesurgeons.org**

April 12-16, 2004. **Clinical Endocrinology 2004. Massachusetts General Hospital and Harvard Medical School Postgraduate Course, The Westin Copley Place Boston, Massachusetts. Website: www.cme.hms.harvard.edu**

April 12-16, 2004. **Clinical Endocrinology 2004. Boston, Massachusetts. Contact: hms-cme@hms.harvard.edu**

April 16-18, 2004. **14th Annual Advances & Controversies in Clinical Nutrition, Naples, Florida. Contact: cme-jax@mayo.edu**

April 28 - May 2, 2004. **AACE 13th Annual Meeting and Clinical Congress, Sheraton Boston Hotel, John B. Hynes Veterans Memorial Convention Center, Boston, Massachusetts. Website: www.aace.com**

May 10-11, 2004. **Lipids and the Pathophysiology of Obesity. Renaissance Marriott Hotel, Washington, DC. Website: www.niddk.nih.gov**

May 11-14, 2004. **Centers for Disease Control and Prevention Diabetes Translation Conference, the Fairmont Chicago in Chicago, Illinois. Website: www.cdc.gov/diabetes/conferences/index.htm**

May 12-14, 2004. **ESEO/AACE Joint Meeting Alexandria Library Congress Center, Alexandria, Egypt. Contact: aly abbassye@excite.com**

May 12-14, 2004. **10th Malvern Diabetic Conference, Malvern, UK. Contact: anne.roscoe@man.ac.uk**