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Editorial

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Welcome to this internet-based daily review service at the ADA meeting, San Antonio, Texas, USA, 2000. From this city originates the San Antonio Heart Study which among other important observations has showed an alarming increase in the incidence of Type 2 diabetes. This emphasizes the need for methods of prevention of diabetes and its many serious complications, and, therefore, also for conferences such as the present ADA meeting.

Aim

The aim of our review service is to provide a topical overview of what has taken place in scientific sessions, symposia and lectures of specific interest to clinicians working in the fields of diagnosis and treatment of diabetes and diabetes-related complications. It is important to emphasize that the reviews generally will not address frontline scientific research, the results of which are still far from implementation in clinical practice. Recent findings will of course be

mentioned whenever the reporters cannot restrain their personal interest and enthusiasm. However, the results of basal science will already be known by participants with specific interest in these fields. What you will find in this daily review are extended abstracts chosen because they address problems and raise questions of considerable interest in daily clinical practice. You will find summaries from sessions of clinical, pathophysiological or epidemiological research of relevance to the clinical diabetologist; sessions which have attracted the attention of the reporters as being of particular interest to summarize in this daily review. A few weeks after the meeting the three internet issues will be published in printed format and distributed to doctors around the world, some who have attended the meeting, some who have not. It is our hope that this joint effort by the editor and reporters will prove to be useful whenever you want to recall the most important messages relating to your daily clinical routine. ■

Meet-the-Professor Session

Diabetes and obesity worldwide: epidemics in full flight



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Coca-colonization

'Globalization' and 'Coca-colonization' are having profound effects on health worldwide. We face a huge public health challenge from both Type 2 diabetes and obesity, from childhood through to old age. Obesity has reached epidemic proportions globally. The situation is worsening. In Europe, USA and Australia, the prevalence is high and increasing. Over 60% of the adult population of the USA and Australia is either overweight

Over 60% of the adult population of the USA and Australia is either overweight or obese

(BMI 25–29.9) or obese (BMI > 30). Over 20% of adults fall into this latter category. In some developing countries as well as among disadvantaged groups in developed countries, e.g. Mexican-Americans, Afro-Americans, Native Canadians and Australian Aborigines, an even more extreme situation exists. Generalized and abdominal adiposity, and physical inactivity are independent risk factors for Type 2 diabetes and impaired glucose tolerance.

Epidemic obesity

Epidemic obesity with some of the highest prevalence in the world exists in these populations, e.g. 70% of Samoans have a BMI in excess of 30. In both Samoa and

Mauritius, two populations where longitudinal data are available, there have been dramatic increases in prevalence over relatively short time periods (Figure 1). Similar trends have been noted in American Pima Indians, Australian Aborigines, migrant Asian Indians and Mexican-Americans.

There are 120 million people worldwide with Type 2 diabetes

Coincident with the high rates of obesity, the prevalence of Type 2 diabetes is also escalating. This increase is expected to continue, and recent projections show that there are currently 120 million people worldwide with Type 2 diabetes, and by the year 2010, this figure is expected to climb to well over 230 million. This represents an epidemic of major proportions. The majority of the

new cases will be those with Type 2 diabetes and the majority of these will be in China, the Indian subcontinent and Africa. We estimate that from 65 million cases of Type 2 diabetes in Asia and Oceania in 1995, the number will double to 135 million by 2010. Some of the highest recorded rates of Type 2 diabetes are found in the Pacific Islands with 1 in 3 adults affected in a number of countries. A major concern here is the growing socio-economic burden of cardiovascular disease, blindness, renal failure and amputations resulting from the diabetes epidemic. Obesity and Type 2 diabetes represent just two constituents of the Metabolic Syndrome, a cluster of cardiovascular disease risk factors also described as 'The New World Syndrome'. Sooner, rather than later, serious morbidity and mortality from cardiovascular disease is inevitable.

Type 2 in the young

Another issue of major concern is that Type 2 diabetes has generally been believed to be rare in children, adolescents and young adults. Not so any longer! An important and alarming feature of the diabetes epidemic is that Type 2 diabetes is increasing in these younger age groups. This poses significant problems as the safety of therapies used in Type 2 diabetes, apart from insulin, has not been tested in this age group. Obesity has been implicated in this trend in Afro- and Mexican-Americans and Pacific Islanders. ■

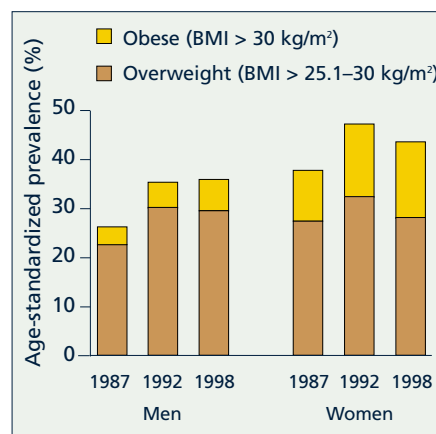


Figure 1: Trend in prevalence of overweight and obesity – Mauritius.

Poster

Evaluation of the GlucoWatch biographer: an automatic and non-invasive glucose monitor

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Background

The GlucoWatch® biographer is designed to facilitate the acceptance and success of intensive diabetes management by providing frequent, automatic glucose readings. The GlucoWatch biographer is worn on the arm like a watch. Glucose is sampled through skin by application of a low-level electric current, a process known as reverse iontophoresis, and the extracted glucose is measured with an electrochemical biosensor. The biographer displays up to three readings per hour for as long as 12 hours, following a single glucose measurement taken with a traditional blood glucose meter three hours after application. The biographer features user-adjustable high and low alert settings to warn of potential hypo- or hyperglycemia and stores 4000 readings, which can provide long-term glycemic pattern data. Data integrity checks screen for potentially erroneous data and the biographer displays a “skip” message to the user instead of a measurement.

Objective

The objective of this clinical study was to assess the performance of the GlucoWatch biographer in a demographically diverse diabetic population in a variety of environmental settings.

Table 1: Biographer results.

	Environment		
	Clinic	Home simulated	Home use
No. of subjects	221	120	111
No. of biographer profiles	406	212	420
No. of paired data points	6909	3771	2996
MD (mg/dl)	-0.1	0.3	4.7
MRD (%)	3.7	2.8	7
MARD (%)	19	21	21.3
Correlation coefficient	0.85	0.81	0.8
Error grid analysis			
A+B (%)	95.3	95.5	94.2
E (%)	0	0.1	0.1

MD, mean difference; MRD, mean relative difference; MARD, mean absolute relative difference.

Methods

The accuracy of the biographer vs serial blood glucose measurements was studied in diabetic subjects in a

controlled clinic environment, a simulated home environment, and the home environment. The subject population consisted of over 400

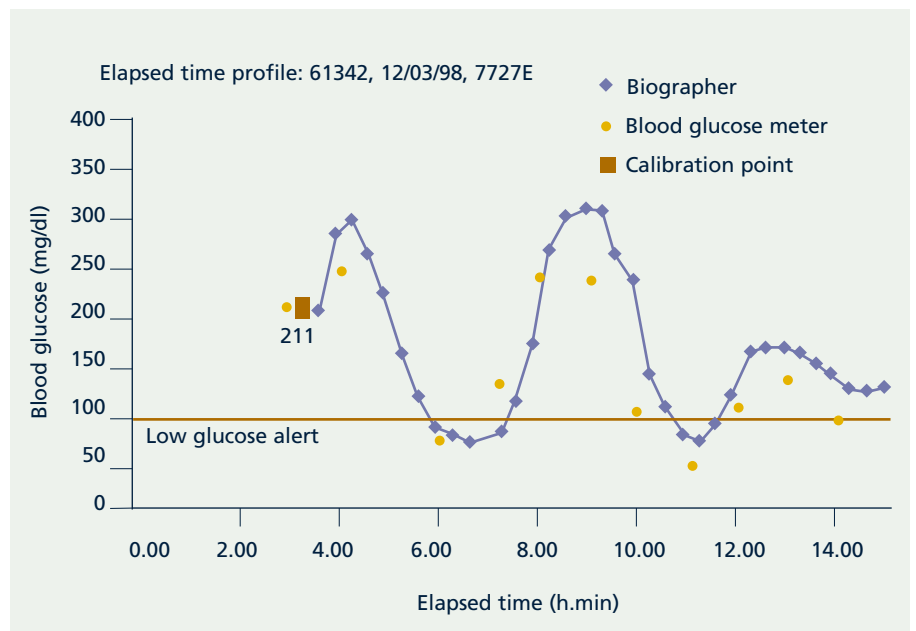


Figure 2: Sample plot of biographer results with fingerstick blood glucose measurements.

adult subjects diagnosed with Type 1 or Type 2 diabetes who required insulin treatment. Performance was assessed by analyzing paired glucose readings between the biographer and a traditional blood glucose meter. A number of blood glucose meters for both calibration and comparative blood measurements were utilized. Over 1000 biographer uses and 14,000 paired glucose measurements were studied.

Results

Time profiles over 12 hours of measurement show close tracking of the biographer results with fingerstick blood glucose measurements. *Figure 2* shows a sample plot. The mean difference (MD) between the two measurements is less than 5 mg/dl over all studies. The mean absolute value of the relative difference (MARD) is approximately 20%. Over 94% of the data was in the clinically acceptable Error Grid A and B zones. Overall performance was comparable in all environments as shown in *Table 1*.

The GlucoWatch biographer provides frequent measurement, can detect trends and track patterns in glucose levels

Conclusions

The GlucoWatch biographer provides frequent measurements of glucose over a 12-hour period with good clinical accuracy. It can detect trends and track patterns in glucose levels in diabetic subjects with diverse demographic characteristics. The GlucoWatch biographer should facilitate improved diabetes management by the diabetic patient and caregiver. ■

Poster

Development of a sensitive, specific quality of life inventory for peripheral neuropathy

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A number of generic quality of life (QOL) instruments are available; however, few of them address the specific problems associated with peripheral neuropathy. From years of clinical experience, we postulated a correlation between subjective and relative query information and results of objective neuropathy tests. To explore this possibility, we needed a sensitive and specific QOL questionnaire to inventory symptoms and the effect of symptoms on activities of daily living and their relationship to quantitative testing for diabetic peripheral neuropathy. Our objective was to develop a non-invasive tool not only explicitly tailored to measure QOL in neuropathy, but also sensitive to the different features of the disease – small and large fiber neuropathy as well as autonomic neuropathy – and clinically relevant for the assessment of the severity of the disease and for monitoring the response to therapy.

Methods

We used the Delphi method to construct a 68-item questionnaire that inventories symptoms, signs and impact on activities of daily life (ADLs) that are condition-specific for diabetic neuropathy. We sought to validate this instrument as a whole, each item individually, and several subscales: autonomic, large fiber (motor and sensory), small fiber (sensory), signs/symptoms, and ADLs.

Subjects

We studied 121 subjects in three groups: 44 normal healthy control subjects (controls, age 54 ± 3, 18 men, 25 women), 35 diabetic subjects without neuropathy (DC, age 62 ± 2, 19 men, 16 women), and 42 diabetic subjects with peripheral neuropathy (DN, age 62 ± 3, 20 men, 22 women) according to the ADA/AAN San Antonio 1989 criteria.

Table II: Sensitivity, specificity and group mean scores.

	Sensitivity	Specificity	Control	DC	DN
Total score	64%	88%	7.8	13.7	41.9
Signs/symptoms	76%	92%	1.3	2.3	10.9
ADLs score	55%	90%	6.5	11.4	31.0
Small fiber score	74%	92%	0.7	1.5	7.4
Large fiber score	55%	87%	0.8	2.4	10.3
Autonomic score	31%	91%	0.5	0.7	2.3

Results

Table II shows sensitivity, specificity, and group mean scores for the instrument and each of the subscales. On mean scores, the DN group had significantly higher scores ($p < 0.001$ using ANOVA) for all parameters. The large fiber score correlated more strongly than other subscales with the total score and ADLs ($r > 0.95$, $p < 0.0001$). We examined each individual question for its sensitivity and specificity. Of the 66 original questions, 38 were found to have >90% specificity when compared with normal controls and diabetics without neuropathy. These were then selected to construct a new tool comprised of those unambiguous questions specific for the different components of neuropathy, QOL and ADLs.

Conclusions

The preliminary results of this study demonstrate that the instrument is specific for diabetic neuropathy and sensitive to the different features of the disease. The small fiber subscale and symptom inventory are particularly sensitive to the presence of neuropathy, while the large fiber score affects more actual QOL items. The high correlation between symptoms and objective tests of neuropathy shows that this instrument has the capacity for providing non-invasive clinical guidelines for assessing disease severity and may be useful for evaluating responses to treatment. Further refinement of this simple, non-invasive tool is now called for.

Treatment modalities according to the different features of neuropathy are available in print. ■

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Symposium

New therapeutics to enhance insulin secretion

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At the symposium, Dr. Jens J. Holst discussed the role of DPP-IV inhibitors in enhancing the action of GLP-1 as a new therapeutic modality in Type 2 diabetes or impaired glucose-tolerant individuals.

GLP-1

GLP-1 is a polypeptide produced and secreted mostly by intestinal and pancreatic cells that exert beneficial influence on the body's glucose metabolism. Some of the physiological actions of GLP-1 include potentiation of glucose and insulin secretion (which makes hypoglycemia unlikely), increases all steps of insulin biosynthesis, up-regulates insulin gene expression and genes essential for beta-cell function, and is mitotic for beta-cells. Moreover, and perhaps most importantly, GLP-1 inhibits glucagon secretion. Other

beneficial effects of GLP-1 include inhibition of gastrointestinal secretion/motility and also moderation of appetite and overall food intake.

Given intravenously to experimental animals with glucose intolerance, GLP-1 has been shown to be able to almost normalize postprandial glucose level.

But...

GLP-1 is degraded almost immediately after its release (into GLP-1_[9-36]amide) by an enzyme called DPP-IV. Unfortunately, the breakdown product of GLP-1 has been shown to have antagonistic activities against GLP-1. In other words, the metabolite of GLP-1 is its own antagonist. Subsequently, all the beneficial effects of GLP-1 are lost immediately as a result of the DPP-IV action. Experimental rats deficient in DPP-IV protein show

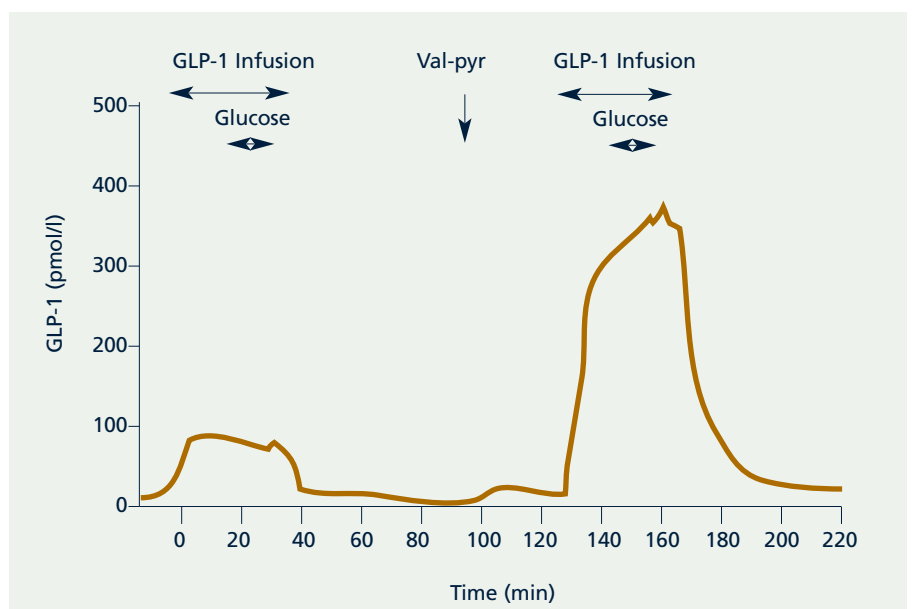


Figure 3: GLP-1 concentration measured over time with GLP-1 infusion before and after valine-pyrrolidide (val-pyr) administration.

that they have decreased propensity for developing diabetes or impaired glucose tolerance after a prolonged diet high in fat content, unlike their control counterparts.

DPP-IV inhibitor (logically)

The possible strategies to overcome these unfortunate biochemical findings are several. However, a compound taken orally that inhibits the actions of DPP-IV, and therefore GLP-1 degradation, appears most promising. Several studies in experimental animals with and without impaired glucose tolerance have shown that administration of a compound called valine-pyrrolidide inhibits the actions of DPP-IV and increases the subsequent levels of GLP-1. In turn, DPP-IV inhibition completely protects both endogenous and exogenous GLP-1 from being degraded, insulin secretion is enhanced, and glucose tolerance improved particularly in glucose-intolerant animals (Figure 3).

In summary...

It can be expected that in patients developing NIDDM, the usage of such compounds that inhibit DPP-IV action, and in turn enhance GLP-1 action, can restore insulin deficiency, normalize glucose level, remove the stress on the beta-cell, lower body weight, improve insulin sensitivity, and enhance beta-cell survival.

And in conclusion...

DPP-IV inhibitors such as valine-pyrrolidide (still highly experimental) may be helpful in the management of NIDDM. Because of the said proposed mechanisms of action, DPP-IV inhibitors may also be effective for use in patients who have impaired glucose tolerance since the transition to overt NIDDM may be prevented. ■

Symposium

The link between obesity and diabetes

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A symposium chaired by Dr Michael W. Schwartz, highlighting potential connections between the pathogenetic mechanisms underlying Type 2 diabetes and obesity, was entitled "Obesity and Diabetes: The Odd Couple".

Paradox

The theme of the session was to explore the apparent paradox between these two commonly co-existing conditions. That paradox is: since elevated insulin levels are associated with obesity, and decreased or deficient insulin secretion is associated with the clinical development of diabetes, how do we explain the occurrence of both in the same individual? While the insulin resistance and hyperinsulinemia related to obesity are certainly one potential

explanation, the symposium's first presenter, Dr Daniel Porte, Jr, focused on the possible primary

Insulin has direct CNS effects resulting in appetite suppression

role of the beta-cell in the link between diabetes and obesity, presenting data that insulin (and insulin deficiency) is (are) a key mediator of adiposity through CNS effects. His hypothesis develops first from the fact that, while insulin-resistant individuals tend to become more insulin-resistant over time, not all develop diabetes. In fact, only those whose islets fail develop diabetes. Dr Porte points to a decrease in the processing of proinsulin (hyperproinsulinemia) which

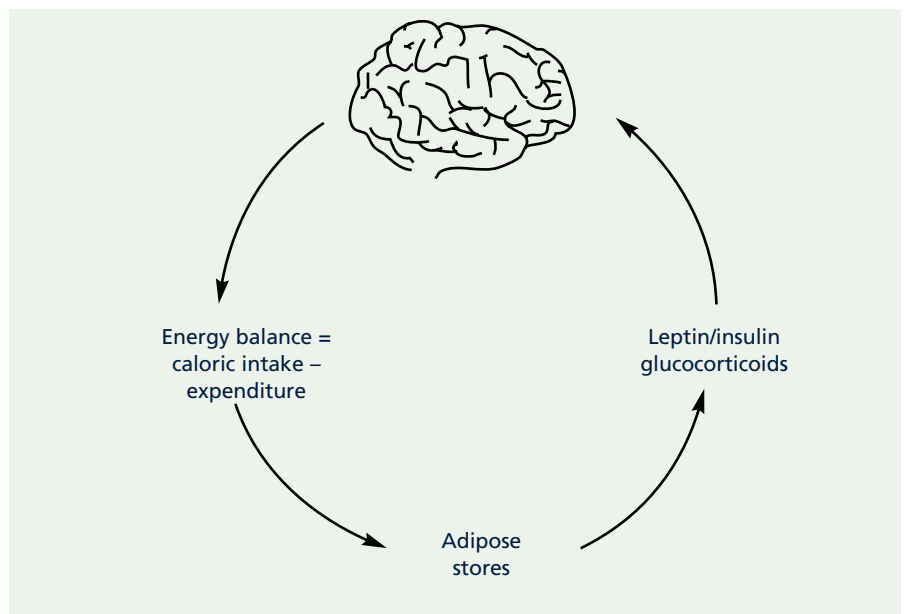


Figure 4: Insulin modulates appetite via effects on increasing Neuropeptide Y (NPY), a potent anorexogenic substance. Insulin deficiency results in a decrease in NPY, resulting in increased food intake and adiposity.

results in an increased deposition of amyloid in the islets as potential mechanisms which lead to apoptosis of beta-cells, and resultant islet failure. He further discusses evidence that insulin has direct CNS effects resulting in

The unifying link between diabetes and obesity could lie in beta-cell failure

appetite suppression probably via stimulatory effects on neuropeptide Y, a potent anorexogenic substance. Therefore, the unifying link between diabetes and obesity could lie in beta-cell failure and

may be explained thus: as beta-cells fail to secrete adequate insulin to overcome insulin resistance, which results from a combination of genetic and environmental factors, hyperglycemia develops. Body adiposity increases when insulin secretion is impaired and insulin action is reduced in the CNS. In fact, there is evidence in some populations, Japanese men for example, that an impairment in insulin secretion is present up to 5 years before the presence of intraabdominal fat, a powerful predictor of insulin resistance in this population. Whether this hypothesis explains the sequence of events leading to the development of diabetes in most populations who develop diabetes is controversial. Many

investigators still believe that insulin resistance precedes beta-cell failure in many, if not most, individuals with Type 2 diabetes, and in the obese population, at least, beta-cell failure is a result of the inevitable inability of the beta cell to adequately compensate for this resistance. It may prove, however, that beta-cell failure preceding obesity and insulin resistance may represent one sequence of events in the development of this most heterogeneous disease, diabetes. If this hypothesis is correct in some cases of Type 2 diabetes development, an unanswered question begs explanation: why are the effects of insulin deficiency on body adiposity different in Type 1 diabetes? ■

Posters

Insulin secretagogue therapy and hypoglycemic risk

A pharmacological and clinical comparison of the prandial glucose regulator repaglinide with sulphonylureas

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Sulphonylureas are widely used in Type 2 diabetes, in which the prandial insulin response is, characteristically, impaired. However, sulphonylureas were designed for once- or twice-daily dosing and have extended durations of action that can increase insulin secretion in the late postprandial timeframe. Furthermore, the secretagogue action of sulphonylureas is not nutrient-dependent in vitro. Consequently, sulphonylureas may put patients at risk of hypoglycemia in the interprandial period.

Repaglinide

Repaglinide is the first insulin

secretagogue specifically designed for use in mealtime regimens. It has a rapid onset of action (10–15 minutes after oral administration, with t_{max} occurring at approximately 1 hour) and fast elimination ($t_{1/2}$, approximately 30 minutes). In vitro, its insulinotropic action is glucose-dependent. These properties raise expectations that prandial repaglinide will carry a low risk of hypoglycemia compared with sulphonylurea regimens. Data from two studies now strengthen this expectation.

Results

Twelve patients with Type 2

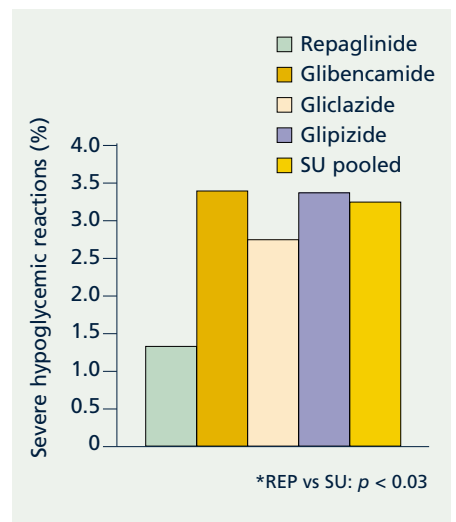


Figure 5: Major hypoglycemic reactions during repaglinide treatment versus sulphonylurea treatment.

Table III: Estimated insulin secretion in healthy volunteers and individuals with Type 2 diabetes: comparison of repaglinide with glibenclamide. Data are mean differences in log (AUC, nmol.min/kg) [95% CI] between repaglinide and glibenclamide during early (-15 to 30 minutes) and late (120 to 240 minutes) phases of the prandial response.

	-15 to 30 minutes	p	120 to 240 minutes	p
Healthy volunteers Repaglinide vs. glibenclamide	0.096 [0.057; 0.134]	< 0.0001	-0.165 [-.325; -0.006]	0.0426
Type 2 diabetes Repaglinide vs. glibenclamide	0.046 [0.011; 0.082]	0.0126	-0.031 [-0.176; 0.115]	NS

diabetes and 12 healthy volunteers were given a standardized 500 kcal meal on three separate occasions preceded by a single dose of either repaglinide (2 mg), glibenclamide (5 mg) or placebo. Each subject received each treatment, with blood samples assayed over 4 hours. In patients and volunteers, the secretagogues increased insulin output relative to placebo. There was no overall between-treatment difference in insulin output, but early-phase secretion (-15 to 30 minutes) was significantly greater with repaglinide than glibenclamide (Table III). The longer duration of action of glibenclamide was evident in a greater late-phase insulin secretion (120-240 minutes), reaching statistical

significance among the healthy volunteers (Table III).

The relative frequency of major hypoglycemic events was assessed in a meta-analysis of four randomized, double-blind, comparative studies, in which prandial repaglinide (0.5-4 mg) was compared with recommended doses of glibenclamide, gliclazide and glipizide over 1-year periods in patients with Type 2 diabetes. In line with sulphonylurea requirements, patients followed a strict pattern of three daily meals, fixed mealtimes and optional snacks. Patients (repaglinide n = 761, sulphonylurea n = 367) performed home blood glucose monitoring whenever hypoglycemia was suspected. The rate of major hypoglycemic episodes (defined as

blood glucose < 2.5 mmol/l plus symptoms) associated with repaglinide and sulphonylureas, respectively, was 1.31% and 3.27% (p < 0.03; Figure 5), with a relative risk of 2.8 for sulphonylurea-treated patients (p = 0.01). Fifty-seven percent of sulphonylurea-related hypoglycaemic events were associated with blood glucose < 3.33 mmol/l; with repaglinide 62% of events occurred with blood glucose > 3.33 mmol/l. Most hypoglycaemic episodes associated with repaglinide occurred between 8 am and midnight with repaglinide, whereas with glibenclamide most episodes were nocturnal.

Conclusion

In conclusion, prandial repaglinide is characterized, pharmacologically, by rapid, selective augmentation of early-phase insulin secretion. In clinical practice, repaglinide incurs a lower risk of major hypoglycemia than sulphonylureas, and there is evidence that patients may preserve a greater awareness of falling blood glucose concentrations and may incur a lower burden of nocturnal hypoglycemia. ■

