Glial cell–derived neurotrophic factor (GDNF) belongs to the neurotrophic factor family. GDNF functions are not restricted to neurons but are also implicated in glial cell development (1). We observed high expression levels of GDNF receptor family α-component 2 (GFRα2) in epiretinal membranes (ERMs) in proliferative diabetic retinopathy (PDR), indicating the involvement of GFRα2 in ERM formation in PDR (2). Here, we examined the vitreous of patients with PDR for the presence of GDNF.

We assayed GDNF levels in vitreous and serum samples from 75 consecutive patients with PDR (54 patients) and macular hole (nondiabetic control subjects, 21 patients) who underwent vitrectomy. PDR was classified as active (33 patients) when there were perfused, multibranched iridic or preretinal capillaries and as quiescent (21 patients) when only large vessel or fibrosis was present. Informed consent was obtained from each patient. Undiluted vitreous samples were obtained during the vitrectomy before intravitreal infusion. Enzyme-linked immunosorbent assay was performed to determine GDNF level using a commercially available immunoassay kit (Pro-mega, Madison, WI). Mann-Whitney U test was used to compare GDNF levels.

GDNF was undetectable in all the serum samples examined. Intravitreous GDNF level was significantly higher in the PDR patients (means ± SD: 156.1 ± 221.0 pg/ml) than in the control subjects (26.5 ± 53.2 pg/ml) (P = 0.0042). Intravitreous GDNF level was significantly higher in active PDR (206.0 ± 250.7 pg/ml) than in quiescent PDR (77.7 ± 133.5 pg/ml) (P = 0.0388).

Glia cells are one of the main components of ERMs. Our previous study (2) showed that GFRα2 mRNA expression level is significantly higher in PDR ERMs than in idiopathic ERMs, and this high expression level is specific for GFRα2 among neurotrophin receptors. GFRα2 protein is detected in the glial component of PDR ERMs. These results suggest that GDNF is involved in the formation of the glial cell component of PDR ERMs. Results of the present study support this suggestion. Because GDNF increases basic fibroblast growth factor (bFGF) production in Müller cells (3), released bFGF may stimulate endothelial proliferation.

In conclusion, intravitreous GDNF level increased in PDR and was associated with the activity of PDR. These results suggest that GDNF is involved in the pathogenesis of PDR.

From the 1Department of Ophthalmology, School of Medicine, Sapporo Medical University, Sapporo, Japan; the 2Department of Molecular Neurobiology, Tokyo Metropolitan Institute for Neuroscience, Tokyo, Japan; and the 3Department of Pathology, School of Medicine, Sapporo Medical University, Sapporo, Japan.

Address correspondence to Nami Nishikiori, MD, Department of Ophthalmology, School of Medicine, Sapporo Medical University, S-1, W-16, Chuou-ku, Sapporo 060-8543, Japan. E-mail: nnishimi@sappmed.ac.jp.

© 2005 by the American Diabetes Association.
The prevalence of metabolic syndrome was 22.3, 22.6, and 15.4% according to the IDF, ATP III, and WHO definitions, respectively.

The IDF definition failed to detect 7.6% of ATP III patients with metabolic syndrome, whereas 5.2% of the participants who were classified as normal by the ATP III definition had metabolic syndrome according to IDF criteria (sensitivity and specificity of 92.4 and 94.8%). The \( \kappa \) statistic for the agreement between IDF and ATP III definitions was 0.873.

The IDF definition failed to detect 15.7% of the WHO subjects with metabolic syndrome, whereas 26.8% of the participants who were classified as normal by the WHO definition had metabolic syndrome by IDF criteria (sensitivity and specificity of 84.3 and 73.1%). The \( \kappa \) statistic for the agreement between the IDF and WHO definition was 0.511.

The IDF criteria detected a higher prevalence of obesity (33.7%) than the ATP III and WHO criteria (23.7 and 22.6%, respectively). The WHO definition detected significantly fewer subjects with high blood pressure (5.7 vs. 12.3% of ATP III and IDF definitions) and low HDL cholesterol (22.9 vs. 34.1% of ATP III and IDF criteria). The prevalence of hyperglycemia and hypertriglyceridemia included 53.6 and 7.1% of the overweight and weight gain increased by 6.0 kg (5.4–6.6). A1C reduction was similar in both the obese and nonobese groups. Concomitant metformin ameliorated weight gain in the nonobese patients (5.1 [3.8–6.4] vs. 7.4 kg [6.4–8.4], \( P < 0.01 \)) and reduced daily insulin requirements in the obese (0.59 [0.53–0.65] vs. 0.77 units \( \cdot \) \( \text{kg}^{-1} \cdot \text{day}^{-1} \) [0.69–0.85], \( P < 0.001 \)) for equivalent reductions in A1C.

Africans and Caribbeans benefited from a greater reduction in A1C (2.7% [2.2–3.2]) than Caucasians (2.1% [1.8–2.4]) and Asians (1.6% [1.3–2.0]) (\( P < 0.01 \)) despite smaller insulin requirements (African/Caribbeans 0.53 [0.48–0.57], Caucasians 0.64 [0.60–0.69], and Asians 0.67 units \( \cdot \) \( \text{kg}^{-1} \cdot \text{day}^{-1} \) [0.56–0.77], \( P = 0.007 \)). Concomitant metformin use was similar across all ethnic groups. Weight gain was greater in African/Caribbeans (7.5% for at least 6 months) than Caucasians (5.6 [4.7–6.4]) and Asians (4.8 kg [3.3–6.4], \( P < 0.01 \)). Our observation, at variance with a previous study (1), indicates that baseline BMI does not affect the benefit of insulin treatment on metabolic control in type 2 diabetic patients but that obese type 2 diabetic patients require more insulin to overcome their greater insulin resistance. Weight gain is virtually an obligate consequence of insulin therapy-induced glycemic improvement in patients who have failed oral agents, but this is modulated by concomitant metformin treatment, degree of obesity, and ethnicity. Moreover, metformin reduced the requirement of insulin in obese type 2 diabetic patients for equivalent glycemic amelioration, an effect that may mitigate further weight gain.

Determinants of Response to Insulin Therapy Following Failure of Oral Agents in Type 2 Diabetes

Obesity, ethnicity, and concomitant metformin therapy may modify the metabolic response to insulin in patients with type 2 diabetes (1–3). We performed a retrospective case note analysis of 280 type 2 diabetic patients who had failed oral drug therapy, defined as HbA1c (A1C) >7.5% for at least 6 months despite maximum doses of sulfonylurea and metformin, and received treatment with exogenous insulin for at least 12 months for indications other than pregnancy, acute coronary syndrome, stroke, sepsis, or renal failure. Main outcome measures were A1C, body weight, and daily insulin dose. For the purpose of analysis, patients with BMI below and above the median for the whole cohort (28.2 kg/m²) were termed nonobese and obese, respectively. Following 12 months of insulin, overall mean (95% CI) A1C fell 2.2% (1.9–2.6), and weight gain increased by 6.0 kg (5.4–6.6). A1C reduction was similar in both orthopedic and chronic systemic conditions (4). Insulin is an effective long-term treatment for type 2 diabetes, and early treatment with insulin may improve overall outcomes in patients with type 2 diabetes.

**Determinants of Response to Insulin Therapy Following Failure of Oral Agents in Type 2 Diabetes**

**References**

5. From the Department of Endocrinology, Diabetes and Internal Medicine, King’s College London, Guy’s Hospital, London, U.K.
6. Address correspondence to Dr. J. Karalliedde, Department of Endocrinology, Diabetes and Internal Medicine, King’s College London, 5th Floor Thomas Guy House, Guy’s Hospital, London SE1 9RT, U.K. E-mail: j.karalliedde@kcl.ac.uk.

© 2005 by the American Diabetes Association.
Kremezin (AST-120) Delays the Progression of Diabetic Nephropathy in Japanese Type 2 Diabetic Patients

S trict control of blood glucose and blood pressure levels sometimes fail to delay the development of diabetic nephropathy, and effective therapy for diabetic nephropathy is not yet available. AST-120, a spherical adsorptive carbon preparation, absorbs uremic toxins, such as indoxyl sulfate, in the gut. Since indoxyl sulfate can generate profibrotic cytokines, the accumulation of uremic toxins is toxic to the kidney. The removal of indoxyl sulfate by the adsorptive carbon should be renoprotective (1). AST-120 decreases circulating indoxyl sulfate in patients with chronic kidney diseases (2). In a nonrandomized study, we sought to determine whether AST-120 can delay the progression of diabetic nephropathy.

We explained the clinical usefulness of AST-120 for diabetic nephropathy to type 2 diabetic outpatients who also had overt proteinuria with increased serum creatinine levels (>1.3 mg/dl), and 2.0 g AST-120 was administered three times a day between meals to those choosing to receive it. Serum creatinine and blood pressure levels were measured every month for 6 months. In control subjects not taking AST-120 (n = 12), serum creatinine levels significantly increased (before 2.50 ± 0.26 mg/dl, after 6 months 3.27 ± 0.34 mg/dl, P < 0.005). In contrast, serum creatinine levels were not changed in AST-120-treated patients (n = 9) (before 2.63 ± 0.36 mg/dl, after 6 months 2.40 ± 0.20 mg/dl, NS). The slope of serum creatinine was significantly (P < 0.01) higher in AST-120-treated subjects (0.0043 ± 0.0036 dl·mg⁻¹·week⁻¹) than in control subjects (−0.0174 ± 0.0043 dl·mg⁻¹·week⁻¹).

AST-120 did not affect HbA₁c levels (control subjects: before 7.4 ± 0.2%, after 6 months 7.5 ± 0.2%, NS, vs. AST-120–treated subjects: before 7.0 ± 0.4%, after 6 months 6.8 ± 0.4%, NS) or systolic and diastolic blood pressure levels (control subjects: before 136.4 ± 4.9/67.0 ± 4.4 mmHg, after 6 months 136.1 ± 3.6/70.9 ± 1.9 mmHg, NS, vs. AST-120–treated subjects: before 131.5 ± 4.3/63.8 ± 5.5 mmHg, after 6 months 130.3 ± 2.5/69.8 ± 3.0 mmHg, NS).

Since AST-120 in the gut did not adsorb creatinine in the blood, and there is no exchange of serum creatinine levels between the gut and blood (3), the observed attenuation of increase of serum creatinine levels by AST-120 should not be attributable to the excretion of creatinine into the feces. Although the results are limited because of the nonrandomized self-selection study design, our findings indicate that AST-120 should contribute to the delay of the development of renal dysfunction in type 2 diabetic patients.

HIROYUKI SHIMIZU, MD, PHD
SHUICHI OKADA, MD, PHD
ON-I SHINSAKE
MASATOMO MORI, MD, PHD

From the 1Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan.

Address correspondence to Dr. Hiroyuki Shimizu, MD, PhD, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371, Japan. E-mail: ishimizu@sho wa.gunma-u.ac.jp

© 2005 by the American Diabetes Association.

References

Sex Differences of Age-Dependent Changes of Insulin Sensitivity in Japanese Nondiabetic Subjects

Impaired insulin sensitivity is associated with type 2 diabetes, hypertension, and atherosclerosis. This abnormality occurs by various causes such as genetic background, obesity, high-calorie diet, and low physical activity. Sex hormones also influence insulin sensitivity, which might be a cause for sex differences of the development of diabetes, hypertension, and atherosclerosis (1,2). Collectively, however, there is no population-based study of sex differences in insulin sensitivity. Here, we aimed to determine whether there are sex and age differences of insulin sensitivity and insulin secretory activity in middle-aged nondiabetic subjects.

Of 1,934 Japanese subjects who visited the Kinki Central Hospital between April and October 2003 for their health examinations, we evaluated 1,395 subjects (854 men and 541 women) after exclusion of subjects with diabetes, malignant diseases, chronic or acute inflammatory diseases, elevated serum creatinine levels (>106 μmol/l), autoimmune disorders, or subjects aged ≤40 years or ≥61 years.

Glucose tolerance status, homeostasis model assessment (HOMA) determinants (3), and BMI stratified by sex and age groups (40–49 and 50–59 years) are shown in Table 1. Prevalence of impaired glucose tolerance was significantly higher in men than in women of both age groups. In the 41–50 age group, the index for insulin sensitivity (HOMA-%S) was higher in women than in men, whereas in the 51–60 age group, there was no sex difference. The index for pancreatic β-cell function (HOMA-%B) was not different between men and women of both age groups. BMI was lower in women than in men of both age groups. In women, HOMA-%S was significantly
higher in the 41–50 age-group than in the 51–60 age-group (P = 0.0275), whereas in men it was lower in the 41–50 age-group than in the 51–60 age-group (P = 0.0348).

We found that there were sex differences of age-dependent changes of insulin sensitivity, but not of insulin secretory activity, in Japanese nondiabetic subjects. Serum sex hormone levels differ between men and women, and in women, serum estrogens rapidly fall after menopause occurring around age 50. Therefore, sex hormones may be involved in the sex differences of age-dependent changes of insulin sensitivity. It has been reported that postmenopausal hormone replacement therapy lowered fasting glucose and insulin levels in nondiabetic women (4) and improved glycemic control in type 2 diabetic women (5), although disparate results have also been shown (6,7). In men, serum testosterone levels have been shown to be inversely related to serum insulin level and BMI (8). In addition, it has been shown that androgens decreased the insulin-sensitizing adipocyte-derived protein adiponectin (9). Thus, as a whole, estrogens may have favorable effects on insulin sensitivity, whereas androgens may have undesirable effects on it.

In summary, insulin sensitivity depends on sex and age. Insulin sensitivity is higher in women than in men until age 50, but it falls to levels similar to men after age 50. Therapeutic strategies for eliminating insulin resistance for the prevention of diabetes and atherosclerosis should be classified by sex and age.

**References**


**Isolated Bibrachial Plexopathy in a Patient With Type 2 Diabetes**

Diabetic amyotrophy is typically a lumbosacral radiculoplexus neuropathy resulting in weakness, muscle wasting, and pain (1). Brachial plexus involvement has been occasionally described with lumbosacral radiculoplexus neuropathy (2–6), but isolated diabetic brachial plexopathy has been described only in a patient with diabetic ketoacidosis (7). We describe a patient with well-controlled type 2 diabetes who developed isolated bibrachial diabetic plexopathy.

A 56-year-old African-American man with a 13-year history of well-controlled diabetes (total glycohemoglobin 6.2%, normal 3.9–6.3%), on insulin for 5 years and having no other major medical illness, developed left shoulder pain that extended to the hand over a few weeks and right shoulder, extending into the right hand 3 months later.

Pain was dull with intermittent shooting and sharp pains. He denied sensory symptoms in the arms. Progressive left arm weakness evolved >3 months after the onset of pain and stabilized thereafter.

### Table 1—Glucose tolerance status, HOMA-%S, HOMA-%B, and BMI in 1,395 Japanese nondiabetic subjects

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>41–50 age-group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>378</td>
<td>183</td>
<td></td>
</tr>
<tr>
<td>Glucose tolerance status (NGT/IGT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-%S (%)</td>
<td>122 ± 60</td>
<td>150 ± 69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA-%B (%)</td>
<td>77 ± 24</td>
<td>73 ± 20</td>
<td>0.0670</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 2.8</td>
<td>22.3 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>51–60 age-group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>476</td>
<td>358</td>
<td></td>
</tr>
<tr>
<td>Glucose tolerance status (NGT/IGT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-%S (%)</td>
<td>132 ± 73</td>
<td>138 ± 57</td>
<td>0.1687</td>
</tr>
<tr>
<td>HOMA-%B (%)</td>
<td>72 ± 25</td>
<td>71 ± 19</td>
<td>0.6670</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 2.6</td>
<td>23.1 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are n or means ± SD. *By Student’s t test or Fisher’s exact test. IGT, impaired glucose tolerance; NGT, normal glucose tolerance.
Right arm weakness developed over the preceding 3 months and has continued to progress. He denied leg symptoms. He reported a 60-lb weight loss in the preceding year. Examination revealed strength as follows: MRC (Medical Research Council) grade 1–5 (3 in bilateral deltoid and biceps; 5 in right triceps, bilateral finger abduction, and right finger extension; and 4 in left triceps, bilateral wrist extension, and left finger extension). Strength was normal in the legs. Reflexes were absent in bilateral brachioradialis and biceps muscles but were normal in other areas. Babinski’s sign was absent.

Electromyography and nerve conduction studies revealed bilateral upper-trunk brachialplexopathy; fibrillation potentials in upper-trunk innervated muscles (biceps, deltoid, infraspinatus, and brachioradialis); and sparing of triceps, pronator teres, first dorsal interosseus and abductor pollicis brevis, and cervical paraspinal muscles. Radial, ulnar, and median sensory nerve action potential amplitudes were reduced. (Only the reduction in median sensory nerve action potentials could be accounted for by median nerve entrapment at the wrist.)

Despite treatment with prednisone, gabapentin, and narcotics, pain and weakness are still prominent 2 years after initiation of symptoms. However, the patient’s weight increased to baseline.

Brachialplexopathy in this patient was likely related to his diabetes because there was no other obvious etiology; pain and weakness were prominent with relative paucity of sensory symptoms, and there was preceding weight loss, both characteristic features of lumbosacral radiculoplexus neuropathy.

In conclusion, isolated lumbosacral radiculoplexus neuropathy can occur as the initial complication of diabetes, even with good glycemic control. Thus, it is likely due to microvasculitis-causing nerve infarction rather than metabolic abnormalities in diabetes (1). Efficacy of immunosuppressive treatments is unproven and is being evaluated in clinical trials.

SURAJ A. MULEY, MD1,2
GARETH J. PARRY, MD2
NACIDE G. ERCAN-FANG, MD3,4

From the 1Neurology Section, VA Medical Center, Minneapolis, Minnesota; the 2Department of Neurology, University of Minnesota, Minneapolis, Minnesota; the 3Metabolic Section, VA Medical Center, Minneapolis, Minnesota; and the 4Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

Address correspondence to Nacide G. Ercan-Fang, MD, VA Medical Center, Metabolic Section, One Veterans Dr., Minneapolis, MN 55417. E-mail: ercan001@umn.edu.

© 2005 by the American Diabetes Association.

References

Proposal for the Reconsideration of the Definition of Gestational Diabetes

In 1997, the American Diabetes Association (ADA) announced a new diagnostic criterion for diabetes and set the definition of gestational diabetes mellitus (GDM). Before 1991, GDM was defined as “a transient abnormality of glucose tolerance during pregnancy” (2–4). However, the 1997 definition of GDM by the ADA includes diabetes diagnosed during pregnancy. This definition ignores the added risks to the mother and to the fetus when the mother has undiagnosed type 2 diabetes. We propose reconsideration of the definition, which would separate diabetes and slight abnormal carbohydrate, so-called GDM, to provide a better model of care for type 2 diabetic pregnant women.

There are three problems concerning an undiagnosed type 2 diabetic woman that are not major issues in pregnant women who are first diagnosed with abnormal glucose tolerance in pregnancy that resolves after pregnancy. First, the entire pregnancy is associated with abnormal carbohydrate metabolism, not just the second half. The second problem is related to the rate of congenital malformations of newborns from these pregnant women. The third is concerned with undiagnosed diabetic retinopathy.

In our Japanese cohort, we observed the results of 75-g oral glucose tolerance tests (OGTTs) (Japan criteria: two or more values above fasting glucose >100 mg/dl, 1-h glucose >180 mg/dl, and 2-h glucose >150 mg/dl) for 1,416 pregnant women who had risk factors for GDM. We found the frequency of GDM in the first trimester is the highest (33/250 [13.2%]), followed by the second (32/417 [7.7%]) and third trimesters (37/749 [4.9%]). Similarly, the frequency of type 2 diabetes is the highest in the first trimester at 6.0%, with 2.6% in the second trimester and 1.3% in the third trimester. Thus, in women with positive OGTT, GDM accounts for 7.2% and type 2 diabetes diagnosed during pregnancy accounts for 2.5% of the total pregnant population. In other words, 35% of women with a positive OGTT have type 2 diabetes diagnosed for the first time in pregnancy.

In this cohort, the congenital malformation rate from GDM patients was 1.9% and was no different from the rate in the general Japanese population. In contrast, the congenital malformation rate in infants of type 2 diabetic mothers diagnosed during pregnancy was higher than that of children from pregestational diabetic mothers treated during pregnancy, 12.7 vs. 4%, respectively.

There were no GDM patients with retinopathy. However, the rate of background retinopathy was 12.7% and proliferative retinopathy was 4.2% in the type 2 diabetic women diagnosed for the first time during pregnancy.

Similar rates and complications were seen in a cohort of pregnant women in Santa Barbara, California, where a total of 49,861 pregnancies occurred in our Mexican-American population from 1997 to 2004. A total of 4,133 (8.3%) had a positive OGTT based on the ADA criteria (1). However, 40% of the GDM women had type 2 diabetes first diagnosed during pregnancy based on our criteria: anacanthosis nigricans, requiring insulin before the 12th week of gestation, because they failed to maintain goals with dietary intervention alone (6). Five percent of the type 2 women had retinopathy, and 7% had significant proteinuria at time of diagnosis.
Infancy-Onset Cystic Fibrosis-Related Diabetes

Cystic fibrosis is a genetic disorder characterized by hyperviscous secretions and progressive obstructive end organ damage. Common presentations include meconium ileus, recurrent pulmonary infections, and failure to thrive. Although cystic fibrosis–related diabetes (CFRD) usually presents in the second decade of life, it has been reported in children as young as 2 years (1). Here we present a 7-month-old infant who had CFRD at the time of presentation with cystic fibrosis.

A 7-month-old Caucasian male presented for evaluation of failure to thrive despite adequate intake of high-calorie formula. He was born at term but small for gestational age (birth weight <3rd percentile). Review of systems was significant for a chronic nonproductive cough, three to five loose bowel movements per day, and no history of polydipsia or polyuria. Random blood glucose obtained during a hospitalization for bronchiolitis at 4 months of age was normal. His only medication was multivitamin solution.

At 7 months of age, his weight and length were below the 3rd percentile. Laboratory studies revealed sodium 134 mmol/l (135–145), glucose 119 mg/dl, albumin 2.9 g/dl (3.1–4.7), and sweat chloride 105 mmol/l (0–40). A diagnosis of cystic fibrosis was made. Cystic fibrosis gene analysis revealed homozygous ΔF508 mutation.

Pancreatic elastase was <50 mcg El/g stool (normal >200), consistent with exocrine insufficiency. Salt and pancreatic enzyme supplemental medications were initiated. Total parenteral nutrition (TPN) with glucose infusion rate of 9.7 mg·kg⁻¹·min⁻¹ was initiated. The infant developed a marked hyperglycemia (250–559 mg/dl), persistent despite the discontinuation of TPN administration. HbA₁c (A1C) was 6.4% (4.0–5.9), and C-peptide 0.6 ng/ml (0.9–4.2) with blood glucose 215 mg/dl. GAD 65, islet cell antibodies (ICA 512), human insulin antibodies (ICA 512), human insulin antibodies, and urinary ketones were negative. Subcutaneous insulin was initiated. The patient was discharged on insulin (0.35 units·kg⁻¹·day⁻¹) and pancreatic enzyme supplemental medications and displayed excellent catch-up of linear growth (Fig. 1). At 24 months of age, he required 0.4 units·kg⁻¹·day⁻¹ of insulin and had A1C of 8.7%.

While transient glucose intolerance associated with steroid administration in an infant with cystic fibrosis has been reported (2), to our knowledge our case
represents the youngest patient with permanent CFRD ever described. The lack of autoimmunity, continued insulin requirements beyond the age of 18 months, later age at diagnosis, and absence of phenotypic abnormalities (3) effectively exclude type 1 diabetes and transient and permanent neonatal diabetes, respectively.

In conclusion, this case expands the clinical spectrum of CFRD and emphasizes the importance of aggressive nutritional therapy and insulin replacement. Although rare in this age-group, CFRD needs to be considered in clinically unstable children with cystic fibrosis and should be included in the differential diagnosis of non–type 1 diabetes of infancy.

REFERENCES


Letters

Use of Insulin Glargine During Pregnancy in Seven Type 1 Diabetic Women

Insulin glargine is a human insulin analog with an activity that results in a relatively constant concentration/time profile over 24 h with no pronounced peak. It is increasingly recognized to provide good glycemic control and to reduce the risk of hypoglycemia in type 1 diabetes (1). There may be a place for insulin glargine in diabetic pregnancies in which strict glycemic control and prevention of hypoglycemia reduce the higher adverse outcome risk. Despite animal studies showing the safety and efficacy of insulin glargine during pregnancy (2), its use in human pregnancies is currently not recommended. There are two case reports on the occasional use of insulin glargine during pregnancy (3,4) and a notification of its safety in five patients during the first weeks of pregnancy (5). To date, there are no reports on the use of insulin glargine during the entire pregnancy in patients with diabetes.

We examined the hospital files of three outpatient pregnancy clinics in the Netherlands and identified seven women with type 1 diabetes who deliberately used insulin glargine during pregnancy while being aware of the unknown pregnancy risks. The women (three primiparae and four multiparae) had a mean age of 34 years (range 29–39) and a diabetes duration of 12 years (5–8). Five patients continued their preconceptional use of insulin glargine during the entire pregnancy. Two patients converted from intermediate-acting NPH insulin to insulin glargine after 15 and 27 weeks of amenorrhea because of recurrent episodes of nocturnal hypoglycemia. Glycemic control during pregnancy was excellent in six of the seven women and the disappearance of hypoglycemia reduced in the fetus at risk. This, in combination with the present observation of the use of insulin glargine in seven human diabetic pregnancies, justifies a large randomized trial to establish the efficacy and safety of insulin glargine in diabetic pregnancies.

REFERENCES

1. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A: Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabe-

DIABETES CARE, VOLUME 28, NUMBER 10, OCTOBER 2005

2594
I read with interest the article by Sever et al. in the May 2005 issue of *Diabetes Care* (1). I agree with the authors’ conclusion in the abstract that atorvastatin may or may not be eventually found to be useful for all levels of LDL cholesterol. However, this article does not give an answer as to how low a level of LDL cholesterol a patient should obtain for a statin to continue or cease to be useful. For example, based on the article’s information, I cannot yet say whether a 55-year-old diabetic patient without overt cardiovascular disease and LDL cholesterol of 1.8 mmol/l (70 mg/dl) will benefit from atorvastatin. That would have to await further studies and cannot be answered by the present article.

**KINGSTON H. TSENG, MBBS, FACP, FACE**

From the Endocrinologist Office, Pacific Medical Associates, Kowloon, Hong Kong.

Address correspondence to Kingston H. Tseng, Endocrinologist, Pacific Medical Associates, Suite 1305, 102 Austin Rd., TST, Kowloon, Hong Kong. E-mail: tseng@netvigator.com.

© 2005 by the American Diabetes Association.
Self-Monitoring of Blood Glucose in Patients With Type 2 Diabetes Who Are Not Using Insulin

Response to Welschen et al.

We read the article by Welschen et al. (1) in Diabetes Care with interest. It systematically reviewed the effect of self-monitoring of blood glucose (SMBG) in patients with type 2 diabetes who are not using insulin. This review is important and provides an answer to the extensive debate about this interesting topic.

The same authors published a systematic review on the same topic in April 2005 in the Cochrane Library (2). The same articles were included in both reviews. The authors performed a meta-analysis in the review published in Diabetes Care and concluded that there is a 0.39% decrease in HbA1c (A1C) when allowing SMBG. This effect should be interpreted with caution because of the methodological quality of the trials as addressed in the “Methodological issues” section of the review. Also, in one of the two studies in which a statistically significant decrease of A1C was found, only the SMBG group received education (3). A meta-analysis from Ellis et al. (4) concluded that on average, the influence of education itself on A1C is ~0.32%.

However, in the Cochrane Library review, the authors write “Because of differences in baseline data of the patients and type of interventions between the studies, it was not possible to perform either a meta-analysis and/or subgroup or sensitivity analyses.” In this review, they conclude “SMBG might be effective in improving glycemic control in patients with type 2 diabetes who are not using insulin.”

Within a few months, the authors reach different conclusions regarding methodology and supposed effects based on the same set of available information. Which is true: a clinically relevant reduction in A1C or a conclusion that SMBG might be effective in improving glycemic control in patients with type 2 diabetes who are not using insulin?

Nanne Kleefstra, MD
Sebastiaan T. Houteling, MD
Evert van Ballegoede, MD, PhD
Henk J.G. Bilo, MD, PhD, FRCP

From the 1Department of Internal Medicine, Isala Clinics, Zwolle, the Netherlands, and the 2Department of General Practice, University of Groningen, Groningen, the Netherlands.

Address correspondence to Nanne Kleefstra, MD, Langerhans Foundation, Department of Internal Medicine, Isala Clinics, Wezenlanden Location, P.O. Box 10500, 8000 GM Zwolle, Netherlands. E-mail: kleefstra@langerhans.com.

© 2005 by the American Diabetes Association.

References
Self-Monitoring of Blood Glucose in Patients With Type 2 Diabetes Who Are Not Using Insulin

Response to Welschen et al. and Kleefstra et al.

I should take responsibility for the differences between the Cochrane Library analysis and the review that appeared in Diabetes Care (1). In the Cochrane Library analysis, no meta-analysis was done for the reasons given in the letter written by Kleefstra et al. (2). However, in the initial submission to this journal, which utilized the same approach as in the Cochrane Library analysis, the authors concluded that the “level of available evidence for the effect of SMBG on glycemic control in patients with type 2 diabetes who are not using insulin is at present only moderate.” The decision to cite “moderate” evidence was based on their statement, “we did not want to depend on statistical significance only because the studies were rather small. Therefore, findings were considered consistent if more than one of the studies reported the same direction of the effect on the outcome measure.” Thus, regardless of statistical significance in individual studies and in the absence of a meta-analysis, studies going in the same direction could constitute “moderate” evidence.

The reviewers of the initial manuscript recommended rejection. However, I obtained other opinions because I felt that this topic was an important one for our readership. One of the subsequent statistical reviewers argued strongly that there was no reason why a meta-analysis of A1C levels could not be carried out on the data in the randomized clinical trials (RCTs) in spite of the fact that the initial values were different among studies and since initial A1C levels were similar in the control and SMBG groups in each study. This is the genesis of the statistically significant difference of 0.39% in A1C levels between the control and SMBG groups in the six RCTs (3–8) in the recent review in Diabetes Care (1). Statistical significance was found in only two (6,7) of these six RCTs, however.

I would like to point out that in one of them, there were 48 and 40% drop-out rates in the SMBG and control groups, respectively (7). If the nearly half of the SMBG group that failed to complete the study were enriched in those who were showing the least response, the results could be due to self-selection. In the second statistically significant study (6), a difference in counseling between the two groups does not allow the lowered A1C levels to be ascribed to SMBG alone.

In my view, the available evidence does not show that SMBG in diabetic patients not taking insulin leads to lower A1C levels.

MAYER B. DAVIDSON, MD
EDITOR-IN-CHIEF

From the Charles R. Drew University, Los Angeles, California. Address correspondence to Mayer B. Davidson, Clinical Trials Unit, Charles R. Drew University, 1731 E. 120th St., Los Angeles, CA 90059. E-mail: madavid@c dreuw.edu.
© 2005 by the American Diabetes Association.

References

Self-Monitoring of Blood Glucose in Patients With Type 2 Diabetes Who Are Not Using Insulin

Response to Kleefstra et al. and Davidson

In response to Kleefstra et al. (1), we will try to eliminate the confusion concerning the conclusions of our systematic reviews on self-monitoring of blood glucose (SMBG) in patients with type 2 diabetes who are not using insulin, published in Diabetes Care (2) and the Cochrane Library (3).

In the Cochrane Library, we performed a qualitative analysis, and because of the consistency of the results of rather heterogeneous trials, we concluded that the level of evidence that SMBG might be effective in improving glycemic control was moderate. After a lengthy discussion, we decided not to perform a meta-analysis because of clinical heterogeneity between the studies.

Because we considered this topic to be very important to health care professionals in the diabetes field, we also submitted the review to Diabetes Care. The editor also urged us to perform a meta-analysis, as pointed out in his response letter (4), to which we responded positively. We believed that this offered an interesting opportunity to explore the added value of having a quantitative summary estimate. On the basis of the meta-analysis, we concluded that SMBG significantly lowered HbA1c (A1C) by 0.39%, which is clinically relevant compared with the control groups (5).

However, we respectfully disagree with Davidson’s conclusion that the available evidence does not show that SMBG is effective in decreasing A1C levels (4). We believe that the current level of evidence is only moderate, but the direction of the evidence is positive. It is likely that in future studies, this will be shown again, as
Letters

C-Reactive Protein for Cardiovascular Risk Assessment in the Metabolic Syndrome

Response to Kholeif et al.

We appreciate the comments of Dr. Kholeif (1) regarding the utility of C-reactive protein (CRP) measurement in stratifying cardiovascular disease (CVD) risk as it relates to our report of patients with the metabolic syndrome (2). While our data must be interpreted cautiously because they are of a cross-sectional nature, our findings are consistent with those of Ridker et al. (3) showing metabolic syndrome patients with elevated CRP levels to have a less optimistic prognosis than those with normal CRP levels.

We agree with Dr. Kholeif that a single CRP measurement, given its intra-individual biological variability, is not suitable and that the use of multiple measures would establish the certainty of a given level. Our study relied on the single measurement provided by the National Health and Nutrition Examination Survey (NHANES) study and thus did not have duplicate measures over time. Recently, the Centers for Disease Control (CDC)/American Heart Association (AHA) workshop on markers of inflammation and cardiovascular disease did recommend that the mean of only two measures taken 2 weeks apart could be averaged to provide a clinically useful value (4). We also agree that high-sensitivity CRP assays are critical for examining the range over which CHD risk varies; our NHANES report did utilize high-sensitivity CRP measures as recommended by the CDC/AHA statement on the use of CRP in cardiovascular risk stratification (5).

We agree with Dr. Kholeif that more accurate risk assessment might be possible if CRP were regarded as a continuum and included within Framingham risk or other global risk algorithms modeling 10-year risk of coronary heart disease, for example, as Ridker et al. (3) have recommended. Until this is done, however, we feel that the CDC/AHA cut points (6) for categorizing CRP into normal (<1 mg/l), borderline (1–3 mg/l), and high-risk (>3 mg/l) levels are appropriate for stratifying patient risk in combination with Framingham risk estimates or other risk factor information such as LDL cholesterol levels.

We also agree with the CDC/AHA statement regarding the appropriateness of screening those at intermediate global risk for CRP. Given this, many such persons with metabolic syndrome would be indicated for possible screening by CRP to better identify their CVD risk where Framingham or other global risk algorithms may fail to fully address risk given their exclusion of abdominal obesity, elevated triglycerides, and glucose intolerance. Of note is that we have also shown that many with metabolic syndrome have subclinical atherosclerosis (defined by having significant levels of coronary calcium) regardless of estimated Framingham risk. While ~20% of such patients have >20% 10-year CHD risk, ~40% have significant calcium and/or >20% 10-year risk (7), indicating the need to better identify those at significant CVD risk beyond what global risk assessment provides. Nonetheless, we agree that more work from clinical trials is needed to establish whether intervention targeting “high-risk” metabolic syndrome patients, identified either on the basis of elevated CRP or other screening tests, effectively lowers CVD risk.

NATHAN D. WONG, PHD, MPH
SHAISTA MALIK, MD, PHD, MPH

From the Heart Disease Prevention Program, Division of Cardiology, Department of Medicine, University of California, Irvine, Irvine, California.
Address correspondence to Dr. Nathan D. Wong, Heart Disease Prevention Program, C240 Medical Sciences, University of California, Irvine, Irvine, California 92697. E-mail: ndwong@uci.edu.
© 2005 by the American Diabetes Association.

References

References
1. Kleefstra N, Houweling ST, van Ballekom-Campherstraat 7, 1081 BT Amsterdam, the Netherlands.

© 2005 by the American Diabetes Association.


