

OBSERVATIONS

Glial Cell Line-Derived Neurotrophic Factor in the Vitreous of Patients With Proliferative Diabetic Retinopathy

Glial cell line-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 (GFR α 2) in epiretinal membranes (ERMs) in proliferative diabetic retinopathy (PDR), indicating the involvement of GFR α 2 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, multibranching 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 intraocular infusion. Enzyme-linked immunosorbent assay was performed to determine GDNF level using a commercially available immunoassay kit (Promega, Madison, WI). Mann-Whitney *U* test was used to compare GDNF levels.

GDNF was undetectable in all the serum samples examined. Intravitreal GDNF level was significantly higher in the PDR patients (means \pm SD: 156.1 \pm 221.0 pg/ml) than in the control subjects (26.5 \pm 53.2 pg/ml) ($P = 0.0042$). Intravitreal GDNF level was significantly higher in active PDR (206.0 \pm 250.7 pg/ml) than in quiescent PDR (77.7 \pm 135.5 pg/ml) ($P = 0.0388$).

Glial cells are one of the main components of ERMs. Our previous study (2) showed that GFR α 2 mRNA expression level is significantly higher in PDR ERMs than in idiopathic ERMs, and this high

expression level is specific for GFR α 2 among neurotrophin receptors. GFR α 2 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 this study, GDNF was undetectable in the serum samples. It is suggested that the increased level of vitreous GDNF in PDR reflects intraocular GDNF production but not breakdown of the blood-retina barrier.

In conclusion, intravitreal 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.

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References

1. Strelau J, Unsicker K: GDNF family members and their receptors: expression and functions in two oligodendroglial cell lines representing distinct stages of oligodendroglial development. *Glia* 26:291–301, 1999
2. Harada T, Harada C, Mitamura Y, Akazawa C, Ohtsuka K, Ohno S, Takeuchi S, Wada K: Neurotrophic factor receptors in epiretinal membranes after human diabetic retinopathy. *Diabetes Care* 25:1060–1065, 2002
3. Harada C, Harada T, Quah HM, Maekawa F, Yoshida K, Ohno S, Wada K, Parada LF, Tanaka K: Potential role of glial cell line-derived neurotrophic factor receptors in Müller glial cells during light-induced retinal degeneration. *Neuroscience* 122:229–235, 2003

Concordance Between the 2005 International Diabetes Federation Definition for Diagnosing Metabolic Syndrome With the National Cholesterol Education Program Adult Treatment Panel III and the World Health Organization Definitions

Recently, the International Diabetes Federation (IDF) consensus (1) proposed a new definition for diagnosing metabolic syndrome. The new IDF definition includes a lower waist circumference than the National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria (2) for diagnosing abdominal obesity.

Since the most frequently used definitions for metabolic syndrome involve different criteria for diagnosis of obesity, and because differences in the prevalence of metabolic syndrome seem to reproduce differences in the prevalence of adiposity (3), we determined the concordance between the 2005 IDF definition for metabolic syndrome with the ATP III and World Health Organization (WHO) (4) definitions in a population from northern Mexico.

This is a report of a population-based study of apparently healthy men and non-pregnant women aged 30–64 years from Durango City in northern Mexico who were selected through a randomized two-stage cluster sampling procedure.

The cutoff value we used for abdominal obesity was recommended for the IDF consensus for ethnic South and Central Americans (≥ 90 cm in men and ≥ 80 cm in women) and corresponds to the upper quartile in our population. To assess the degree of agreement between different metabolic syndrome definitions, we used the weighted κ test.

A total of 472 (67.4%) women and 228 (32.6%) men were studied. The mean age was 44.7 \pm 11.8 years, and the mean BMI was 29.1 \pm 5.3 kg/m².

derson WG, Levin SR, Sawin CT, Silbert CK, Nuttall FQ, Comstock JP, Colwel JA: Ethnic differences in the glycemic response to exogenous insulin treatment in the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM). *Diabetes Care* 21:510–515, 1998

- Aviles-Santa L, Sinding J, Raskin P: Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 131:182–188, 1999

Kremezin (AST-120) Delays the Progression of Diabetic Nephropathy in Japanese Type 2 Diabetic Patients

Strict 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, adsorbs 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 1/serum creatinine slope was significantly

($P < 0.01$) higher in AST-120-treated subjects (0.0043 ± 0.0036 dl \cdot mg $^{-1}$ \cdot week $^{-1}$) than in control subjects (-0.0174 ± 0.0043 dl \cdot mg $^{-1}$ \cdot week $^{-1}$). AST-120 did not affect HbA_{1c} levels (control subjects: before $7.4 \pm 0.2\%$, after 6 months $7.5 \pm 0.2\%$, NS, vs. AST-120-treated subjects: before $7.0 \pm 0.4\%$, after 6 months $6.8 \pm 0.4\%$; NS) or systolic and diastolic blood pressure levels (control subjects: before $136.4 \pm 4.9/67.0 \pm 4.4$ mmHg, after 6 months $136.1 \pm 3.6/70.9 \pm 1.9$ mmHg, NS, vs. AST-120-treated subjects: before $131.5 \pm 4.3/63.8 \pm 5.5$ mmHg, after 6 months $130.3 \pm 2.5/69.8 \pm 3.0$ 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.

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References

- Aoyama I, Niwa T: An oral adsorbent ameliorates renal overload of indoxyl sulfate and progression of renal failure in diabetic rats. *Am J Kidney Dis* 37 (Suppl. 2):S7–S12, 2001
- Schulman G, Agarwal R, Acharya M, Berl T, Blumenthal S, Kopyt N: KREMEZIN (AST-120) reduces indoxyl sulfate (IS), a profibrotic compound in patients with chronic kidney disease (CKD): results from a multicenter, randomized, double-blind study (Abstract). In *American Society of Nephrology (ASN) 37th Annual Meeting and Scientific Exposition, St. Louis, MO*. Washington, DC, ASN, 2004, p. 162
- Salazar D, Galitz L, Vargas R, Maner J-F: Effect of the oral adsorbent AST-120 on

serum creatinine and other renal markers in patients with chronic kidney disease (Abstract). In *6th International Meeting of the International Federation of Kidney Foundations, Dublin, Ireland, 2005*. New York, IFKF, 2005

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 μ mol/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-% β) 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

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

	Men	Women	P value*
41–50 age-group			
n	378	183	
Glucose tolerance status (NGT/IGT)	296/82	161/22	0.0054
HOMA-%S (%)	122 \pm 60	150 \pm 69	<0.0001
HOMA-% β (%)	77 \pm 24	73 \pm 20	0.0670
BMI (kg/m ²)	24.0 \pm 2.8	22.3 \pm 2.9	<0.0001
51–60 age-group			
n	476	358	
Glucose tolerance status (NGT/IGT)	321/155	290/68	<0.0001
HOMA-%S (%)	132 \pm 73	138 \pm 57	0.1687
HOMA-% β (%)	72 \pm 25	71 \pm 19	0.6670
BMI (kg/m ²)	23.9 \pm 2.6	23.1 \pm 2.9	<0.0001

Data are n or means \pm SD. *By Student's t test or Fisher's exact test. IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

higher in the 41–50 age-group than in 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.

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References

1. Goodman-Gruen D, Barrett-Connor E: Sex differences in the association of endogenous sex hormone levels and glucose tolerance status in older men and women. *Diabetes Care* 23:912–918, 2000
2. Galipeau DM, Yao L, McNeill JH: Relationship among hyperinsulinemia, insulin resistance, and hypertension is dependent on sex. *Am J Physiol Heart Circ Physiol* 283:H562–H567, 2002
3. Levy JC, Matthews DR, Hermans MP: Correct homeostasis model assessment (HOMA) evaluation uses the computer program (Letter). *Diabetes Care* 21:2191–2192, 1998
4. Barret-Connor E, Laakso M: Ischemic heart disease risk in postmenopausal women: effects of estrogen use on glucose and insulin levels. *Arteriosclerosis* 10:531–534, 1990
5. Friday KE, Dong C, Fontenot RU: Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type 2 diabetes. *J Clin Endocrinol Metab* 86:48–52, 2001

6. Kimmerle R, Heinemann L, Heise T, Bender R, Weyer C, Hirschberger S, Berger M: Influence of continuous combined estradiol-norethisterone acetate preparations on insulin sensitivity in postmenopausal nondiabetic women. *Menopause* 6:36–42, 1999
7. Vehkavaara S, Westerbacka J, Hakala-Ala-Pietilä T, Virkamäki A, Hovatta O, Yki-Järvinen H: Effect of estrogen replacement therapy on insulin sensitivity of glucose metabolism and preresistance and resistance vessel function in healthy postmenopausal women. *J Clin Endocrinol Metab* 85:4663–4670, 2000
8. Phillips GB, Jing T, Heymsfield SB: Relationships in men of sex hormones, insulin, adiposity, and risk factors for myocardial infarction. *Metabolism* 52:784–790, 2003
9. Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, Matsuda M, Kondo H, Furuyama N, Kihara S, Nakamura T, Tochino Y, Funahashi T, Matsuzawa Y: Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes* 51:2734–2741, 2002

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.

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 brachial plexopathy; 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.

Brachial plexopathy 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.

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References

1. Dyck PJ, Norell JE, Dyck PJ: Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. *Neurology* 53: 2113–2121, 1999
2. Leedman PJ, Davis S, Harrison LC: Diabetic amyotrophy: reassessment of the clinical syndrome. *Aust NZ J Med* 18:768–773, 1988
3. Riley DE, Shields RW: Diabetic amyotrophy with upper extremity involvement (Abstract). *Neurology* 34 (Suppl. 1):216, 1984
4. Sander HW, Chokroverty S: Diabetic amyotrophy: current concepts. *Semin Neurol* 16:173–178, 1996
5. Wilbourn AJ: Diabetic neuropathies. In *Clinical Electromyography*. Brown WF, Bolton CF, Eds. Boston, MA, Butterworth-Heinemann, 1993, p. 501
6. Williams IR, Mayer RF: Subacute proximal diabetic neuropathy. *Neurology* 26:108–116, 1976
7. Santillan CE, Katirji B: Brachial plexopathy in diabetic ketoacidosis. *Muscle Nerve* 23:271–273, 2000

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: acanthosis nigrans, 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.

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.

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References

1. Reisman J, Corey M, Canny G, Levison H: Diabetes mellitus in patients with cystic fibrosis: effect on survival. *Pediatrics* 86: 374–377, 1990
2. Lombardi F, Raia V, Spagnuolo M, Nugnes R, Valerio G, Ciccarelli G, Franzese A: Diabetes in an infant with cystic fibrosis. *Pediatr Diabetes* 5:199–201, 2004
3. Polak M, Shield J: Neonatal and very-early-onset diabetes mellitus. *Semin Neonatol* 9:59–65, 2004

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 amenorrhoea because of recurrent episodes of nocturnal hypoglycemia. Glycemic control during pregnancy was excellent in six patients (HbA_{1c} [A1C] 5.2–6.9%) and suboptimal in one (A1C 6.4–8.1%), and overall the mean A1C was 6.4%. The occurrence of hypoglycemia reduced in the two patients that converted to insulin glargine. Hypertension complicated two pregnancies, while five were uncomplicated. All patients delivered at term (37–40 weeks), three vaginally and four by cesarean section. Seven children, mean weight 4,180 g (2,475–4,675), were born without congenital abnormalities and had no neonatal complications during routine observation at the neonatal care unit.

Insulin glargine has several potential advantages in the glucose management of type 1 diabetes, as illustrated by the excellent glycemic control with its use in six of the seven women and the disappearance of nocturnal hypoglycemia after conversion in two of them. Insulin glargine differs from human insulin by the addition of two arginine residues to the B-chain and a substitution of an asparagine residue for a glycine at position 21 of the A-chain. This modified human insulin molecule had no adverse effects on

reproduction, embryo-fetal development, and postnatal development in rats (2). The present observational study in seven pregnancies puts forward the notion that insulin glargine is a possible safe insulin in human pregnancy.

Insulin glargine shares a similar time course with human insulin for insulin receptor binding, despite a somewhat lower affinity for the insulin receptor (6). In contrast, insulin glargine has a sixfold-higher binding affinity for IGF-1 receptors, and experimental studies suggest an increased mitogenicity on tumor cell-lines at high doses (6). Does this justify a ground to fear the use of insulin glargine in human pregnancy? Only small amounts of maternal insulin (1–5%) pass the placenta and enter the fetal circulation. This has been documented for human insulin (7) and the short-acting insulin analog insulin lispro (8), with insulin levels of (very) high magnitude. It is most likely that the placental transfer of insulin glargine is similar to the transfer of human insulin and that of other insulin analogs (7,8), although this has to be proven conclusively. Considering the expected marginal amount of placental insulin transfer, if any, the use of insulin glargine in pregnancy is not likely to put 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.

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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-

tes. *Diabetes Care* 28:950–955, 2005

- Hofmann T, Horstmann G, Stammberger I: Evaluation of the reproductive toxicity and embryotoxicity of insulin glargine (LANTUS) in rats and rabbits. *Int J Toxicol* 21:181–189, 2002
- Devlin JT, Hothersall L, Wilkis JL: Use of insulin glargine during pregnancy in a type 1 diabetic woman. *Diabetes Care* 25:1095–1096, 2002
- Holstein A, Plaschke A, Egberts EH: Use of insulin glargine during embryogenesis in a pregnant woman with type 1 diabetes. *Diabet Med* 20:779–780, 2003
- Di Gianni G, Volpe L, Lencioni C, Chatzianagnostou K, Cuccuru I, Ghio A, Benzi L, Del Prato S: Use of insulin glargine during the first weeks of pregnancy in five type 1 diabetic women. *Diabetes Care* 28:982–983, 2005
- Bolli GB, Owens DR: Insulin glargine. *Lancet* 356:443–445, 2000
- Challier JC, Haugel S, Desmaizieres V: Effects of insulin on glucose uptake and metabolism in the human placenta. *J Clin Endocrinol Metab* 62:803–807, 1986
- Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G: Transfer of insulin lispro across the human placenta: in vitro perfusion studies. *Diabetes Care* 26:1390–1394, 2003

seems reasonable to recommend that ALL (capitalization mine) patients with type 2 diabetes and hypertension . . . should be routinely considered for statin therapy.”

The American Diabetes Association Clinical Practice Recommendations (2), published in January 2005, stated that for lipid control, the primary goal is an LDL level <2.6 mmol/l (100 mg/dl) and a lower LDL cholesterol goal of <1.8 mmol/l (70 mg/dl) for diabetic patients with overt cardiovascular disease. In Sever et al.’s article (1), the subject’s average LDL cholesterol was 3.3 mmol/l (128 mg/dl) at the baseline and decreased to a trough of an average of 2.08 mmol/l (80.4 mg/dl) at 2 years and an average of 2.15 mmol/l (83.1 mg/dl) at the end of the study.

The article’s eligibility criteria included subject cholesterol:HDL cholesterol ratio ≥ 6 and total cholesterol ≤ 6.5 mmol/l (251 mg/dl) but did not break them down further into different degrees of lower cholesterol or LDL cholesterol categories. I am drawing a distinction between what the article showed (lowering of cardiovascular events by atorvastatin for a certain group of patients, excluding those with cholesterol >6.5 mmol/l [250 mg/dl], etc.) and what the authors claimed to show that “It now therefore seems reasonable to recommend that ALL (capitalization mine) patients with type 2 diabetes and hypertension (at least all those >50 years of age and/or having diabetes for ≥ 10 years) should be routinely considered for statin therapy.” 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.

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COMMENTS AND RESPONSES

Reduction in Cardiovascular Events With Atorvastatin in 2,532 Patients With Type 2 Diabetes: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA)

Response to Sever et al.

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 made a significant impact in reducing cardiovascular events in diabetic patients without markedly elevated cholesterol.

However, I cannot agree with the authors’ conclusion that “It now therefore



References

- Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O’Brien E, Ostergren J: Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA). *Diabetes Care* 28:1151–1157, 2005
- American Diabetes Association: Standards of medical care in diabetes. *Diabetes Care* 28 (Suppl. 1):S4–S36, 2005

Reduction in Cardiovascular Events With Atorvastatin in 2,532 Patients With Type 2 Diabetes: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA)

Response to Tseng

We agree with current recommendations (1,2) that the use of statins should be based on absolute risk rather than lipid levels. All those with diabetes and hypertension who are >50 years old and/or have had diabetes for ≥ 10 years are at $\geq 20\%$ risk of a major cardiovascular event in the next 10 years and as such are above the currently recommended threshold for statin therapy (1,2).

In the diabetic subgroup of the Heart Protection Study (3), those allocated simvastatin 40 mg who had an LDL cholesterol <3 mmol/l at baseline did at least as well in terms of major vascular events prevented as those with higher LDL cholesterol. Furthermore, mean levels in this diabetic group overall fell to 1.8 mmol/l on statin treatment. Hence, the LDL levels of about half of the diabetic subjects fell to <1.8 mmol/l. In the Collaborative Atorvastatin Diabetes Study trial (4), 84% of the diabetic patients were also hypertensive, and the striking cardiovascular benefits observed were equally large (38 and 37% reduction in the primary end point) among those with LDL cholesterol

≥3.1 mmol/l and <3.1 mmol/l, respectively.

These results are commensurate with those reported for the diabetic subgroup of ASCOT-LLA stratified by baseline total cholesterol (28, 26, and 16% reductions in total cardiovascular events and procedures for those with baseline cholesterol concentrations of <5.0, 5.0 to <6.0, and ≥6.0 mmol/l, respectively) (5).

These three datasets provide compelling evidence that the benefits of statin therapy are likely to be realized across the full range of LDL cholesterol. For optimal effect, statins should be targeted at those above a given level of absolute risk rather than above an arbitrary lipid level so that the reductions in relative risk of cardiovascular events will generate sufficient absolute benefit. The threshold for cardiovascular risk currently recommended is ≥20% over 10 years (1,2); hence, we feel the final concluding statement of our article (5) is fully justified and commensurate with best evidence.

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© 2005 by the American Diabetes Association.

References

- Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM, BHS guidelines working party for the British Hypertension Society: British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 328:634–640, 2004
- European Society of Hypertension-European Society of Cardiology Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 21:1011–

1053, 2003

- Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005–2016, 2003
- Collhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH on behalf of the CARDS investigators: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364:685–696, 2004
- Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers, G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, O'Brien E, Ostergren J: Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). *Diabetes Care* 28:1151–1157, 2005

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 HbA_{1c} (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?

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References

- Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 28:1510–1517, 2005
- Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. *Cochrane Database Syst Rev* 2:CD005060, 2005
- Schwedes U, Siebolds M, Mertes G; SMBG Study Group: Meal-related structured self-monitoring of blood glucose: effect on diabetes control in non-insulin-treated type 2 diabetic patients. *Diabetes Care* 25:1928–1932, 2002
- Ellis SE, Speroff T, Dittus RS, Brown A, Pichert JW, Elasy TA: Diabetes patient education: a meta-analysis and meta-regression. *Patient Educ Couns* 52:97–105, 2004

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 glyce-mic 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.

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References

1. Welschen LMC, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stolman WAB, Bouter LM: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 28:1510–1517, 2005
2. Kleefstra N, Houweling ST, van Balle-goie E, Bilo HJG: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin (Letter). *Diabetes Care* 28:2596, 2005
3. Fontbonne A, Billault B, Acosta M, Percheron C, Varenne P, Besse A, Eschwege E, Monnier L, Slama G, Passa P: Is glucose self-monitoring beneficial in non-insulin-treated diabetic patients? Results of a randomized comparative trial. *Diabetes Metab* 15:255–260, 1989
4. Allen BT, DeLong ER, Feussner JR: Impact of glucose self-monitoring on non-insulin-treated patients with type II diabetes mellitus: randomized controlled trial comparing blood and urine testing. *Diabetes Care* 13:1044–1050, 1990
5. Muchmore DB, Springer J, Miller M: Self-monitoring of blood glucose in overweight type 2 diabetic patients. *Acta Diabetol* 31:215–219, 1994
6. Schwedes U, Siebolds M, Mertes G for the SMBG Study Group: Meal-related structured self-monitoring of blood glucose: effect on diabetes control in non-insulin-treated type 2 diabetic patients. *Diabetes Care* 25:1928–1932, 2002
7. Guerci B, Drouin P, Grange V, Bougneres P, Fontaine P, Kerlan V, Passa P, Thivolet C, Vialettes B, Charbonnel B: Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveil-

lance Intervention Active (ASIA) study. *Diabetes Metab* 29:587–594, 2003

8. Davidson MB, Castellanos M, Kain D, Duran P: The effect of self-monitoring of blood glucose concentrations on glycosylated hemoglobin levels in diabetic patients not taking insulin: a blinded, randomized trial. *Am J Med* 118:422–425, 2005

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 HbA_{1c} (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

was also suggested in the point discussion in *Diabetes Care* accompanying our review (6).

We explicitly mentioned in our discussion of the review in *Diabetes Care* that the results of the meta-analysis should be interpreted with caution since the methodological quality of the trials was poor in more than half of the studies and the studies were heterogeneous. This implies that there are important limitations on the meta-analysis.

In our two reviews, we used a different approach to reach the same conclusion: there may be a clinically relevant effect of SMBG on A1C, although the evidence for this effect is still moderate. Both reviews give similar recommendations for research and clinical practice and point out the need for a large randomized controlled trial to draw final conclusions on this important topic.

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References

1. Kleefstra N, Houweling ST, van Balle-gooye E, Bilo HJG: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin (Letter). *Diabetes Care* 28:2596, 2005
2. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care* 28:1510–1517, 2005
3. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, Bouter LM: Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. *Cochrane Database Syst Rev* 2:CD005060, 2005
4. Davidson MB: Self-monitoring of blood glucose in patients with type 2 diabetes

who are not using insulin (Letter). *Diabetes Care* 28:2597, 2005

5. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
6. Ipp E, Aquino RL, Christenson P: Point: self-monitoring of blood glucose in type 2 diabetic patients not receiving insulin: the sanguine approach. *Diabetes Care* 28: 1528–1530, 2005

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 intraindividual 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. (5) 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.

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References

1. Kholeif MA: C-reactive protein for cardiovascular risk assessment (Letter). *Diabetes Care* 28:1833–1834, 2005

2. Malik S, Wong ND, Frankin SS, Pio J, Fairchild C, Chen R: Cardiovascular disease in U.S. persons with metabolic syndrome, diabetes, and elevated C-reactive protein. *Diabetes Care* 28:690–693, 2005
3. Ridker PM, Buring JE, Cook NR, Rafai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 107:391–397, 2003
4. Myers GL, Rifai N, Tracy RP, Roberts WL, Alexander RW, Biasucci LM, Catravas JD, Cole TG, Cooper GR, Khan BV, Kimberly MM, Stein EA, Taubert KA, Wamick GR, Waymack PP, the Centers for Disease Control, the American Heart Association: CDC/AHA workshop on markers of inflammation and cardiovascular disease: application to clinical and public health practice: report from the Laboratory Science Discussion Group. *Circulation* 110:545–549, 2004
5. Ridker PM, Wilson PWF, Grundy SM: Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation* 109:2818–2825, 2004
6. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F, the Centers for Disease Control and Prevention, the American Heart Association: Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107:499–511, 2003
7. Wong ND, Sciammarella M, Miranda-Peats R, Whitcomb B, Gallagher A, Hachamovich R, Friedman J, Hayes S, Berman DS: The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. *J Am Coll Cardiol* 41:1547–1553, 2003