OBSERVATIONS

A Comparison in a Clinical Setting of the Efficacy and Side Effects of Three Thiazolidinediones

Three thiazolidinediones (TZDs) are currently available for clinical use in the U.S.: troglitazone, rosiglitazone, and pioglitazone. Because we are aware of no comparative studies of these three agents, we wish to report our initial experience with their efficacy in lowering glucose and improving dyslipidemia, as well as their side effects.

When clinically indicated, patients were started consecutively on each of the three TZDs as they became available. Results from the TZD groups, each of which comprised ~50 patients, were reviewed. We excluded patients who were not on maximal recommended doses of TZDs; namely, 600 mg of troglitazone, 8 mg of rosiglitazone (twice a day for monotherapy), and 45 mg of pioglitazone. Patients were also excluded if they started during the observation period on a medication that would influence their lipid profile or weight. Only data at baseline and between 2 and 4 months of treatment were analyzed.

After exclusion, the total numbers of patients in each group, troglitazone, rosiglitazone, and pioglitazone were 35, 36, and 30, respectively. Their average ages were 60.1, 59.2, and 60.2 years; sex, 65, 50, and 38% male to total patients; weight, 89.7, 92.1, and 87.2 kg; and initial HbA_{1c}, 8.50, 8.73, and 8.72%. Patients were taking other medications for hyperglycemia treatment in 89, 76, and 81% of each group.

Table 1 compares the effect of each TZD. HbA_{1c} was similarly reduced with each agent, especially when patients with an initial HbA_{1c} >7.9% were studied. The magnitude of reduction reported is greater than that reported elsewhere (1) and may reflect the self-education and self-monitoring of blood glucose that is part of our program.

We observed that the beneficial effect on lipids was most with pioglitazone and least with rosiglitazone during this 2- to 4-month observation period. The average initial HDL cholesterol in each group, namely, troglitazone, rosiglitazone, and pioglitazone was 46.6, 43.1, and 50.7 mg/dl, respectively; LDL cholesterol was 109.1, 102.9, and 96.4 mg/dl, respectively; and the triglycerides were 223, 172, and 207 mg/dl, respectively. The lack of effect of rosiglitazone on triglycerides and the elevation of LDL cholesterol (2) and the beneficial effect on HDL and triglycerides of pioglitazone (3) have been previously reported.

In addition, the weight increase with pioglitazone was noticeably greater than that observed with the other two agents. However, the incidence of edema as the reason for discontinuing a medication was not greater with pioglitazone than with rosiglitazone. The weight gain cannot be explained on improvement of glucose control since all agents reduced the HbA_{1c} equally. Perhaps the increase in weight is due to the increase in the number and size of adipocytes (4).

We conclude from our observations that each TZD appears equal in its glucose lowering ability, and thus, the selection of an agent is based on other factors, such as its lipid benefit and side effects. We look forward to larger and longer-term studies to confirm this finding and to compare the liver toxicity of each agent.

Table 1—*Comparison of the effects of the three TZDs*

	Troglitazone	Rosiglitazone	Pioglitazone
HbA_{1c} (%)	−1.57 (34)	−1.89 (25)	−1.93 (27)
Initial HbA_{1c} >7.9% (%)	−2.37 (19)	−2.66 (18)	−2.54 (17)
HDL cholesterol (mg/dl)	1.5 (17)	0.5 (23)	6.5 (18)
LDL cholesterol (mg/dl)	7.2 (17)	11.5 (17)	−1.1 (17)
Triglycerides (mg/dl)	−5 (17)	47 (23)	−21 (17)
Weight (kg)	0.7 (34)	0.5 (25)	2.6 (26)
Edema	0 (35)	3 (38)	2 (30)
Other side effects*	0 (35)	5 (38)	1 (30)

*With rosiglitazone, one case each of alanine aminotransferase elevation two times the upper limit of normal with return to normal in 1 month; abdominal pain; rash; dizziness; and "felt bad." With pioglitazone, one case of noncardiac chest pain. The number of patients in each treatment group is presented within parentheses.

ALLEN B. KING, MD

From the Diabetes Care Center, Salinas, California.

Address correspondence to Allen B. King, MD, Diabetes Care Center, 1119 Pajaro St., Salinas, CA 93901. E-mail: dmcarectr@aol.com.

A.B.K. has been on an advisory panel and received honoraria for speaking engagements from Parke-Davis, Sankyo, SmithKline Beecham, Lilly, and Takeda.

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Nocturnal Glucose Control and Free Insulin Levels in Children With Type 1 Diabetes by Use of the Long-Acting Insulin HOE 901 as Part of a Three-Injection Regimen

Asymptomatic nocturnal hypoglycemia is a common problem in patients with type 1 diabetes: prevalence rates of up to 70% in children and 50% in adolescents have been reported (1,2). Failure to recognize hypoglycemia may reduce counterregulation (3), which could then increase the risk of subsequent

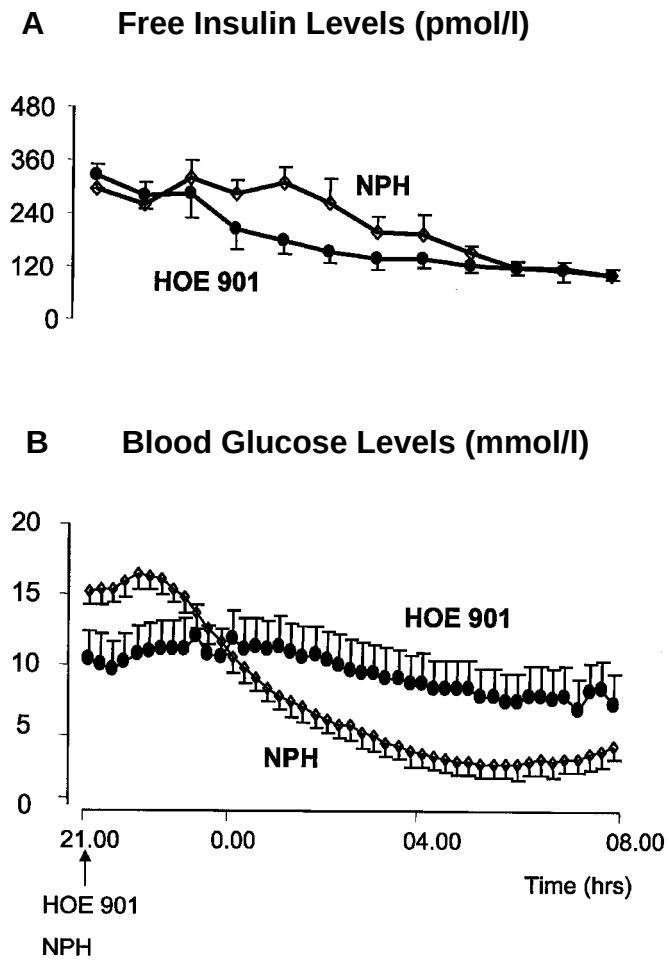

Figure 1—*Overnight (9:00 P.M. to 8:00 A.M.) mean free insulin (A) and blood glucose (B) levels after subcutaneous injection of HOE 901 (●) and NPH insulin (◇).*

prolonged and severe hypoglycemia. It is widely accepted that one of the most important risk factors for the development of nocturnal hypoglycemia is overinsulinization during the early part of the night (4). This phenomenon is attributed mainly to the pharmacokinetic properties of current insulin preparations, especially those used for basal insulin supply, such as NPH insulin. In contrast to NPH insulin, which shows a peak of absorption 4–6 h after injection, the new insulin analog HOE 901 (Hoechst Marion Roussel, Frankfurt, Germany) provides a constant 24-h supply without any peak of absorption. This action profile should theoretically result in lower free insulin levels during the early hours of the morning, thereby reducing the risk of nocturnal hypoglycemia. To test this hypothesis, we examined insulin kinetics and glucose levels overnight in subjects given HOE 901 compared with those in subjects given NPH insulin as part of a three-injection regimen during a randomized parallel open clinical trial.

A total of 12 children with type 1 diabetes (8 boys) with a mean diabetes duration of 4.1 years (range 1.1–6.6), a mean age of 11.7 years (11.3–14.2), and a mean HbA_{1c} concentration of 8.8% (range 7.3–10.0) were recruited in Oxford as part of a large multicenter clinical trial in which 361 patients were randomized in 30 centers from 10 countries. In Oxford, six children were randomized to HOE 901, and six children were randomized to NPH insulin. The children in the HOE 901 treatment group injected HOE 901 once a day at bedtime (8:00–10:00 P.M.) and regular insulin before breakfast (7:30–8:00 A.M.) and dinner (5:30–6:00 P.M.). The children in the NPH treatment group injected a mixture of NPH insulin and regular insulin before breakfast, regular insulin before dinner, and NPH insulin at bedtime. None of the children was taking drugs other than insulin, and none had diabetic complications. In Oxford, all children were also asked to undergo an overnight profile. The randomized study and the overnight profiles were approved by the local ethics committee, and informed consent was obtained from all of the patients and their parents.

A cohort of two girls and two boys from the HOE 901 group and four boys from the NPH group agreed to undergo a single overnight metabolic profile (9:00 P.M. to 8:00 A.M.), performed after 3 months of treatment, when metabolic control had been stabilized. On the day of the overnight studies, the patients administered their usual regular insulin into the periumbilical region of the abdominal wall before dinner and administered their long-acting insulin in the thigh. The insulin dosages were established by medical history. The children received a standard evening meal (50% carbohydrates, 15% protein, and 35% fat) and a snack at 9:00 P.M.; both meals were adjusted to the children's usual intake of carbohydrates, as determined by a dietician. At 9:00 P.M., the patients went to bed and were encouraged to sleep. Samples were taken every 15 min for measurements of blood glucose levels and every 60 min for measurements of free insulin levels. Blood glucose levels were measured with a YSI 2300 Stat Plus Analyzer (YSI, Yellow Springs, OH) (intra-assay coefficient of variation 2.6%, interassay coefficient of variation 8.8%). Asymptomatic hypoglycemia was defined as two consecutive blood sugar results of <3.5 mmol/l without spontaneously reported symptoms. Free insulin levels were determined by means of a radioimmunoassay (Insulin RIA; BioChem ImmunoSystems, Freiburg, Germany) (within-run precision 0.9–5.3%, accuracy 92–107%; between-run precision 4.8–6.7%, accuracy 91–108%). HbA_{1c} values were determined by means of high-pressure liquid chromatography (Diamat; Bio-Rad Laboratories, Hemel Hempstead, Herts., U.K.). The normal HbA_{1c} range was 4.3–6.1%.

Data are means (range). The HOE 901 and NPH groups, respectively, were comparable for age (11 years [10.3–13.8] vs. 12.1 years [10.3–14.3]), duration of diabetes (4.1 years [2.0–6.6] vs. 2.5 years [1.7–3.5]), HbA_{1c} values (7.8% [7.5–8.2] vs. 7.6% [6.3–8.7], BMI (21 [18–25] vs. 18

[17–26]), and total insulin requirement at baseline (1.2 U/kg [1.0–1.5] vs. 1.1 U/kg [0.9–1.6]). The total percentage of insulin given as long-acting insulin each day was 53.2% (49.9–58.5) in the HOE 901 group and 73.2% (70.1–78.0) in the NPH group. However, in the HOE 901 group, the total amount of long-acting insulin given at bedtime was 0.6 U/kg (0.56–0.75) and the total amount of NPH insulin at bedtime was 0.3 U/kg (0.2–0.48). Children in the HOE 901 treatment group required more regular insulin in the evening than those children in the NPH insulin group (0.3 U/kg [0.26–0.4] vs. 0.14 U/kg [0.07–0.2], respectively).

At 9:00 P.M., blood glucose levels (10.6 mmol/l [4.3–18.3] vs. 15.8 mmol/l [12.6–17.8]) and free insulin levels (294.6 pmol/l [180.6–570] vs. 321 pmol/l [240–371.4]) in the HOE 901 and NPH groups, respectively, were not different. For the first 2 h, free insulin levels were high in both groups. Subsequently, in the HOE 901 group, despite the administration of significantly higher doses of insulin at bedtime, no further peak of insulin was observed. Free insulin levels only declined slowly, thus confirming that HOE 901 is absorbed slowly and regularly, which results in a smoother and almost peakless profile, as shown in previous pharmacokinetic studies (5). In contrast, after the injection of NPH insulin, free insulin levels continued to rise and did not decline until 4:00 A.M., which caused unphysiological high insulin levels during the early part of the night, when, physiologically, relatively small amounts of insulin are required (Fig. 1*A*) (4). These differences in free insulin levels were reflected in the overnight blood glucose control. In the NPH treatment group, blood glucose levels fell slowly but dramatically during the first part of the night. The nadir was reached in the early hours of the morning (4:00–6:00 A.M.), when insulin levels were already waning. In contrast, in the HOE 901 group, blood glucose levels showed minimal excursion, staying stable for almost the whole duration of the study night (Fig. 1*B*). We observed three episodes of asymptomatic hypoglycemia in the NPH treatment group, in contrast to one episode in the HOE 901 group. It might be argued, however, that blood glucose control overnight was not optimal in the HOE 901 treatment group and that more long-acting insulin should have been administered to obtain normoglycemia. Normally, the target for adjusting the evening long-acting insulin dose is the fasting blood glucose measurement of the following morning. In the HOE 901 group, the mean fasting blood glucose level was 6.8 mmol/l (range 4.4–13.4). When using the regimen of NPH insulin and regular insulin, we might be reluctant to increase the evening NPH insulin based on these readings, because doing so might increase the already high risk of nocturnal hypoglycemia. However, a more stringent titration might be possible with HOE 901 because of the reduced frequency of nocturnal hypoglycemia.

These data indicate that the use of NPH insulin leads to high free insulin levels overnight, whereas the use of the insulin analog HOE 901 supplies lower free insulin levels that lead to more stable blood glucose control. This might be beneficial to the treatment of type 1 diabetes, especially in terms of prevention of nocturnal hypoglycemia.

ANGELIKA MOHN, MD
SALLY STRANG, SRN, RSCN
KARIN WERNICKE-PANTEN, MD
ANNA M. LANG, PHD
JULIE A. EDGE, MD
DAVID B. DUNGER, MD

From the Department of Paediatrics (A.M., S.S., J.A.E., D.B.D.), John Radcliffe Hospital, University of Oxford, Oxford, U.K.; and the Clinical Development (K.W.-P.) and Drug Metabolism/Pharmacokinetics (A.M.L.) Departments, Hoechst Marion Roussel, Frankfurt, Germany.

Address correspondence to David B. Dunger, FRCP, MD, Department of Paediatrics, John Radcliffe Hospital, Headley Way, OX3 9DU, Oxford, U.K. E-mail: david.dunger@paediatrics.ox.ac.uk.

K.W.-P. and A.M.L. are employed by Hoechst Marion Roussel, which manufactures and markets the insulin analog HOE 901.

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Increase in Serum Ceruloplasmin Levels Is Correlated With a Decrease of Serum Nitric Oxide Levels in Type 2 Diabetes

Ceruloplasmin (Cp) is a circulating blue multicopper oxidase that contains >95% of copper in the plasma. Although its precise physiological roles are still unknown, Cp's multiple functions, including oxidization of LDL, have been reported (1,2). Oxidized LDL (Ox-LDL) is a well-known atherogenic factor (3). Therefore, an increase in serum Cp levels is expected to act as an atherogenic factor. Increases in serum Cp levels have been reported under many conditions, including diabetes (2,4). Therefore, in diabetes, observable increased serum Cp levels should cause LDL oxidization. An increased level of Ox-LDL is known to inhibit nitric oxide (NO) production (5), and a decreased level of NO is known to impair the endothelium-dependent relaxation of arteries, the impairment of which is a factor causing atherosclerosis (6). Thus, increased serum Cp levels in diabetes might account for the early progression of atherosclerosis in the condition through the mechanisms of increasing Ox-LDL and thereby inhibiting NO production. To assess the hypothesis mentioned above, we attempted to determine whether the serum Cp levels correlate with the serum NO levels.

We recruited 50 outpatients with type 2 diabetes (DM group) and 50 healthy nondiabetic subjects (control group) for this study. None of the subjects in the DM group had additional diseases known to

increase or decrease serum Cp levels. Patients who were positive for an antibody against human GAD were excluded as having type 1 diabetes. Age and sex were matched between the two groups (DM group vs. control group: age, 49.5 ± 10.3 vs. 47.4 ± 6.8 years; sex [male/female], 29 vs. 21). Duration of illness (8.5 ± 4.5 years) and blood level of HbA_{1c} (7.7 ± 1.1%) were also monitored in the DM group. Serum levels of NO were determined as NOx, which is the amount of NO metabolites, NO_2^- and NO_3^-. Serum Cp and NOx levels were measured at a commercial laboratory (Mitsubishi Kagaku Bioclinical Laboratory, Tokyo). Measured values of serum Cp levels were transformed to their logarithms for statistical analysis. The statistical significance of the differences between groups was determined by the Student's *t* test. Correlations between variables were assessed using a univariate linear-regression analysis. $P < 0.05$ was accepted as statistically significant.

The serum NOx levels of the DM group were significantly lower than those of the control group (36.0 ± 25.6 vs. 52.1 ± 27.8 mmol/l, $P = 0.003$). This decrease seemed to be explained by the fact that the serum NOx levels were significantly correlated with the serum Cp levels in the DM group ($r = -0.382$, $P = 0.006$) but not in the control group ($r = 0.004$, $P = 0.976$). Namely, the serum NOx levels were decreased in the DM subjects with the increased serum Cp levels. Serum NOx levels were not correlated with age, duration of illness, or urinary albumin excretion, but they were significantly different between the sexes (male/female: 52.2 ± 30.8 vs. 32.9 ± 18.0, $P = 0.001$). Although serum NOx levels were different between the sexes, the correlation of serum NOx levels with the serum Cp levels observed in the DM group was similar between the sexes. These results support the aforementioned hypothesis.

MAKOTO DAIMON, MD
KAZUHIKO SUGIYAMA, MD
TAMOTSU SAITOH, MD
HIROSHI YAMAGUCHI, MD
AKIHIKO HIRATA, MD
HIROSHI OHNUMA, MD
MASAHIKO IGARASHI, MD
HIDEYUKI EGUCHI, MD
HIDEO MANAKA, MD
TAKEO KATO, MD

From the Third Department of Internal Medicine (M.D., T.S., H.Y., A.H., H.O., M.I., H.E., H.M., T.K.), Yamagata University School of Medicine; and the Department of Internal Medicine (K.S.), Yamagata Saisei Hospital, Yamagata, Japan.

Address correspondence to Makoto Daimon, MD, the Third Department of Internal Medicine, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan. E-mail: mdaimon@med.id.yamagata-u.ac.jp.

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CCTTT-Repeat Polymorphism in the Human *NOS2*-Promoter Confers Low Risk of Diabetic Nephropathy in Type 1 Diabetic Patients

Diabetic nephropathy (DN) is a partly genetically determined life-threatening complication of diabetes that affects ~40% of all people with type 1 diabetes. Nitric oxide (NO) has widespread physiological functions ranging from cell communication to cell defense and injury. In the kidney, under normal physiological conditions, NO participates in the regulation of the glomerular microcirculation by modulating afferent arteriolar tonus and relaxation of the mesangium cells and contributes to the regulation of renal sodium and renin release. Reducing the NO levels by inhibition of the NO-generating enzymes resulted in glomerular disease and systemic as well as glomerular hypertension in animal models, suggesting a renoprotective role for NO. In the pathogenesis of DN, NO has been proposed to induce glomerular hyperfiltration, which is characteristic of the early stage of DN. In the later stages, endothelial damage due to hyperglycemia-induced accumulation of advanced glycosylation end-products may result in *1*) decreased NO production due to the endothelial damage, and/or *2*) quenching of NO by the advanced glycosylation end-products themselves, and/or *3*) impaired NO-mediated cyclic guanosine 3′,5′-monophosphate generation due to hyperglycemia-induced protein kinase C, with a subsequent decrease in glomerular function. The inducible form of nitrogen oxide synthase (iNOS), initially isolated from macrophages upon cytokine and endotoxin stimulation, has also been identified in glomerular mesangial cells, vascular smooth muscle cells, and vascular endothelial cells (1).

Recently, a penta-repeat polymorphism within the human iNOS gene (*NOS2*) promoter was identified (2). In a recent study, association of this polymorphism to low risk of diabetic retinopathy in a mixed type 1 and type 2 diabetic population was reported (3). Furthermore, in a promoter activity assay, the disease protective allele was shown to exhibit increased promoter activity (3). In the present study, we have tested this penta-repeat polymorphism 2.6 kb upstream in the *NOS2*promoter region in a large Danish series of type 1 diabetic patients selected for overt DN or persistent normoalbuminuria, 358 and 193 individuals, respectively (Table 1). In total, 10 alleles were identified, ranging from 8 to 17 penta-repeats (A8–A17). The allelic distribution in type 1 diabetic patients with and without nephropathy is shown in Table 2. No significant difference in overall distribution of alleles was observed comparing the two groups (χ^2: 14.51; df: 9; $P = 0.11$). Since the allele A14 has been previously suggested to protect against one form of microangiopathy (severe diabetic retinopathy) (3), we compared the distribution of this particular allele between the two groups

Table 1—*Demographic data*

	Nephropathy	Normoalbuminuria	*P*
Sex (M/F)	213/145	119/74	NS
Age (years)	42.7 ± 10.9	42.7 ± 10.2	NS
Duration of diabetes (years)	28 ± 8	27 ± 8	NS
Creatinine	104 (54–684)	76 (40–116)	0.001
HbA_{1c} (%)	9.4 ± 1.5	8.5 ± 1.1	0.001
Systolic blood pressure (mmHg)	146 ± 22	132 ± 18	0.001
Diastolic blood pressure (mmHg)	83 ± 12	76 ± 10	0.001
Urinary albumin excretion rate (mg/24 h)	614 (10–14,545)*	10 (1–30)	—

Data are means ± SD or medians (range). Patient groups were matched by sex, age, and diabetes duration. The clinical diagnosis of nephropathy was based on the following criteria: persistent albuminuria >300 mg/24 h in at least two of three consecutive 24-h urine collections; presence of retinopathy; and the absence of any clinical or laboratory evidence of other kidney or renal tract disease. *Some patients with previously persistent albuminuria had at the time of investigation a urinary albumin excretion rate <300 mg/24 h due to antihypertensive treatment.

Table 2—*Allelic distribution of the CCTTT repeat polymorphism among type 1 diabetic patients with diabetic nephropathy and persistent normoalbunimuria*

	Nephropathy		Normoalbuminuria	
Allele	*n*	Frequency	*n*	Frequency
A8	5	0.007	9	0.02
A9	28	0.04	19	0.05
A10	93	0.13	39	0.1
A11	142	0.20	75	0.19
A12	253	0.35	128	0.33
A13	127	0.18	67	0.17
A14*	37	0.05	35	0.09*
A15	19	0.03	8	0.02
A16	11	0.02	6	0.02
A17	1	0.001	0	0
Total	716	1.0	386	1.0

No significant differences in overall allelic distributions for nephropathy versus normoalbuminuria were noted. *When comparing the frequency of the A14 allele between normoalbuminuric patients (9%) and patients with DN (5%), a significant difference is observed (P = 0.02, corrected for two comparisons). Samples were genotyped by polymerase chain reaction (FP: 5′-CAC CCC TGG AAG CCT ACA ACT-3′ and RP: 5′-GCC TGG GCA ACA TAG TGA GAT-3′) and [α-^{33}P]dCTP incorporation, followed by 6% PAGE and exposure to X-ray films.

and found a significantly higher frequency of A14 among normoalbuminuric type 1 diabetic patients (9%) compared with type 1 diabetic patients with DN (5%) (P = 0.02, corrected for two comparisons). Only one patient (normoalbuminuric) was homozygous for the A14 allele. When we stratified the two groups for retinopathy, no statistical differences in overall allelic distribution or the A14 frequencies were seen between groups (data not shown).

From the work of Warpeha et al. (3), it is not clear how the data from a mixed type 1 and type 2 diabetic population were stratified for nephropathy status. In an attempt to replicate the findings of Warpeha et al., we compared the frequency of A14 in all type 1 diabetic patients having proliferative retinopathy regardless of nephropathy status (29 of 524 individuals) to the frequency observed among normoalbuminuric type 1 diabetic patients without retinopathy (13 of 134 individuals). A trend was seen in A14 being negatively associated to retinopathy (χ^2: 2.81; df: 1; P = 0.09). In our study group, selected for studying effects in patients with DN, we found that the A14 allele was primarily associated with low risk of DN, whereas only a trend for association with proliferative retinopathy could be demonstrated.

Other genes have been investigated in relation to DN. Since the main cause of premature death in insulin-dependent subjects with DN is cardiovascular events, genes potentially increasing the risk for cardiovascular disease have been the subject of investigation. Because experimental and clinical studies (4) suggest that an increase in glomerular capillary pressure can cause diabetic glomerulosclerosis, genes of the renin-angiotensin system, especially, have been investigated. The DD genotype of the ACE gene I/D polymorphism has been associated with higher levels of circulating ACE than ID and II genotypes, and has been found to be more frequent in patients with myocardial infarction (5). A recent meta-analysis has suggested that the II-genotype is protective against DN with a pooled odds ratio across all studies in type 1 diabetes of 0.72 (95% CI: 0.51–1.01), P = 0.06 (6). Another characteristic of DN is the proliferation of the mesangium. Recently, a polymorphism in the transforming growth factor (TGF)-β1 gene involved in expansion of the mesangial matrix, has been found to be associated with DN (7). This makes NO an interesting molecule in the pathogenesis of DN, since *1*) NO downregulates the synthesis of ACE, the angiotensin II type 1 receptor, and TGF-β, and *2*) since chronic NO synthesis inhibition results in glomerular and tubulointerstitial injury (8,9). In this context, it is of interest that we find an allele of the *NOS2* promoter polymorphism, reported to correlate with increased promoter activity at a significantly higher frequency in normoalbuminuric type 1 diabetic patients compared with type 1 diabetic patients with overt nephropathy. Taken together, these observations suggest that DN development may have a polygenetic basis in the form of gene- or promoter polymorphisms controlling expression levels of iNOS, TGF-β, ACE, angiotensin II receptor type 1, and possibly other molecules involved in renal pathophysiology.

Thus, the CCTTT polymorphism of the *NOS2* promoter may contribute to the susceptibility to DN, but our findings need to be confirmed in other data sets and populations.

JESPER JOHANNESEN, MD
LISE TARNOW, MD
HANS-HENRIK PARVING, MD, DMSC
JØRN NERUP, MD, DMSC
FLEMMING POCIOT, MD, DMSC

From the Steno Diabetes Center, Gentofte, Denmark.

Address correspondence to Flemming Pociot, MD, DMSc, Steno Diabetes Center, Niels Steensensvej 2, DK-2820 Gentofte, Denmark. E-mail: fpoc@novo.dk.

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COMMENTS AND RESPONSES

Capillary Blood Volume and Pain Intensity Depend on Lancet Penetration

Pacaud et al. (1) aimed to study blood volumes and pain after skin punctures at two different depths. For this purpose, they used an older SoftTouch (Roche Diagnostics, Indianapolis, IN) lancing device with only one fixed penetration depth instead of a more modern device with several depth settings. The authors used this SoftTouch device with either the cap tightly screwed on or the cap unscrewed three-fourths of a turn, assuming that by unscrewing the cap, they would obtain a shallower penetration. However, in this device, the lancet is accelerated by the expanding spring until the shoulder of its plastic body hits the bottom of the cap. From there, it rebounds and is likewise retracted by the now-extended spring. The length that the lancet maximally protrudes from the cap is the nominal penetration depth; this should be largely independent of the setting of the cap and could only be influenced by the ratio between the kinetic energy of the advancing lancet and the retracting forces of the spring. We tested this assumption with a high-speed video camera measuring the actual lancet protrusion when this penetrated into a transparent silicon block at either cap setting (SoftTouch; lancet dimension 3.3×0.4 mm). When the cap was properly screwed on, we obtained a lancet protrusion of 1.85 mm. When the cap was unscrewed three-quarters of a turn (which corresponds to a lift of 0.7 mm), the lancet protrusion was 1.70 mm. This result supports our view that Pacaud et al. used nearly the same lancet protrusion for normal and shallow penetrations. Therefore, it is not surprising that the authors did not find different pain intensities for both cap settings. Consequently, their results do not diverge from earlier findings demonstrating a relationship between lancet protrusion and pain intensity (2), a result that has recently been confirmed (3). The important message inherent in the article of Pacaud et al. (1) is the increase of capillary blood volumes in adolescents with growing age.

HEINRICH FRUHSTORFER, MD
GÜNTHER SCHMELZEISEN-REDEKER, PHD
THOMAS WEISS

From the Institute of Physiology (H.F.), University of Marburg, Marburg; and Roche Diagnostics (G.S.-R., T.W.), Mannheim, Germany.

Address correspondence to Heinrich Fruhstorfer, MD, Institute of Physiology, University of Marburg, Deutschhaustrasse 2, D-35033 Marburg, Germany.

H.F. receives funds from Roche Diagnostics for research on lancing devices. G.S.-R. and T.W. are employed by Roche Diagnostics.

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Response to Fruhstorfer et al.

We would like to thank Dr. Fruhstorfer and his colleagues (1) for their interesting comments regarding our article on blood volumes and pain after capillary punctures in children and adolescents with diabetes (2). They suggest that the unscrewing of the cap of the SoftTouch device (Roche Diagnostics) did not lead to a shallower penetration, as evidenced by their test with a silicon block.

While we unscrewed the cap of the SoftTouch device, the new version of this finger-poking device (BD Lancet Device; Becton Dickinson Canada, Mississauga, ON, Canada) uses the same approach with an adjustable tip. This new adjustable tip allows for a change in the length of the tip and presumably in the depth of the puncture. The distribution package advertises this device as having a controlled depth penetration. We believe that our approach did result in a lower penetration, as evidenced by the significantly reduced amounts of blood obtained with the

unscrewed cap (8.6 vs. 11.6 µL; $P = 0.03$). The pertinence of the silicon simulation may depend on its resistance compared with that of normal tissue. We do agree, however, that the effects of unscrewing on the depth are difficult to predict since the lancet in spring-designed devices can reach the tip, although with a lower kinetic energy, and protrude the tip by the same length. The track-type lancet devices, which stop the lancet in its path independently of the cap, probably have greater accuracy in controlling depth of puncture.

As for the absence of a significant association between depth of puncture and pain in this pediatric population, it is possibly due to the multiple factors influencing pain perception in children.

Finally, we thank Fruhstorfer et al. (1) for highlighting the importance of our findings of small blood volumes after capillary punctures in younger children.

DANIÈLE PACAUD, MD
JEAN-FRANÇOIS YALE, MD

From the Alberta Children's Hospital (D.P.), University of Calgary, Calgary, Alberta; and the Royal Victoria Hospital (J.-F.Y.), McGill Nutrition and Food Science Centre, McGill University, Montréal, Québec, Canada.

Address correspondence to Jean-François Yale, MD, McGill Nutrition and Food Science Centre, Royal Victoria Hospital, 687 Pine Ave. W., Montréal, PQ, Canada. E-mail: yale@rvhmed.lan.mcgill.ca.

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Screening for Silent Myocardial Ischemia in Diabetic Patients

We read with great interest the recent article by Janand-Delenne et al. (1). They screened 203 diabetic patients for silent myocardial ischemia (SMI), using either exercise test (ET), thallium myocardial scintigraphy (TMS), or both, as recommended by the Association de Langue Française pour l'Etude du Diabète et des Maladies Métaboliques (ALFEDIAM) guidelines (2). They found 32 patients (15.7%) with SMI. There were 26 patients who underwent a coronary angiography, which displayed significant lesions (i.e., stenosis ≥50%) in 19 patients (9.3%). Risk factors for this positive screening were peripheral artery disease, retinopathy, and familial history of coronary artery disease (CAD). We assessed in a hospital-based sample the same ALFEDIAM guidelines for screening of asymptomatic CAD among diabetic patients. We retrospectively studied 136 patients, 111 with type 2 diabetes (30 women and 81 men, regardless of the duration of diabetes) and 25 with type 1 diabetes (7 women and 18 men with a diabetes duration of ≥10 years), who underwent either an ET ($n = 54$) or TMS in first ($n = 82$) or second ($n = 9$) line. Screening was strictly positive (excluding doubtful results) in 17 cases (12.5 %). This result was confirmed by coronary angiography in 11 cases: 10 (8.1%) angiograms showed significant (i.e., stenosis ≥70%) coronary lesions, and 1 angiogram was negative (despite a positive ET). In the positive screening group, there was a significant ($P < 0.05$) difference for duration of diabetes (odds ratio [OR] 3.7), high blood pressure (OR 4.9), retinopathy (OR 4.4), a higher number of risk factors (OR 6.58), and microalbuminuria (OR 7.8). Moreover, 8 of 11 patients with significant stenosis upon coronary arteriography displayed severe lesions (5 patients with two-vessel lesions, 3 patients with three-vessel lesions). In conclusion, compared with the data of Janand-Delenne et al., we found a similar prevalence of SMI (12.5 vs. 15.7%) and significant coronary lesions (8.1 vs. 9.3%, though our criteria for positive results of coronary angiograms were more restrictive than those used by Janand-Delenne et al. [stenosis ≥70 vs. 50%]). However, we pointed out a different pattern of risk factors for SMI in our diabetic population: duration of diabetes, high blood pressure, presence of retinopathy and nephropathy, and a high number of risk factors were significantly linked to a positive screening of silent CAD. Additionally, in most of our cases, coronary angiograms displayed severe multivessel lesions. These combined results prompt us to carefully weigh cardiovascular risk factors for selective screening of SMI among diabetic patients.

ALEXANDRE FREDENRICH, MD
STÉPHANE CASTILLO-ROS, MD
SYLVIE HIERONIMUS, MD
MARCEL BAUDOUY, MD
MICHEL HARTER, MD
BERTRAND CANIVET, MD

From the Departments of Diabetology (A.F., S.C., B.C.) and Cardiology (M.B.), Pasteur Hospital; and the Department of Endocrinology (S.H., M.H.), Archet Hospital, Nice, France.

Address correspondence to Alexandre Fredenrich, MD, Service de Diabétologie, Hôpital Pasteur, BP 69, 06002 Nice Cedex 1, France. E-mail: afredenrich@compuserve.com.

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Response to Fredenrich et al.

Fredenrich et al. (1) report results very similar to ours (2) in terms of prevalence of silent myocardial ischemia (SMI) in diabetic patients evaluated with the same procedure. In our study, presence of SMI was associated with retinopathy and a high number of cardiovascular risk factors. Moreover, Fredenrich et al. found a correlation with duration of disease and microalbuminuria. These slight differences may be explained by small methodological differences (their study is retrospective and was conducted in hospitalized patients, with probably more risk factors. Moreover, results in type 1 and type 2 diabetic patients are pooled). In fact, correlation between SMI and known cardiovascular risk factors and diabetes characteristics are very variable in the literature: for example, the Milan Study (3) did not find any link between microalbuminuria, retinopathy, and SMI, but patients with severe retinopathy had been excluded from the study, and correlation with hypertension was found only in men. It seems that the pattern of risk factors really depends on inclusion criteria and methods. However, these combined results from Nice and Marseille on the prevalence of SMI emphasize the need for screening SMI, even in diabetic patients with a "Mediterranean lifestyle."

VÉRONIQUE LASSMANN-VAGUE, MD

From La Timone Hospital, Marseille, France.

Address correspondence to Véronique Lassmann-Vague, MD, Hôpital La Timone, Bvd. Jean Moulin, 13385 Marseille Cedex 5, France.

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Link Between Diabetes and Osteoporosis

I thoroughly enjoyed reading the article by Tuominen et al. (1) that appeared in the July 1999 issue of *Diabetes Care*. Tuominen et al. studied the prevalence of osteoporosis in type 1 and type 2 diabetic individuals in the Finnish population and found that the former had lower bone mineral density (BMD) than type 2 diabetic subjects and age-matched control subjects. Although the authors did look into certain risk factors that are determinants of osteoporosis, such as physical activity, alcohol use, smoking, and calcium intake, I was surprised to find that the two common endocrine problems that can result in osteoporosis in individuals with diabetes were not addressed, namely thyrotoxicosis and primary hyperparathyroidism (PHP).

Osteoporosis and fractures are known consequences of PHP (2). It is clear from the literature that diabetes and PHP prevail simultaneously in the same individual with an increased frequency. The prevalence of diabetes is 7–8% in patients with known PHP (3). Similarly, there is an increased prevalence of PHP in patients with diabetes than in the general population (0.82 vs. 0.36%) (3). On the same grounds, the syndrome of thyrotoxicosis (especially Graves' disease) and diabetes (type 1) also coexist. The incidence of diabetes in hyperthyroidism is 2–3% (4). Diabetes generally precedes the development of thyrotoxicosis by many years. Patients with Graves' disease and type 1 diabetes share a common HLA system, which may explain the increased concurrent prevalence of these two entities. Thyrotoxicosis is a well-established and reversible cause of osteoporosis (5). Its incidence increases with age and affects postmenopausal women predominantly. It is possible that the authors may have taken a history for symptoms of thyrotoxicosis, but it is important to remember that most of the elderly patients have "apathetic hyperthyroidism," whereby patients are asymptomatic and often present with cardiac arrhythmia or bone fracture as an initial manifestation of their thyroid disorder.

I feel that any diabetic patient who is found to have osteoporosis should have his or her levels of thyroid stimulating hormone and parathyroid hormone evaluated. Although PHP can occur with equal frequency in patients with type 1 and type 2 diabetes, it is clear that autoimmune hyperthyroidism is more common in patients with type 1 diabetes and therefore may be responsible (along with other factors) for resulting in a greater incidence of osteoporosis in these patients. Although it is possible, as the authors suggested in their conclusion, that the prevalence of a lower peak bone mass in people with type 1 diabetes may be due to a common genotype in this group that makes them susceptible to these two diseases, I think that common causes predisposing diabetic people to osteoporosis, such as thyrotoxicosis and PHP, must be ruled out before one looks for other rare etiologies.

SHEHZAD BASARIA, MD

From the Johns Hopkins University School of Medicine, Baltimore, Maryland.

Address correspondence to Shehzad Basaria, MD, Johns Hopkins University School of Medicine, 1830 E. Monument St., Suite 332, Baltimore, MD 21287. E-mail: sbasaria@welchlink.welch.jhu.edu.

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Bone Mineral Density and Diabetes

Response to Basaria

We appreciate the comments made by Dr. Basaria (1) concerning our article in the July 1999 issue of *Diabetes Care* (2). In this study, we measured femoral bone mineral density (BMD) in type 1 and type 2 diabetic subjects and in nondiabetic control subjects. Our main finding was that BMD, adjusted for age and BMI, was significantly lower in type 1 diabetic patients as compared with type 2 patients and control subjects. Thus, unlike as stated by Dr. Basaria, we did not study the prevalence of osteoporosis, whether defined according to standard BMD criteria or otherwise. Instead, we wanted to study whether the two diabetic groups differ in terms of BMD from each other or from control subjects and whether the differences might be explained by known risk factors for osteoporosis.

We agree that whenever a type 1 diabetic subject is found to have significant osteoporosis, the potential causes of secondary osteoporosis, including hyperparathyroidism (PHP) and hyperthyroidism, should be considered. We did not measure serum parathyroid hormone or thyroid stimulating hormone levels. However, it is unlikely that hyperparathyroidism or hyperthyroidism could have affected our results.

First, as stated by Dr. Basaria, the prevalence of PHP is reported to be 0.82% in a diabetic population as compared with 0.36% in a nondiabetic population (3). Our study included 56 type 1 and 68 type 2 diabetic patients. A PHP prevalence of 0.82% would mean one diabetic PHP patient in our sample with little effect on the mean BMD value. Second, PHP seems to be overrepresented only among diabetic

women (3); yet, we found decreased BMD in both male and female type 1 diabetic patients. Third, even if the prevalence of PHP is higher also in type 2 diabetic populations as compared with control populations (3), there was no difference in BMD between type 2 patients and control subjects in our study.

Hyperthyroidism is an established cause of osteoporosis (4). However, there is no clear evidence that hyperthyroidism occurs more frequently in diabetic subjects than in nondiabetic subjects, except possibly during the postpartum period in type 1 patients (5). Therefore, it is unlikely that our type 1 diabetic subjects would have had an increased prevalence of hyperthyroidism resulting in lower mean BMD values. On the other hand, the prevalence of hypothyroidism is increased in both type 1 and type 2 diabetes because of autoimmune thyroiditis (6,7). If these patients are treated with excessively high doses of thyroxin, the possibility for increased bone loss emerges. However, this is not a problem in usual thyroxin substitution therapy for hypothyroidism in postmenopausal women, although high-suppression doses of thyroxin used in the treatment of thyroid cancer are associated with low BMD in postmenopausal women (8).

We think that thyroid disorders or PHP is unlikely to explain why type 1 diabetic patients in general are prone to decreased BMD. Nevertheless, individual type 1 diabetic patients with osteoporosis may well have subclinical PHP or subclinical hyperthyroidism, which can be detected or ruled out while the patient is assessed for potential causes of osteoporosis.

TAPANI RÖNNEMAA, MD
OLLI IMPIVAARA, MD
PAULI PUUKKA, MPOLSC
JUSSI T. TUOMINEN, MB

From the Department of Medicine (T.R., J.T.T.), University of Turku; and the Research and Development Center (O.I., P.P.), Social Insurance Institution, Turku, Finland.

Address correspondence to Tapani Rönnemaa, MD, Department of Medicine, University of Turku, FIN-20520, Turku, Finland. E-mail: tapani.ronnemaa@utu.fi.

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Erratum

Petitti DB, Contreras R, Ziel FH, Dudl J, Domurat ES, Hyatt JA: Evaluation of the effect of performance monitoring and feedback on care process, utilization, and outcome. *Diabetes Care* 23:192–196, 2000

Joel D. Hyatt, MD, was incorrectly listed as Joel A. Hyatt, MD, in the above article.