diabetes (2). The title "Standards of Medical Care in Diabetes" was chosen because in the view of the American Diabetes Association (ADA), the recommendations represent what we consider the "standards" for the care of patients with diabetes. We see a need to define these so that providers have a guide for assessing their care. They have become the basis for the diabetes guidelines of many organizations and for the diabetes measures now used by the Health Plan Employer Data and Information Set (HEDIS), as well as for many of the quality improvement initiatives by the government, payers, and medical groups.

Each of the recommendations is given an evidence level so the reader can clearly see what supports the recommendation. Dr. Power is correct that "expert consensus" is the lowest level of evidence, although it is important to realize that a great deal of what is done in medical care is based on this level of evidence. On the other hand, many of the recommendations made in the "Standards of Medical Care in Diabetes" have higher levels of evidence.

Regarding our recommendation on screening for diabetes, we actually recommend that "screening be considered," leaving a clear component of clinical judgment in the decision process as to whether a particular patient should or should not be screened. The U.S. Preventive Services Task Force (USPSTF) was evaluating the evidence for "routine screening," not the consideration of what we regard as "targeted screening," which may explain the different evidence levels. Of note, the ADA was asked to comment on the USPSTF statement before its publication and felt that their approach to only recommend screening for those with documented hypertension or dyslipidemia was problematic, as the very definition of what constitutes high blood pressure and dyslipidemia is different for those with diagnosed diabetes than for those without diabetes. We were (and continue to be) concerned that following their advice might allow a person with undiagnosed diabetes to remain undiagnosed until their blood pressure or lipid levels increase over time to a higher level than recommended for those with diabetes. As we know that cardiovascular disease (CVD) risk begins at levels of blood glucose below the diagnostic threshold for diabetes, such an approach could lead to advanced levels of CVD (and other complications of diabetes) when the diagnosis is finally made.

We continue to feel that the title "Standards of Medical Care in Diabetes" is appropriate and that screening of individuals (as opposed to populations) for diabetes should be considered based on the risk factor analysis described.

VIVIAN FONSECA, MD[1]
NATHANIEL G. CLARK, MD, MS, RD[2]

From the [1]Department of Medicine, Division of Endocrinology, Tulane University, New Orleans, Louisiana; and the Department of Clinical Affairs, American Diabetes Association, Alexandria, Virginia.

Address correspondence to Nathaniel G. Clark, MD, MS, RD, Clinical Affairs, American Diabetes Association, 1701 N. Beauregard St., Alexandria, VA 22311. E-mail: nclark@diabetes.org

References

1. Power D: Standards of medical care in diabetes (Letter). *Diabetes Care* 29:476, 2006
2. American Diabetes Association: Standards of medical care in diabetes–2006 (Position Statement). *Diabetes Care* 29 (Suppl. 1):S4–S42, 2006

The Effect of Insulin Antibodies on the Metabolic Action of Inhaled and Subcutaneous Insulin

Response to Heise et al.

Although several authors have previously shown that circulating anti-insulin antibodies do affect the pharmacokinetics and pharmacodynamics of injected insulin (1–4), Heise et al. (5) were unable to show this effect in relation to the increase in anti-insulin antibodies induced by inhaled insulin. Heise et al., however, have applied a study design based on the questionable method of the euglycemic clamp (5), which had been criticized before because of its potential imprecision in demonstrating the biological effects of exogenous insulin (6). This method had not been used in the earlier studies (1–4), which, however, had reported serum free insulin levels (Heise et al. failed to do so). I wonder if the determination of serum free insulin levels would help to explain the apparent discrepancy between the data reported by Heise et al. (5) and those of the previous studies (1–4)?

ERNST CHANTELAU, MD, PHD

From the MNR-Klinik, Heinrich-Heine-University of Düsseldorf/Germany, Düsseldorf, Germany.

Address correspondence to Ernst Chantelau, MD, PhD, MNR-Klinik, Heinrich-Heine-University of Düsseldorf/Germany, PO Box 10 10 07, D-40001 Düsseldorf, Germany. E-mail: lobnig@med.uni-duesseldorf.de .

References

1. Bolli G, de Feo P, Compagnucci P, Cartechini MG, Angeletti G, Santeusanio F, Brunetti P, Gerich JE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. *Diabetes* 32:134–141, 1983
2. Peters A, Klose O, Hefty R, Keck F, Kerner W: The influence of insulin antibodies on the pharmacokinetics of NPH insulin in patients with type-1 diabetes treated with human insulin. *Diabet Med* 12:925–939, 1995
3. Chantelau E, Sonnenberg GE, Heding LG, Berger M: Impaired metabolic response to regular insulin in the presence of a high level of circulating insulin-binding immunoglobulin G (Letter). *Diabetes Care* 7: 403–404, 1984
4. Van Haeften TW: Clinical significance of insulin antibodies in insulin-treated diabetic patients. *Diabetes Care* 12:641–648, 1989
5. Heise T, Bott S, Tusek C, Stephan JA, Kawabata T, Finco-Kent D, Liu C, Krasner A: The effect of insulin antibodies on the metabolic action of inhaled and subcutaneous insulin. *Diabetes Care* 28:2161–2169, 2005
6. Kerner W, Keck FS, Pfeiffer EF: Glucose infusion rates during euglycaemic clamp do not precisely reflect action profiles of subcutaneously injected insulin (Letter). *Diabetologia* 34:60, 1991

The Effect of Insulin Antibodies on the Metabolic Action of Inhaled and Subcutaneous Insulin

Response to Chantelau et al.

We thank Prof. Chantelau (1) for his inquiry about serum free insulin levels in our study (2). Free insulin levels were measured in the fasting state (i.e., before trial drug administration) at baseline and at weeks 12 and 24.

These free insulin levels (resulting from both the constant intravenous insulin infusion that was maintained throughout the in-patient study days as well as any residual concentration remaining from the previous dose of subcutaneous or inhaled insulin) did not show changes from baseline to posttreatment values (mean of weeks 12 and 24) with either treatment (median baseline 16.6, 16.4; posttreatment 18.0, 18.4 uU/ml; inhaled and subcutaneous insulin, respectively).

Free insulin concentrations would not be expected to reconcile the lack of glucose changes observed in this study with pharmacokinetic changes observed in previous studies cited by Prof. Chantelau. In fact, the referenced investigations not only showed relationships between antibodies and free insulin levels, but also with postprandial glucose and other pharmacodynamic parameters (3–6). If insulin levels showed changes in the absence of glucodynamic consequences, the significance and/or accuracy of the insulin data would necessarily be called into question.

We also do not agree that use of the euglycemic clamp technique is the reason no glucodynamic correlates with insulin antibodies were demonstrated in our study. Importantly, the primary end point of the study, postprandial glucose, was not measured with the glucose clamp technique. Furthermore, the clamp technique is precise enough to determine glucodynamic changes secondary to insulin antibodies as was in fact demonstrated in one of the studies cited by Prof. Chantelau (6). We agree with others that the euglycemic clamp technique is the gold standard for assessment of pharmacodynamic responses to insulin (7,8).

The difference in glucodynamic results from this study compared with others may be related to methodologic differences (including prospective study design and optimization of test drug doses for test meal), as well as the ranges of insulin antibody levels achieved (as discussed in our article). Nevertheless, the results of this study show that insulin antibody levels measured prospectively during treatment with inhaled insulin are not associated with relevant changes in insulin pharmacodynamics or with adverse clinical effects.

Tim Heise, md[1]
Susanne Bott, md[1]
Corinna Tusek, md[1]
Jens-Armin Stephan, md[1]
Tom Kawabata, phd[2]
Deborah Finco-Kent, ms[2]
Cameron Liu, phd[2]
Alan Krasner, md[2]

From the [1]Profil Institute for Metabolic Research, Medical, Neuss, Germany; and [2]Pfizer Global Research and Development, Groton, Connecticut.

Address correspondence to Tim C. Heise, MD, CEO, Clinical Science, Profil Institut fur Stoffwechselforschung, Hellersbergstr 9, D-41460, Neuss, Germany. E-mail: tim.heise@profil-research.de.

References

1. Chantelau E: The effect of insulin antibodies on the metabolic action of inhaled and subcutaneous insulin (Letter). *Diabetes Care* 29:477, 2006
2. Heise T, Bott S, Tusek C, Stephan JA, Kawabata T, Finco-Kent D, Liu C, Krasner A: The effect of insulin antibodies on the metabolic action of inhaled and subcutaneous insulin. *Diabetes Care* 28:2161–2169, 2005
3. Van Haeften TW: Clinical significance of insulin antibodies in insulin-treated diabetic patients. *Diabetes Care* 12:641–648, 1989
4. Bolli G, de Feo P, Compagnucci P, Cartechini MG, Angeletti G, Santeusanio F, Brunetti P, Gerich JE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. *Diabetes* 32:134–141, 1983
5. Chantelau E, Sonnenberg GE, Heding LG, Berger M: Impaired metabolic response to regular insulin in the presence of a high level of circulating insulin-binding immunoglobulin G. *Diabetes Care* 7:403–404, 1984
6. Peters A, Klose O, Hefty R, Keck F, Kerner W: The influence of insulin antibodies on the pharmacokinetics of NPH insulin in patients with type-1 diabetes treated with human insulin. *Diabet Med* 12:925–939, 1995
7. Heinemann L, Richter B: Clinical pharmacology of human insulin (Review). *Diabetes Care* 16 (Suppl. 3):90–100, 1993
8. European Agency for the Evaluation of Medicinal Products/Committee for Proprietary Medicinal Products: Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus [article online], 2002. Available from http://www.emea.eu.int/pdfs/human/ewp/108000en.pdf. Accessed 31 October 2005

Autologous Transplantation of Granulocyte Colony–Stimulating Factor–Mobilized Peripheral Blood Mononuclear Cells Improves Critical Limb Ischemia in Diabetes

Response to Huang et al.

Huang et al. (1), in their small seminal clinical trial of cellular therapy for critical limb ischemia in diabetic patients, did not include presence of diabetic retinopathy among their exclusion criteria. It is known that individuals with diabetes are subjected to poor blood vessel growth in ischemic hearts and limbs and increased angiogenesis in retinal complications. This so-called "diabetic paradox" has been attributed to the differential regulation of angiogenic factors in the retina versus the systemic circulation (2). While decreased levels of endothelial progenitor cells are seen in diabetic patients with peripheral arterial disease (3), a role for endothelial progenitor cells in the development of proliferative diabetic retinopathy (PDR) also has been demonstrated (4). Possible harmful side effects of progenitor cell transplantation may include pathologic neoangiogenesis favoring the development or progression of cancer or PDR (5). Moreover, although data on blood cells are not presented, the increased blood viscosity due to the leukemoid response to granulocyte colony–stimulating factor may favor retinal vessel occlusion. Therefore, it was desirable that patients were screened for PDR before and after cell transplantation, in order to identify or exclude such an undesirable effect.

Finally, the achievement of a better metabolic control in the transplant group than in the control group is not unexpected and can be explained without postulating β-cell regeneration, since wound healing per se and reduced inflammation may have improved insulin sensitivity. The authors correctly cite the hypothesis that circulating progenitor cells may have a role in rescue of pancreatic endocrine function (6), but this has not been demonstrated thus far. Transplanted cells are