recruited in the pancreas of streptozotocin-induced diabetic animals, but neither sign of endocrine transdifferentiation nor improvement in blood glucose metabolism have been shown (7). Moreover, this claimed mechanism would clearly interest only those forms of diabetes due to primitive β-cell failure, while only 40% of the study patients had type 1 diabetes.

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

Response to Fadini and Avogaro

Recently, our pilot study provided evidence that autologous transplantation of granulocyte colony–stimulating factor–mobilized peripheral blood mononuclear cells (PBMNCs) may represent a simple, safe, effective, and novel therapeutic approach for diabetic critical limb ischemia (CLI) (1). In our study, we chose diabetic patients with proven CLI, but without hypercoagulable states and/or severe coronary, cerebral, and renal vascular disease. As pointed out by Fadini and Avogaro (2), poor blood vessel growth in ischemic hearts and limbs and increased angiogenesis in retinal complications are paradoxical vascular complications in diabetic patients. This so-called "diabetic paradox" has been attributed to the differential regulation of angiogenic factors in the retina versus the systemic circulation (3). Thus, we may have to choose a compromised approach to balance these two divergent complications. For patients with mild or absent retinal complications but very severe limb ischemia that manifests ulceration, gangrene, or nonhealing wounds, we may give priority to improving CLI. We agree that we must be cognizant of a treatment approach that focuses on improving CLI, as well as remain aware of the potential risk for worsening diabetic retinopathy. In addition, we must monitor undesirable retinal vascular changes.

Dysfunctional endothelial progenitor cells (EPCs) from diabetes (4) may attenuate the effectiveness of our approach for CLI. However, we have observed that mobilized PBMNCs yielded more EPCs from diabetic individuals than nonmobilized ones, partially compensating for the fewer number of EPCs in diabetes. In addition, our results revealed that the mechanism in vivo is not limited to EPCs. Proangiogenic factors secreted by mononuclear cells played an equally important role in vivo (S. Li, B.Z., Z.C.H., unpublished data). Clinically, allogenic transplantation of normal mobilized PBMNCs may be more effective, but such transplanted cells may encounter rejection. Therefore, autologous transplantation of mobilized PBMNCs is still a good, albeit compromised and imperfect, approach.

As for decreased plasma glucose, we proposed that mobilization resulted in more circulating EPCs that could be recruited to the pancreas and that EPC-mediated neovascularization of the pancreas could in principle facilitate the recovery of non–terminally injured cells (5). The precise mechanism of decreased plasma glucose after mobilization awaits further investigation, for which a much higher number of patients will need to be involved.

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Cost-Effectiveness of Self-Monitoring of Blood Glucose in Type 2 Diabetic Patients Not Receiving Insulin

Response to Davidson

In his counterpoint article, Davidson (1) argues that self-monitoring of blood glucose (SMBG) in type 2 diabetic subjects not using insulin is a waste of money. However, as the discussions accompanying and following publication of a new meta-analysis by Welschen et al. (2) demonstrate, the evidence is far from conclusive either for or against use of SMBG in this patient group.

As pointed out by Ipp et al. (3), many of the trials of SMBG conducted thus far have been underpowered to detect a significant impact and therefore individually cannot reliably conclude that SMBG does or does not influence HbA_{1c} (A1C). In an attempt to bring some clarity to the current situation, Welschen et al. performed a meta-analysis based upon pooling of more recent randomized trials with the conclusion that SMBG affords a modest but significant 0.39% reduction in A1C. According to Davidson, even if this effect is clinically relevant, it is likely to be outweighed by the cost of providing SMBG. To accurately answer that claim, we undertook a cost-effectiveness analysis of SMBG using a Markov state model of diabetes to assess the clinical impact and related cost when SMBG is provided to non–insulin-requiring patients within the German health care system. Assuming a modest improvement in A1C of 0.39%, the result was a slight increase in life expectancy (0.083 years) and reduced cost of complications (70% attributable to microvascular events). This finding is in line with the results of the U.K. Prospective Diabetes Study, in which a 1% reduction in A1C corresponded to a reduction in complications (4). In our analysis, the cost per life-year gained was ~€31,000 and therefore, from a health insurance perspective, acceptable. Over a 10-year period and taking into consideration cost savings due to reduced complications, SMBG employed at a frequency of seven times/week would account for ~6% of the total direct costs covered by health insurance.

While current evidence is not perfect, it supports, on both clinical and economic grounds, the use of SMBG in type 2 diabetic subjects not using insulin. Therefore, it would be premature to consider withdrawal of this treatment option. As noted by Ipp et al. (3), now is the time for industry to fund large multicenter trials with sufficient power to confirm the findings obtained by pooling small randomized controlled trials.

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Cost-Effectiveness of Self-Monitoring of Blood Glucose in Type 2 Diabetic Patients Not Receiving Insulin

Response to Neeser et al.

Neeser et al. (1) challenge my argument that self-monitoring of blood glucose (SMBG) in type 2 diabetic patients not taking insulin is not beneficial for lowering glycemia and therefore is a waste of (a lot of) money (2).

In a meta-analysis of six randomized controlled trials, Welschen et al. (3) found a significant reduction of 0.39% in HbA_{1c} (A1C) levels in type 2 diabetic patients not taking insulin who performed SMBG. Welschen et al. did point out that the reduction was only significant in two of the trials and that the conclusion that SMBG was beneficial "should be interpreted with caution, as the methodological quality of the trials . . . was limited in four of the six included studies." A large number of nonrandomized studies were also negative (2,3). Be that as it may, Neeser et al. (1), using a Markov model on data from the German health care system, state that a 0.39% reduction of A1C levels resulted in a 30-day (0.083 years) increase of life expectancy and "reduced cost of complications (70% attributable to microvascular events)." The cost per life-year gained was ~€31,000 (or $36,400) and "therefore, from a health insurance perspective, acceptable." They conclude that it is "premature to consider withdrawal of this treatment option" and suggest that industry should fund large multicenter trials to determine whether SMBG is helpful in this situation.

Several points can be made in response. Although we are not given the costs of SMBG in non–insulin-requiring patients in the German health care system, I would emphasize that in the U.S., a conservative estimate of the cost of SMBG in these patients is nearly $1.5 billion/year (2). This is a tremendous amount of money for an activity for which there is little (to be charitable) or no evidence for a beneficial outcome. If this were a drug, it certainly would not have received Food and Drug Administration approval. In a sense, therefore, SMBG in patients not taking insulin represents a very expensive "off-label" use. Of course, calls for larger