Improved Pharmacokinetic and Pharmacodynamic Profile of Rapid-Acting Insulin Using Needle-Free Jet Injection Technology

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OBJECTIVE—Insulin administered by jet injectors is dispensed over a larger subcutaneous area than insulin injected with a syringe, which may facilitate a more rapid absorption. This study compared the pharmacologic profile of administration of insulin aspart by jet injection to that by conventional insulin pen.

RESEARCH DESIGN AND METHODS—Euglycemic glucose clamp tests were performed in 18 healthy volunteers after subcutaneous administration of 0.2 units/kg body wt of aspart, either administered by jet injection or by conventional pen, using a randomized, double-blind, double-dummy, cross over study design. Pharmacodynamic and pharmacokinetic profiles were derived from the glucose infusion rate (GIR) needed to maintain euglycemia and from plasma insulin levels, respectively.

RESULTS—The time to maximal GIR was significantly shorter when insulin was injected with the jet injector compared with conventional pen administration (51 ± 3 vs. 105 ± 11 min, $P < 0.0001$). The time to peak insulin concentration was similarly reduced (31 ± 3 vs. 64 ± 6 min, $P < 0.0001$) and peak insulin concentrations were increased (108 ± 13 vs. 79 ± 7 mU/L, $P = 0.01$) when insulin was injected by jet injection compared with conventional pen injection. Jet injector insulin administration reduced the time to 50% glucose disposal by ~40 min ($P < 0.0001$). There were no differences in maximal GIR, total insulin absorption, or total insulin action between the two devices.

CONCLUSIONS—Administration of insulin aspart by jet injection enhances insulin absorption and reduces the duration of glucose-lowering action. This profile resembles more closely the pattern of endogenous insulin secretion and may help to achieve better meal insulin coverage and correction of postprandial glucose excursions.

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Administration of insulin by jet injection is a needle-free alternative to conventional insulin administration with syringes or insulin pens. Jet injectors deliver insulin at a high velocity (typically >100 m/s) across the skin in the subcutaneous tissue and may dispense the insulin over a larger area than insulin injected with a syringe (1). This may enhance the efficiency with which insulin is absorbed from the subcutaneous compartment into the circulation so that the insulin peak can be advanced and the duration of (glucose-lowering) action reduced. Studies on jet injection technology for insulin administration date back to the 1960s (2). Most have suggested faster absorption of regular and NPH insulin when injected with a jet injector rather than with a syringe (3–8). Data on the use of jet injectors for the administration of rapid-acting insulin analogs are limited to one open-label study. In that study, peak insulin levels were reached in about half the time when lispro insulin was injected with a jet injector instead of a syringe. However, the glucose-lowering time-action profiles were not significantly different, the number of subjects examined was low ($n = 4$), and the dose of insulin tested was relatively high (30 units for all) (9).

Although rapid-acting insulin analogs have clearly advanced glycemic treatment of type 1 and insulin-requiring type 2 diabetes, their pharmacological profile is still far from mimicking the profile of endogenous insulin release. Indeed, the time until insulin's maximal glucose-lowering effect generally amounts to >90 min, and the duration of significant hyperinsulinemia often exceeds 3 hours (10–12). As a consequence, risks of (immediate) postprandial hyperglycemia and (late) postprandial hypoglycemia remain relatively high in many patients treated with rapid-acting insulin analogs. Faster absorption of insulin may reduce these risks and may provide a more physiological meal-time substitution of insulin. The aim of this study was therefore to compare the pharmacodynamic and pharmacokinetic profile of subcutaneous administration of the rapid-acting insulin analog aspart by jet injection to that of administration by conventional insulin pen in healthy individuals using the euglycemic glucose clamp technique (13). We chose to use an insulin pen as comparator because insulin pens may be more accurate than syringes (14) and are currently used by the vast majority of insulin-treated patients with diabetes in western Europe (15).

RESEARCH DESIGN AND METHODS

—Written informed consent was obtained from 18 healthy, nonsmoking subjects (men/women 5/13, mean ± SD age 27.2 ± 9.4 years, mean BMI 23.6 ± 2.8 kg/m^2, mean fasting plasma glucose level 5.09 ± 0.35 mmol/L) who were recruited by advertisement. None of the participants were on chronic medication (with the exception of oral contraceptives), reported type 2 diabetes among first-degree relatives, or had a history of cardiovascular events. A pregnancy

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test was performed in female subjects at the screening visit to exclude pregnancy. The study was approved by the institutional review board of the Radboud University Nijmegen Medical Centre.

Experimental study design

All participants underwent two euglycemic glucose clamp experiments (13,16) to investigate the pharmacokinetics and pharmacodynamics of rapid-acting insulin delivered by jet injection or conventional pen injection, using a double-blind, double-dummy, randomized cross over study design. There was a washout period of at least 1 week between the two clamps, whereas female subjects were tested at 4- or 8-week intervals to ensure that experiments took place during corresponding periods of the menstrual cycle.

Participants were admitted to the research unit at 0830 h after an overnight fast and having abstained from smoking, alcohol use, and caffeine use for at least 24 h. The experiments were performed in supine position in a temperature controlled room (22–24°C). Two catheters were inserted intravenously. One catheter was inserted in retrograde fashion in a dorsal hand vein for blood sampling. This hand was placed in a heated box, kept at 55°C to arterialize venous blood (17,18). The other catheter was placed in an antecubital vein of the contralateral arm for administration of 20% dextrose.

After instrumentation, a 30-min equilibration period was included before blood was sampled for baseline values of plasma glucose and plasma insulin. Subsequently, all participants received both insulin (aspart, Novo Nordisk, Bagsvaerd, Denmark) in a dose of 0.2 units/kg body wt and a comparable volume of placebo solution (Test Medium Penfill, Novo Nordisk, Bagsvaerd, Denmark) simultaneously injected subcutaneously in the abdomen. On one occasion, insulin was administered by jet injection (Insujet, European Pharma Group bv, Schiphol-Rijk, the Netherlands) and placebo by conventional pen (NovoPen III, Novo Nordisk); on the other occasion, insulin was injected by the conventional pen and placebo by the jet injector. Two-by-two block randomization was used to randomize the sequence by which the two devices were used for insulin and placebo injections. The jet injector device used in this study was equipped with a loaded spring mechanism, kept in place by a counterpressure lock/release system. After pressing the nozzle perpendicular to the skin, the jet injector releases insulin with sufficient force to enter the subcutaneous tissue to a depth equivalent to standard needle syringe. To avoid premature insulin release, the system unlocks only when sufficient pressure has been applied to the nozzle. Both the jet injector and the conventional pen were operated by trained personnel only and were prepared by a nurse who was not involved in the trial. After administration of insulin and placebo solution, plasma glucose was maintained at euglycemic levels (~5.0 mmol/L) for 8 h by a variable infusion of 20% dextrose, the rate of which was determined by plasma glucose measurements at 5-min intervals during the first 4 h and at 10-min intervals thereafter. Blood for plasma insulin levels was sampled every 10 min during the 1st hour and every 30 min for the remainder of the study.

All pharmacodynamic and pharmacokinetic study end points were derived from the exogenous glucose infusion rate (GIR) and insulin concentration profiles. The primary study end point was the time to maximal GIR (T-GIR_{max}), corresponding to the time until the maximal glucose-lowering effect of insulin was obtained. Secondary pharmacodynamic end points were the maximal GIR (C-GIR_{max}), the time to 50% of glucose disposal (T-$GIR_{50\%}$), and the total amount of glucose administered calculated from the area under the curve (AUC) (GIR_{tot}). Secondary pharmacokinetic end points included the time to maximal insulin concentration (T-INS_{max}), the maximal insulin concentration (C-INS_{max}), the area under the insulin concentration curve (INS_{AUC}), and the time until 50% of insulin absorption, calculated as 50% of the area under the insulin concentration curve (T-$INS_{AUC50\%}$).

Analytical procedures

Plasma glucose levels were determined in duplicate, immediately after blood sampling by the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA). Blood sampled for plasma insulin measurements was collected in lithium-heparin tubes and placed on ice. After centrifugation, the supernatant was stored at −20°C. Plasma insulin was measured by radioimmunoassay (19) after all experiments were performed.

Statistical analyses

Assuming a T-GIR_{max} of 94 min with a SD of 46 min for aspart insulin administered subcutaneously in the abdomen by conventional pen injection (10), we calculated that a total of 18 subjects would be needed to find a 20% reduction in the primary end point with 80% statistical power at the conventional P value of 0.05, after correction for small sample sizes.

All data are expressed as means ± SEM, unless otherwise indicated. Mean outcomes for all study end points were tested by paired t tests. The GIR and insulin concentration profiles were compared by ANOVA. All statistical analyses were performed by SPSS 16.0 (Statistical Package for Social Sciences, Chicago, IL). A P value of < 0.05 was considered statistically significant.

RESULTS—All 18 subjects completed the study. In two subjects, one of the clamp experiments had to be rescheduled because insulin levels failed to increase, with both incidents occurring when the jet injector contained insulin. In one instance, the jet injector was incompletely checked for air bubbles in the system. In the other instance, the spring was released before proper contact could be made with the skin, after which the jet injector was returned to the manufacturer and replaced. Injections were well tolerated by the participants, although some participants regarded the firm pressure required for injection with the jet injector as unpleasant. Neither injection mode resulted in skin reactions such as hematomas or redness. Mean plasma glucose levels during the clamps were 5.0 ± 0.1 mmol/L with both devices. The corresponding coefficients of variation were 8.0 ± 0.8% and 7.3 ± 0.5% for the jet injector and conventional insulin pen, respectively.

Pharmacodynamic end points

All results of pharmacodynamic end points are shown in Fig. 1 and listed in Table 1. The time to maximal glucose-lowering effect, as represented by T-GIR_{max}, was reduced by >50% when insulin was administered with the jet injector as compared with conventional insulin administration. There were no differences in maximal glucose-lowering effect (C-GIR_{max}) or the total amount of glucose administered (GIR_{tot}) between the two devices. However, the time to 50% of glucose disposal (T-$GIR_{50\%}$), representing the total duration of insulin action, was approximately 40 min shorter for insulin administration by jet injector than that by conventional insulin pen.

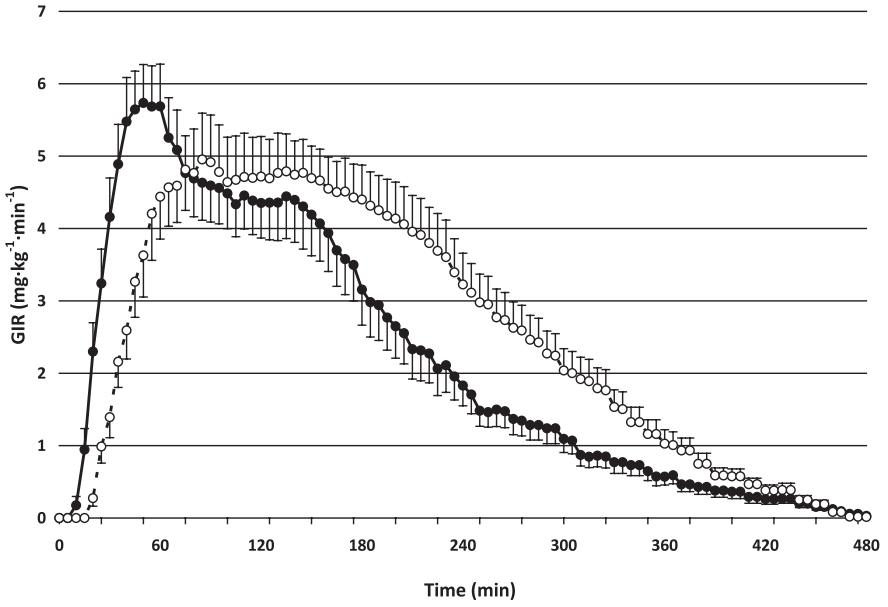

Figure 1—*Mean GIR after administration of rapid-acting insulin by the jet injector (closed symbols, black line) or the conventional insulin pen (open symbols, dashed line) during the euglycemic glucose clamp.*

Pharmacokinetic end points

The results of pharmacokinetic end points are also listed in Table 1. In analogy with the pharmacodynamic results, the time to reach peak insulin levels was reduced by more than 50% after jet injector insulin administration as compared with insulin administration with the conventional pen. Insulin administered with the jet injector also resulted in higher peak insulin levels (C-INS_{max}) than insulin administered with the conventional insulin pen (Fig. 2). The INS_{AUC} did not differ between the jet injector and the conventional insulin pen, but T-$INS_{AUC50\%}$ was significantly shorter for the jet injector, indicating faster insulin absorption from the subcutaneous tissue into the circulation.

There was no indication that sex modified the pharmacodynamic or pharmacokinetic differences between the jet injector and conventional pen for insulin administration. In fact, the jet injector performed significantly better than the conventional pen in both groups, when analyzed separately (data not shown but available upon request).

CONCLUSIONS—In this study, the pharmacodynamic and pharmacokinetic profiles of the rapid-acting insulin analog aspart, injected by either jet injection technique or by conventional insulin pen, were compared. We found that the jet injector greatly enhanced the rate of insulin absorption, resulting in a truly immediate onset of action and approximately halving of the time to reach maximal glucose-lowering effect in comparison with conventional insulin administration. In addition, insulin administration by jet injection reduced the total duration of hyperinsulinemia and insulin action by 30–40 min when compared with conventional insulin administration. There were no indications that these benefits of the jet injector over the conventional pen differed between women and men.

Our data are in line with previous studies that have shown a more rapid increase in insulin levels and shorter duration of hyperinsulinemia after administration of regular insulin by jet injection compared with administration by needle syringe (3–8). The results of the current study also extend those of a recent study performed by Sarno et al. (9), who compared administration of various insulins (including lispro insulin) with jet injection to that with needle syringes. In that study, time to peak insulin levels after lispro insulin administration was shorter for the jet injector than for needle syringe injection, but a statistically significant pharmacodynamic effect could not be established. Also, the number of volunteers examined was small (n = 4) and the dose of insulin used was fixed at a relatively high level (30 units for all). Our study convincingly shows the pharmacokinetic and pharmacodynamic superiority of jet injection over conventional needle pens for administration of rapid-acting insulin at a dose that is realistic for many people with type 1 or type 2 diabetes. It is also the first time that jet injection technology was compared with an insulin pen, which most patients prefer over syringes for their ease of use and high level of accuracy (20).

Insulin injected by jet injection displays a specific cone-like dispersion pattern in the subcutaneous tissue with a relatively large surface area (1,2). It seems plausible that this dispersion pattern enhances absorption of insulin into the circulation, thus explaining a more immediate glucose-lowering effect. The current jet injector uses a high-velocity jet that ensures >90% delivery of injected insulin into the subcutaneous tissue, without risking penetration of the underlying muscle, at a jet stream diameter of ~0.15 mm. These device characteristics compare favorably to the length and diameter of pen needles that typically measure 6–8 mm and 0.5 mm, respectively. A limitation to the use of jet injectors in comparison with insulin pens is that sufficient training is required with both air-free

Table 1—*Pharmacokinetic and pharmacodynamic parameters for insulin administration with the jet injector and the conventional insulin pen*

	Jet injector	Conventional insulin pen	*P* value
Pharmacokinetic parameters			
T-INS_{max} (min)	31 ± 3	64 ± 6	<0.0001
C-INS_{max} (mU/L)	108 ± 13	79 ± 7	0.012
INS_{AUC} (unit · min^{-1} · mL^{-1})	14.6 ± 1.6	15.2 ± 1.4	0.53
T-$INS_{AUC50\%}$ (min)	111 ± 5	147 ± 5	<0.0001
Pharmacodynamic parameters			
T-GIR_{max} (min)	51 ± 3	105 ± 11	0.0001
C-GIR_{max} (mg · kg^{-1} · min^{-1})	6.49 ± 0.58	6.09 ± 0.56	0.50
GIR_{tot} (g)	70.0 ± 6.9	83.3 ± 9.8	0.19
T-$GIR_{50\%}$ (min)	123 ± 7	166 ± 6	<0.0001

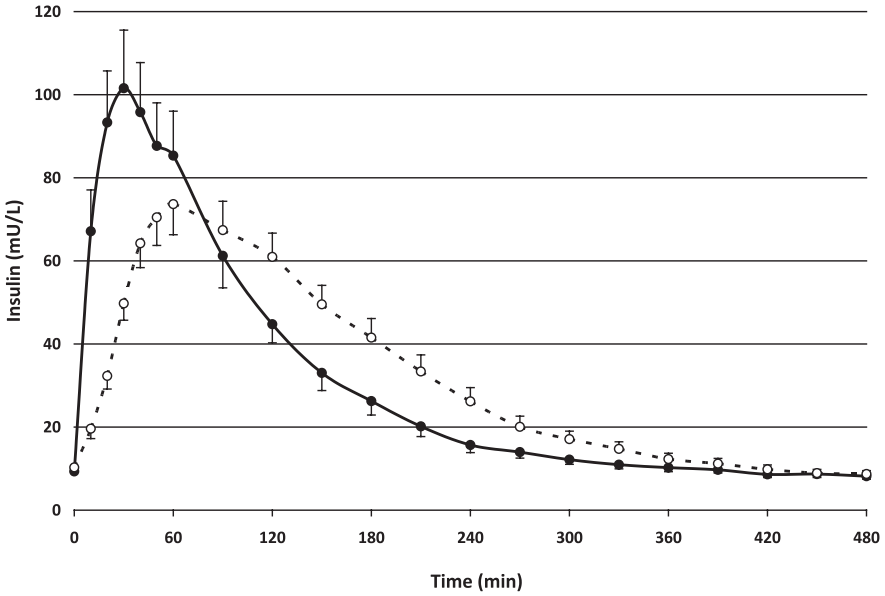

Figure 2—*Mean plasma insulin levels after administration of rapid-acting insulin by the jet injector (closed symbols, black line) or the conventional insulin pen (open symbols, dashed line) during the euglycemic glucose clamp.*

filling of the injection chamber and the injection procedure itself. We had to reschedule the first experiment, probably because of an air bubble in the system, and another experiment because of early discharge of the spring system, possibly related to failure of the lock/release system. However, after proper training, administration of the entire dose of insulin can be achieved in almost all instances (21).

The pharmacokinetic and pharmacodynamic profile of rapid-acting insulin administered by the jet injector approached the physiological pattern of endogenous insulin secretion and subsequent glucose-lowering response more closely than insulin administered by a conventional insulin pen. Consequently, a more physiological meal insulin substitution may decrease immediate postprandial hyperglycemia, whereas the more rapid tapering of hyperinsulinemia may reduce the risk of late postprandial hypoglycemia. Faster insulin action may also advance correction of erratic hyperglycemia. These effects are clinically relevant for patients aiming for strict glycemic control. However, postprandial glucose may contribute less to overall glycemic control than preprandial glucose in patients with diabetes, and the role of postprandial hyperglycemia as an independent cardiovascular risk factor is still uncertain (22). Therefore, appropriately designed studies are needed to determine whether and to what extent the favorable pharmacological properties of insulin administration by jet injection found in this study translate into clinical benefit in the longer term for patients with diabetes.

A strength of our study is the use of a double-dummy cross over study design, ensuring that both participants and investigators were truly blinded during the execution of the experiments. This contrasts with previous studies on jet injectors. Moreover, because we used a placebo solution that contained the same ingredients as the insulin solution (except for insulin), the smell and viscosity of the two liquids were indistinguishable. A limitation of this study is that the euglycemic clamps were performed in healthy individuals rather than in patients with diabetes, the target population for such a device. In addition, only one insulin dose was investigated; it cannot be determined with certainty whether the current differences in time-action profiles can be extrapolated to other insulin doses. Finally, the ease of use of the jet injector was not tested, which is important for a device that is aimed at being used on a daily basis.

In conclusion, the current study shows that when insulin is administered with a jet injector instead of a conventional insulin pen, a more rapid onset of insulin action can be achieved. Insulin administered by the jet injector resembles the pattern of endogenous insulin secretion more closely and could therefore be useful in providing a more physiologic postprandial insulin profile. Future research will need to investigate whether these results can be replicated in patients with diabetes and what the clinical implications are.

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E.E.C.E. performed the experiments, analyzed and interpreted data, wrote the manuscript, and reviewed and edited the manuscript. E.J.A. wrote the study protocol, performed the experiments, analyzed and interpreted data, and reviewed and edited the manuscript. C.J.T. designed the study, interpreted data, and reviewed and edited the manuscript. B.E.d.G. designed the study, wrote the study protocol, performed the experiments, analyzed and interpreted data, and reviewed and edited the manuscript.

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References

1. Mitragotri S. Current status and future prospects of needle-free liquid jet injectors. Nat Rev Drug Discov 2006;5:543–548
2. Weller C, Linder M. Jet injection of insulin vs the syringe-and-needle method. JAMA 1966;195:844–847
3. Taylor R, Home PD, Alberti KG. Plasma free insulin profiles after administration of insulin by jet and conventional syringe injection. Diabetes Care 1981;4:377–379
4. Pehling GB, Gerich JE. Comparison of plasma insulin profiles after subcutaneous administration of insulin by jet spray and conventional needle injection in patients with insulin-dependent diabetes mellitus. Mayo Clin Proc 1984;59:751–754
5. Hallé JP, Lambert J, Lindmayer I, et al. Twice-daily mixed regular and NPH insulin injections with new jet injector versus

conventional syringes: pharmacokinetics of insulin absorption. Diabetes Care 1986;9:279–282
6. Malone JI, Lowitt S, Grove NP, Shah SC. Comparison of insulin levels after injection by jet stream and disposable insulin syringe. Diabetes Care 1986;9:637–640
7. Kerum G, Profozić V, Granić M, Skrabalo Z. Blood glucose and free insulin levels after the administration of insulin by conventional syringe or jet injector in insulin treated type 2 diabetics. Horm Metab Res 1987;19:422–425
8. Lucas A, Ribas L, Salinas I, Audí L, Sanmartí A, Foz M. Insulin levels after injection by jet stream and disposable syringe. Diabetes Care 1988;11:298–299
9. Sarno MJ, Bell J, Edelman SV. Pharmacokinetics and glucodynamics of rapid-, short-, and intermediate-acting insulins: comparison of jet injection to needle syringe. Diabetes Technol Ther 2002;4:863–866
10. Mudaliar SR, Lindberg FA, Joyce M, et al. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. Diabetes Care 1999;22:1501–1506
11. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. Diabetes 1994;43:396–402
12. Heise T, Weyer C, Serwas A, et al. Time-action profiles of novel premixed preparations of insulin lispro and NPL insulin. Diabetes Care 1998;21:800–803
13. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214–E223
14. Luijf YM, DeVries JH. Dosing accuracy of insulin pens versus conventional syringes and vials. Diabetes Technol Ther 2010;12(Suppl. 1):S73–S77
15. Thurman JE. Insulin pen injection devices for management of patients with type 2 diabetes: considerations based on an endocrinologist's practical experience in the United States. Endocr Pract 2007;13:672–678
16. Heinemann L, Anderson JH Jr. Measurement of insulin absorption and insulin action. Diabetes Technol Ther 2004;6:698–718
17. Abumrad NN, Rabin D, Diamond MP, Lacy WW. Use of a heated superficial hand vein as an alternative site for the measurement of amino acid concentrations and for the study of glucose and alanine kinetics in man. Metabolism 1981;30:936–940
18. Abbink EJ, van der Wal PS, Sweep CG, Smits P, Tack CJ. Compared to glibenclamide, repaglinide treatment results in a more rapid fall in glucose level and beta-cell secretion after glucose stimulation. Diabetes Metab Res Rev 2004;20:466–471
19. Abbink EJ, Walker AJ, van der Sluijs HA, Tack CJ, Smits P. No role of calcium- and ATP-dependent potassium channels in insulin-induced vasodilation in humans in vivo. Diabetes Metab Res Rev 2002;18:143–148
20. Asakura T, Seino H, Nakano R, et al. A comparison of the handling and accuracy of syringe and vial versus prefilled insulin pen (FlexPen). Diabetes Technol Ther 2009;11:657–661
21. Bremseth DL, Pass F. Delivery of insulin by jet injection: recent observations. Diabetes Technol Ther 2001;3:225–232
22. Borg R, Kuenen JC, Carstensen B, et al.; ADAG Study Group. HbA_1(c) and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study. Diabetologia 2011;54:69–72