Differences in insulin dosing in women with type 1 diabetes before and after the menopause

Andreas Melmer, Irina Zürrer, Florian Kopp, Nico Trautwein, Martin Pfeifer

Angaben zur Veröffentlichung / Publication details:

Melmer, Andreas, Irina Zürrer, Florian Kopp, Nico Trautwein, and Martin Pfeifer. 2021. "Differences in insulin dosing in women with type 1 diabetes before and after the menopause." *Swiss Medical Weekly* 151 (39-40): w30025. https://doi.org/10.4414/smw.2021.w30025.

Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 30 September 2021 | doi:10.4414/SMW.2021.w30025
Cite this as: Swiss Med Wkly. 2021;151:w30025

Differences in insulin dosing in women with type 1 diabetes before and after the menopause

Andreas Melmer[a], Irina Zürrer[a], Florian Kopp[b], Martin Pfeifer[c], Erna Kamml[d], Gabriele Götz[e], Sabine Hofer[f], Ingrid Schütz-Fuhrmann[g], Andreas Hungele[h], Reinhard W. Holl[hi]

[a] Department of Diabetes,Endocrinology, Nutritional Medicine and Metabolism, Inselspital, University Hospital and University of Bern, Switzerland
[b] Forth Clinical Department of Medicine,Academic Teaching Hospital Augsburg, Germany
[c] Department of Diabetes, Medical Campus Lake Constance, Tettnang, Germany
[d] Medical office for Diabetes, Surheim, Germany
[e] Department of Internal Medicine, Diabetes, Gastroenterology, Tumor Medicine, and Palliative Care, Academic Teaching Hospital Nürtingen, Germany
[f] Department of Pediatrics, Medical University of Innsbruck, Austria
[g] Department of Endocrinology, City Hospital Hietzing, Vienna, Austria
[h] Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Germany
[i] German Centre for Diabetes Research (DZD), Munich-Neuherberg, Germany

Summary

The menstrual cycle increases insulin requirements in a subset of women with type 1 diabetes as a result of reduced insulin action through sexual hormones. If exposure to sexual hormones declines during the menopause, adaptions of insulin dosing may be required. However, there are no validated recommendations available on how to adapt insulin treatment in postmenopausal women with type 1 diabetes. The present study compared insulin dosing profiles of 630 premenopausal and 548 postmenopausal women, who had long-term type 1 diabetes and used continuous subcutaneous insulin infusion. Data were extracted from the German "Diabetes-Patienten-Verlaufsdokumentation".

It was found that total daily insulin (p <0.0001), daily insulin per kilogram bodyweight (p <0.0001), total daily basal insulin (p <0.0001), daily basal insulin per kilogram bodyweight (p <0.0001) and estimated glomerular filtration rate (eGFR) (p <0.0001) were lower in postmenopausal women. Total daily bolus insulin, daily bolus insulin per kilogram, glycated haemoglobin A1, body mass index and the incidence of severe hypoglycaemic events were similar in both cohorts.

Postmenopausal women with type 1 diabetes used lower insulin doses as compared with premenopausal women, whereas glycaemic control and body mass index were comparable. This observation might be explained by lower exposure to sexual hormones and lower eGFR, even though the contribution of other factors such as body composition and eating habits requires further investigation.

Correspondence:
Dr Andreas Melmer, MD
Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism
Inselspital
Freiburgstrasse 15
CH-3010 Bern
andreas.melmer[at]insel.ch

Introduction

During the menstrual cycle higher insulin requirements may occur in a subset of women with type 1 diabetes (T1D) [1]. Subsequently, if menstrual cycles disappear during the menopause, previously higher insulin requirements might decrease in parallel. To date, there is little knowledge about how the menopause affects actual insulin dosing in T1D. Irrespective thereof, the life expectancy of patients with T1D tends to increase, and both age and the duration of T1D correlate to a higher risk of acute complications. In the T1D Exchange study, severe hypoglycaemic events were most frequent in participants >50 years of age, accounting for 15% of the entire study population [2]. In the UK Hypoglycaemia Study, the prevalence of severe hypoglycaemia was highest among adults with a T1D duration >15 years [3]. As the natural menopause occurs around the age of 50, postmenopausal women with long-term T1D are particularly exposed to a higher risk for acute complications. It is clinically well recognised that T1D-related treatment adaptions become necessary during and after the menopausal transition. However, there are no treatment guidelines available on how to adapt insulin treatment in postmenopausal women with T1D. It is therefore relevant to increase knowledge about postmenopausal insulin dosing in order to reduce the risk of adverse glucose fluctuations. The present study compared insulin dosing profiles of pre- and postmenopausal women with long-term T1D, who were using continuous subcutaneous insulin infusion.

Methods

Data from 1686 women were extracted from the "Diabetes Prospective Follow-up" ("Diabetes-Patienten-Verlaufsdokumentation" DPV) registry. The DPV database is a standardised, prospective, computer-based documentation of diabetes care and clinical outcomes. During 1995–2019, 1686 adult women aged ≥35 years with T1D from 420 centers in Germany, Austria and Switzerland were documented. Inclusion criteria were diagnosis of type1 diabetes (T1D), age ≥35 years, use of an insulin pump for 24

hours per day, and complete documentation of basal and bolus insulin doses. The DPV registry does not routinely collect the date of the last menstrual period, a key criterion for the definition of naturally occurring menopause. According to an individual participant meta-analysis of 117 epidemiological studies, age at natural menopause was 49.3 ± 4.6 years in 170,413 women. Of those, 15% (n = 26,285) women reported naturally occurring menopause before age of 45 years, 75% (n = 127,984) between the ages 45 and 54 years and 10% (n = 16,144) at age 55 years or older [4]. Following the aforementioned results, we defined 630 women aged <45 years as premenopausal and 548 women aged ≥55 years as postmenopausal. In order to evaluate a potential effect for earlier menopause in women with T1D, an additional comparison was made between women <40 years of age (n = 340) and women aged 55 years or older. Women between ≥40 and <55 years of age (n = 798) were excluded from this secondary analysis.

The following parameters were analysed: demographic data such as age and duration of T1D, anthropometric parameters such as weight, height and body mass index (BMI), and clinical data such as total daily insulin, daily insulin per kilogram bodyweight, total daily basal insulin, daily basal insulin per kilogram bodyweight, total daily bolus insulin, daily bolus insulin per kilogram bodyweight, the percentage of glycated haemoglobin A1 (HbA1c), and the estimated glomerular filtration rate (eGFR)The most recent basal rate profile together with the total daily bolus insulin dose documented for each patient in the DPV database was used for analysis. EGFR was calculated based on the equation of the Chronic Kidney Disease Epidemiology Collaboration (CKD_EPI). The incidence of severe hypoglycaemic events and the incidence of hypoglycaemic events with coma per patient per year was included in the analysisif available.

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Wilcoxon rank sum test was used to calculate cross-sectional differences between pre- and postmenopausal women. A p-value of less than 0.05 was considered significant. Bonferroni post-hoc correction was applied for the number of tests performed, resulting in an alpha-level of 0.05/15 = 0.0033. Statistical analysis was carried out with SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). Data are presented as mean and standard error.

Results

Table 1 illustrates demographic, clinical and anthropometric parameters in pre- and postmenopausal women. In postmenopausal women, total daily insulin, daily insulin per kilogram bodyweight, total daily basal insulin, daily basal insulin per kilogram bodyweight, and eGFR were significantly lower than in premenopausal women. Doses for total daily bolus insulin, daily bolus insulin per kilogram bodyweight, the percentage of HbA1c, BMI, the incidence of severe hypoglycaemic events, and the incidence of hypoglycaemic events with coma per patient per year were comparable between both cohorts.

Discussion

Postmenopausal women used lower basal insulin doses as compared with premenopausal women, whereas glycaemic control and BMI were comparable between the two cohorts.

When using continuous glucose monitoring, fewer hypoglycaemic events, higher nocturnal glucose, and higher postprandial glucose fluctuations were observed in premenopausal women with T1D during the luteal phase of their menstrual cycle [5]. This may be explained by higher concentrations of progesterone near the time of ovulation and during the luteal phase, which increases insulin resistance [6]. Depot-administration of progesterone in healthy women caused higher fasting plasma glucose concentrations followed by a pronounced secretion of insulin [7].

Table 1:
Differences in demographic, clinical and anthropometric parameters between premenopausal women (age ≥35 to <45 years) and postmenopausal women (age ≥55 years).

Parameter	Premenopausal women	Postmenopausal women	p-value[a]
Number of patients	630	548	Not applicable
Age (years)	39.79 ± 0.12	64.44 ± 0.29	<0.0001
Duration of T1D (years)	21.60 ± 0.40	32.66 ± 0.66	<0.0001
Total daily insulin (IU)	41.29 ± 0.85	39.00 ± 1.27	<0.0001
Daily insulin/kg (IU)	0.57 ± 0.01	0.53 ± 0.02	<0.0001
Total daily basal insulin (IU)	21.26 ± 0.37	19.60 ± 0.48	<0.0001
Daily basal insulin/kg (IU)	0.29 ± 0.01	0.27 ± 0.12	<0.0001
Total daily bolus insulin (IU)	22.38 ± 0.68	21.94 ± 1.14	0.0107
Daily bolus insulin/kg (IU)	0.31 ± 0.01	0.30 ± 0.01	0.0092
HbA1c (%; mmol/mol)	7.61 ± 0.06	7.50 ± 0.05	0.7858
BMI (kg/m^2)	26.23 ± 0.20	26.80 ± 0.22	0.0459
Body weight (kg)	73.04 ± 0.61	72.40 ± 0.63	0.4864
Body height (cm)	166.77 ± 0.28	164.36 ± 0.27	<0.0001
eGFR[b] (ml/min/1.73 m^2 body surface)	90.80 ± 1.2	67.39 ± 1.18	<0.0001
Severe hypoglycaemia (/year)	0.25 ± 0.05	0.24 ± 0.03	0.4335
Hypoglycaemia with coma (/year)	0.05 ± 0.01	0.10 ± 0.02	0.0306

BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin A1; T1D = type 1 diabetes

[a] Wilcoxon rank sum test. A p-value <0.05 was considered statistically significant. Bonferroni post hoc correction was applied for 15 tests performed (alpha-level of 0.05/15 = 0.0033 as level of significance).

[b] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD_EPI) equation.

Moreover, oestradiol was found to augment growth-hormone secretion, which may reduce the glucose-lowering effect of insulin in the luteal phase of the menstrual cycle [8]. As progesterone and oestradiol levels decrease during menopause, these hormonal changes may be one of the reasons for the differences in insulin doses seen in this study.

In addition, the comparatively lower glomerular filtration rate (GFR) in women aged ≥55 years might have contributed to their lower insulin requirements. Endogenously secreted insulin is subject to substantial degradation in the liver. However, exogenous insulin is primarily eliminated by the kidney. Insulin is freely filtered at the glomerulus and extensively reabsorbed in the proximal tubule. Within proximal tubular cells, insulin undergoes enzymatic degradation. Further insulin uptake and degradation is conducted by peritubular endothelial and renal epithelial cells, which is why total renal clearance exceeds GFR [9]. Peritubular insulin absorption is indirectly correlated to renal function, thereby compensating for the decline in degradation of filtered insulin down to a GFR of <20 ml/min. Beyond this threshold, insulin clearance decreases, the half-life of insulin increases and overall requirements for insulin decline [10–12]. The decreased clearance and catabolism of insulin may ultimately translate into longer persistence of short- and long-acting insulin preparations and increase the risk for hypoglycaemia. Kulozik et al. investigated the correlation of eGFR and required doses of long- and short-acting insulin analogues in over 300 patients with T1D. Requirements for insulin lispro were directly correlated to the whole range of eGFR. In patients with eGFR <60 ml/min, insulin dosage was 32.6% lower than in patients with eGFR >90 ml/min. However, requirements for insulin aspart were independent of eGFR [13]. In the present study, mean eGFR was >50 ml/min, below which substantial reductions of insulin dosing are recommended and both cohorts presented a similar risk for severe hypoglycaemic events [14]. Moreover, insulin aspart was commonly used in the older cohort, which might further influence the extent to which insulin doses were reduced. In summary, the decline in renal function observed in women aged ≥55 years may have contributed to reductions of their daily insulin doses. Yet the net effect of renal function on insulin adaptions should be interpreted with consideration of other factors determining insulin requirements in younger and older women.

One of these factors may be a change in caloric intake after the menopause. Changes in appetite and caloric intake are commonly observed during the menstrual cycle. The largest clinical trial on macronutrient intake in premenopausal women - the BioCycle study - revealed the following: caloric intake and appetite, as well as craving for chocolate, sweet and salt peaked during the mid-luteal phase in 259 women, regardless of whether ovulation actually occurred or not [15].The impact of oestrogen and progesterone together with changes in eating habits may increase insulin requirements, particularly during the luteal phase of the menstrual cycle. In an analysis of blood samples obtained from the BioCycle study, a homeostasis model of insulin resistance (HOMA-IR) significantly increased from 1.4 during the mid-follicular phase to 1.6 in the early luteal phase of the menstrual cycle (p <0.001). After adjustment for age, race, cycle and other sex hormones, HOMA-IR was positively associated with oestradiol (p <0.001) and progesterone (p <0.001) [6]. A study using continuous glucose monitoring in 12 women with T1D, who were treated with continuous subcutaneous insulin infusion, showed elevated high blood glucose indices during periovulation and until the early luteal phase [1]. In summary, premenopausal women may require higher insulin doses to compensate for changes in insulin action and caloric consumption during the menstrual cycle. After the menopause, these effects disappear, which might explain the use of lower insulin doses in postmenopausal women.

BMI was similar in both cohorts, which indicates that the observed differences in insulin doses were independent of body weight. However, BMI does not reflect body composition, which might change during transition to the menopause. Data from the longitudinal Study of Women's Health Across the Nation (SWAN), which measured body composition during the menopausal transition in 1246 women showed the following: at the start of menopausal transition, the rate of body fat gain doubled, whereas a significant loss of lean mass was observed. These changes continued until 2 years after the last menstrual bleeding was observed and stabilised afterwards [16]. An increase in body fat mass would likely associate with higher insulin requirements. However, body composition was not obtained in the present study, which precludes estimation ofits contribution to the observed changes in insulin requirements.

The study is subject to the following limitations. First, this was a cross-sectional study, which precludes analysis of changes in insulin dosing profilesprior, during or after transition to the menopause. Nevertheless, bolus insulin doses, HbA1c and BMI were comparable between the two cohorts, which indicates that the observed results were independent of nutrition, glycaemic control and body weight. Second, the DPV database did not include information about the last menstrual period. However, the definition of the menopause in the present study was based on the age of natural occurrence of the menopause in >118,000 women from 117 epidemiological studies, which should reduce the number of women falsely defined as pre- or postmenopausal to a minimum. Information about the final menstrual period would furthermore have identified cases of early menopause. Women with T1D have a higher prevalence of early menopause, which may be related to prolonged hyperglycaemia, long-term complications of T1D, or autoimmune processes directed against the ovary [17–21]. In order to evaluate a potential influence of early menopause, we conducted a comparison of women <40 years of age with women aged ≥55 years. The subanalysis revealed similar resultsto our main analysis, with significant differences in total daily insulin and basal insulin doses (please refer to supplementary table 1 in the appendix). Third, the DPV database did not provide the number of basal rates used by premenopausal women. Multiple basal rates may be used by women with T1D to compensate for variable insulin requirements during the menstrual cycle. If the last basal rate profile entered in the DPV database was a profile that is commonly used outside of the menstrual cycle, it likely provided lower basal insulin doses according to higher insulin requirements during the menstrual cy-

cle. In this case, the present results were rather underestimated. Fourth, the DPV database does not routinely obtain information about the intake of hormone replacement therapy [HRT), which was associated with a reduction of insulin requirements in postmenopausal women [22]. HRT is used independently of diabetes in women in order to treat symptoms associated with the menopausal transition. In order to increase representability of the present results, HRT was not an exclusion criterion in the present study.

In summary, postmenopausal women with T1D used lower basal insulin dose profiles as compared with premenopausal women, despite similar glycaemic control and BMI. Lower eGFR and lower exposure to sexual hormones may be responsible for this observation. However, further research is necessary to determine the contribution of body composition and eating habits to the observed difference in daily insulin doses.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Acknowledgements

We thank all members of the German, Austrian, and Swiss working group on CSII for collecting and documenting data in the DPV-database. For a list of participating centres, see http://www.d-p-v.eu. The authors thank Andreas Hungele and Ramona Ranz for support and the development of the DPV documentation software and Katharina Fink and EstherBollow for the DPV data management (in each case clinical data manager, Ulm University). The DPV registry is supported by the German FederalMinistry for Education and Research (82DZD0017G), the European Foundation for the Study of Diabetes (EFSD), and the Deutsche Diabetes Gesellschaft (DDG).

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Brown SA, Jiang B, McElwee-Malloy M, Wakeman C, Breton MD. Fluctuations of Hyperglycemia and Insulin Sensitivity Are Linked to Menstrual Cycle Phases in Women With T1D. J Diabetes Sci Technol. 2015 Oct;9(6):1192–9. http://dx.doi.org/10.1177/1932296815608400. PubMed. 1932-2968
2. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019 Feb;21(2):66–72. http://dx.doi.org/10.1089/dia.2018.0384. PubMed. 1557-8593
3. Group UK; UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007 Jun;50(6):1140–7. http://dx.doi.org/10.1007/s00125-007-0599-y. PubMed. 0012-186X
4. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012 Nov;13(11):1141–51. http://dx.doi.org/10.1016/S1470-2045(12)70425-4. PubMed. 1474-5488
5. Barata DS, Adan LF, Netto EM, Ramalho AC. The effect of the menstrual cycle on glucose control in women with type 1 diabetes evaluated using a continuous glucose monitoring system. Diabetes Care. 2013 May;36(5):e70. http://dx.doi.org/10.2337/dc12-2248. PubMed. 1935-5548
6. Yeung EH, Zhang C, Mumford SL, Ye A, Trevisan M, Chen L, et al. Longitudinal study of insulin resistance and sex hormones over the menstrual cycle: the BioCycle Study. J Clin Endocrinol Metab. 2010 Dec;95(12):5435–42. http://dx.doi.org/10.1210/jc.2010-0702. PubMed. 1945-7197
7. Berenson AB, van den Berg P, Williams KJ, Rahman M. Effect of injectable and oral contraceptives on glucose and insulin levels. Obstet Gynecol. 2011 Jan;117(1):41–7. http://dx.doi.org/10.1097/AOG.0b013e318202ac23. PubMed. 1873-233X
8. Friend KE, Hartman ML, Pezzoli SS, Clasey JL, Thorner MO. Both oral and transdermal estrogen increase growth hormone release in postmenopausal women—a clinical research center study. J Clin Endocrinol Metab. 1996 Jun;81(6):2250–6. PubMed. 0021-972X
9. Rabkin R, Ryan MP, Duckworth WC. The renal metabolism of insulin. Diabetologia. 1984 Sep;27(3):351–7. http://dx.doi.org/10.1007/BF00304849. PubMed. 0012-186X
10. Rubenstein AH, Mako ME, Horwitz DL. Insulin and the kidney. Nephron J. 1975;15(3-5):306–26. http://dx.doi.org/10.1159/000180518. PubMed. 1660-8151
11. Rave K, Heise T, Pfützner A, Heinemann L, Sawicki PT. Impact of diabetic nephropathy on pharmacodynamic and Pharmacokinetic properties of insulin in type 1 diabetic patients. Diabetes Care. 2001 May;24(5):886–90. http://dx.doi.org/10.2337/diacare.24.5.886. PubMed. 0149-5992
12. Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. Decreased insulin requirement in relation to GFR in nephropathic Type 1 and insulin-treated Type 2 diabetic patients. Diabet Med. 2003 Aug;20(8):642–5. http://dx.doi.org/10.1046/j.1464-5491.2003.01025.x. PubMed. 0742-3071
13. Kulozik F, Hasslacher C. Insulin requirements in patients with diabetes and declining kidney function: differences between insulin analogues and human insulin? Ther Adv Endocrinol Metab. 2013 Aug;4(4):113–21. http://dx.doi.org/10.1177/2042018813501188. PubMed. 2042-0188
14 Charpentier G, Riveline JP, and Varroud-Vial M. Management of drugs affecting blood glucose in diabetic patients with renal failure. Diabetes & metabolism. 2000;26 Suppl 4(73-85.
15. Gorczyca AM, Sjaarda LA, Mitchell EM, Perkins NJ, Schliep KC, Wactawski-Wende J, et al. Changes in macronutrient, micronutrient, and food group intakes throughout the menstrual cycle in healthy, premenopausal women. Eur J Nutr. 2016 Apr;55(3):1181–8. http://dx.doi.org/10.1007/s00394-015-0931-0. PubMed. 1436-6215
16. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, et al. Changes in body composition and weight during the menopause transition. JCI Insight. 2019 Mar;4(5):124865. http://dx.doi.org/10.1172/jci.insight.124865. PubMed. 2379-3708
17. LaBarbera AR, Miller MM, Ober C, Rebar RW. Autoimmune etiology in premature ovarian failure. Am J Reprod Immunol Microbiol. 1988 Mar;16(3):115–22. http://dx.doi.org/10.1111/j.1600-0897.1988.tb00180.x. PubMed. 8755-8920
18. Kalantaridou SN, Davis SR, Nelson LM. Premature ovarian failure. Endocrinol Metab Clin North Am. 1998 Dec;27(4):989–1006. http://dx.doi.org/10.1016/S0889-8529(05)70051-7. PubMed. 0889-8529
19. Yki-Järvinen H, Koivisto VA. Natural course of insulin resistance in type I diabetes. N Engl J Med. 1986 Jul;315(4):224–30. http://dx.doi.org/10.1056/NEJM198607243150404. PubMed. 0028-4793
20. DeFronzo RA, Hendler R, Simonson D. Insulin resistance is a prominent feature of insulin-dependent diabetes. Diabetes. 1982 Sep;31(9):795–801. http://dx.doi.org/10.2337/diab.31.9.795. PubMed. 0012-1797
21. Moncayo R, Moncayo HE. Autoimmunity and the ovary. Immunol Today. 1992 Jul;13(7):255–8. http://dx.doi.org/10.1016/0167-5699(92)90006-S. PubMed. 0167-5699
22. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, et al.; Heart and Estrogen/progestin Replacement Study. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2003 Jan;138(1):1–9. http://dx.doi.org/10.7326/0003-4819-138-1-200301070-00005. PubMed. 1539-3704

Appendix: Supplementary table

Supplementary table S1 illustrates differences between premenopausal and postmenopausal women.

Table S1:
Differences in demographic, clinical, and anthropometric parameters between premenopausal women (age ≥ 35 to <40 years) and postmenopausal women (age ≥ 55 years).

Parameter	Premenopausal women	Postmenopausal women	p-value[a]
Number of patients	340	548	Not applicable
Age (years)	37.38 ± 0.08	64.44 ± 0.29	<0.0001
Duration of T1D (years)	20.16 ± 0.51	32.66 ± 0.66	<0.0001
Total daily insulin (IU)	40.71 ± 1.01	39.00 ± 1.27	0.0004
Daily insulin/kg (IU)	0.56 ± 0.01	0.53 ± 0.02	0.0001
Total daily basal insulin (IU)	20.88 ± 0.49	19.60 ± 0.48	<0.0001
Daily basal insulin/kg (IU)	0.29 ± 0.01	0.27 ± 0.12	<0.0001
Total daily bolus insulin (IU)	22.28 ± 0.70	21.94 ± 1.14	0.0084
Daily bolus insulin/kg (IU)	0.31 ± 0.01	0.30 ± 0.01	0.0030
HbA1c (%; mmol/mol)	7.52 ± 0.08	7.50 ± 0.05	0.1931
BMI (kg/m^2)	26.14 ± 0.28	26.80 ± 0.22	0.0495
Body weight (kg)	72.66 ± 0.82	72.40 ± 0.63	0.8823
Body height (cm)	166.67 ± 0.36	164.36 ± 0.27	<0.0001
eGFR[b] (ml/min/1.73 m^2 body surface)	92.99 ± 1.62	67.39 ± 1.18	<0.0001
Severe hypoglycaemia (/year)	0.32 ± 0.09	0.24 ± 0.03	0.9556
Hypoglycaemia with coma (/year)	0.06 ± 0.01	0.10 ± 0.02	0.1350

T1D = type 1 diabetes; HbA1c = haemoglobin A1; BMI = body mass index; eGFR = estimated glomerular filtration rate

[a] Wilcoxon rank sum test. A p-value <0.05 was considered statistically significant. Bonferroni post hoc correction was applied for 15 tests performed (alpha-level of 0.05/15 = 0.0033 as level of significance).

[b] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD_EPI) equation.