ORIGINAL PAPER

Submitted: 19.06.2024
Accepted: 14.10.2024
Early publication date: 26.11.2024

Endokrynologia Polska
DOI: 10.5603/ep.101234
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 75; Number/Numer 6/2024

Possible changes in glucose metabolism induced by radioligand therapy in patients with neuroendocrine neoplasms

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Abstract

Introduction: Neuroendocrine neoplasms (NENs) belong to a heterogeneous group of tumours originating from neuroendocrine cells. Primary tumours most commonly occur in the gastrointestinal tract, although they can arise in any part of the human body. Radioligand therapy (RLT) is recommended for progressive or inoperable cases in subsequent lines of the therapy. Our study aimed to investigate glucose metabolism alterations during and after radioligand therapy in patients with neuroendocrine neoplasms undergoing radioligand therapy.

Material and methods: The study was performed on 41 patients with inoperable neuroendocrine tumours, who underwent one cycle (4 courses) of radioligand therapy with [^{177}Lu]Lu-DOTA-TATE alone or tandem therapy with [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TATE with a standardised nephroprotection protocol. Laboratory parameters were analysed during the first and fourth courses and one year after the last course of treatment.

Results: The study showed a statistically insignificant increase in fasting glucose concentration during and after radioligand therapy, accompanied by a parallel increase in insulin concentration. In patients treated with tandem therapy, the increase in fasting glucose was higher, but the results were still statistically insignificant. No glycaemic severe adverse events (Common Terminology Criteria for Adverse Events [CTCAE]_G3–G5) were observed.

Conclusions: Radioligand therapy potentially increases fasting glucose concentrations, probably due to changes in peripheral glucose metabolism. However, it remains a safe treatment method for patients with neuroendocrine neoplasms and does not cause severe glycaemic adverse events related to glucose metabolism. **(Endokrynol Pol 2024; 75 (6): 665–671)**

Key words: *RLT; PRRT; glucose; glycaemia; insulin; HbA1c; 177-Lu; 90-Y*

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group derived from neuroectodermal or endodermal cells [1, 2]. These tumours can arise in almost any part of the human body, but the most common location is the gastrointestinal tract. The incidence of NENs is increasing every year [3]. NENs most commonly localise in the small intestine within the gastrointestinal tract. The primary tumour location, however, often remains unknown [4–6]. The majority of NENs are non-functioning (non-secreting) tumours and are diagnosed incidentally due to metastases or the mass effect of the tumour [4, 7, 8].

Radioligand therapy (RLT), previously known as peptide receptor radionuclide therapy (PRRT), is a treatment option used for inoperable tumours or in patients with disease progression confirmed by morphological [magnetic resonance imaging (MRI) and computed tomography (CT)] and functional tests [somatostatin receptor imaging (SRI)] [4, 9, 10]. Qualification for RLT always requires confirmation of somatostatin receptor expression through SRI, typically positron emission tomography (PET)/CT using [^{68}Ga]-DOTA-TATE or scintigraphy (with SPECT/CT) using [^{99m}Tc]-HYNIC-TOC [4]. RLT is administered in G1, G2, and some G3 grading cases with lower proliferation index — Ki-67 and good somatostatin receptor (SSTR) expression [11]. Nowadays, 2 somatostatin analogues labelled with beta-emitters — ^{90}Yttrium (^{90}Y) and ^{177}Lutetium (^{177}Lu) — are used for RLT. In some centres, the so-called "tandem" therapy, which includes both radionuclides, is used in

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clinical trials [13]. Presently, the standard and approved RLT regimen consists of 4 cycles of 7.4 GBq (200 mCi) [^{177}Lu] Lu-DOTA-TATE with intervals of 8–12 weeks [12]. However, the radioisotope of ^{90}Yttrium, due to its higher energy and range, is considered a more limited option due to the possibility of causing a higher number of radiation-related complications. Therefore, it is mainly administered with ^{177}Lutetium at lower activity as a tandem therapy. Thus, most studies advocate for studies using ^{177}Lutetium alone because it is considered less myelo- and nephrotoxic [14].

Withdrawal of the RLT is mainly caused by bone marrow, renal, or, more rarely, hepatic complications [15]. Current guidelines advocate the use of RLT before chemotherapy, an mTOR inhibitor (everolimus), or a multi-kinase inhibitor with antiangiogenic activity (sunitinib); however, these should still be considered a subsequent line of treatment [16-22].

Due to the natural occurrence of somatostatin receptors on normal pancreatic cells, possible injury during or after RTL was taken under initial observation and investigation. The study aimed to assess if RLT influences glucose metabolism.

Table 1. *Characteristics of the study group*

Sex	
Female	19 (46.4%)
Male	22 (53.6%)
Primary NEN location	
Pancreas	15 (36.6%)
Small intestine	13 (31.7%)
Large intestine	5 (12.2%)
Other (lungs, ovaries, stomach)	4 (9.7%)
Unknown	4 (9.7%)
NEN Grading	
G1	20 (48.8%)
G2	21 (51.2%)
BMI	
Mean	24.8 ±5.3
< 18.5	3 (7.3%)
28.5–24.9	20 (48.8%)
24.9–29.9	12 (29.3%)
≥ 30.0	6 (14.6%)
	N = 41(%)

BMI — body mass index; NEN — neuroendocrine neoplasm; N — number of patients; % — percentage of patients

Material and methods

Protocol and study group

A group of 41 patients were qualified for the study. All patients signed an informed consent form and agreed to participate in the study. The study was conducted according to the guidelines of the Helsinki Declaration and approved by the local Bioethical Committee (52/WIM/2017). Patients were enrolled in either the "lutetium" subgroup (7.4 GBq of [^{177}Lu] Lu-DOTA-TATE) or "tandem" subgroup (1.85GBq [^{177}Lu] Lu-DOTA-TATE + 1.85GBq [^{90}Y] Y-DOTA-TATE). A group of 36 patients completed an entire cycle of 4 courses of RLT. During 8- to 14-week intervals, long-lasting somatostatin analogues, lanreotide or octreotide (120 mg *vs*. 30 mg, respectively), were administrated every 4 weeks. Intravenous nephroprotection using amino acids was administered during (1000 ml) and a day after (500 ml) of each course of RLT.

The mean age (with standard deviation) of the patients in the study group was 58.2 ± 13.3 years, and the age range was 23–76 years old. Table 1 presents detailed characteristics of the study group. Thirty-three patients had non-secreting tumours, while 8 presented carcinoid syndromes. All patients had distant metastases at the time of RLT qualification.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

— histological confirmation of functioning or non-functioning NEN (a well- or moderately differentiated unresectable metastatic, progressive neuroendocrine neoplasm (Ki-67 < 20%);
— no possibility of surgery;
— ongoing long-acting somatostatin analogues (lanreotide, octreotide) treatment;
— progression according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1);
— good expression of somatostatin receptors in SRI performed up to 3 months before therapy (scintigraphy radiotracer uptake in most of the lesions higher than in the normal liver [Krenning scale 3] or in [^{68}Ga]-PET/CT [maximum standardised uptake value – SUVmax] in most of the lesions higher than SUVmax in the normal liver);
— morphological tumour presence confirmed in CT or MRI;
— patients with a dominant lesion (metastasis or inoperable primary tumour) ≥ 45 mm in any diameter were qualified for tandem therapy; ones with a dominant lesion < 45 mm for the lutetium subgroup.

The exclusion criteria were as follows:

— lack of informed consent;
— pregnancy or lactation;
— renal disfunction defined a glomerular filtration rate (GFR) < 30 mL/min or serum Creatinine > 1.8 mg/dL;
— liver dysfunction (defined as alanine transaminase [ALT] over 3× upper limit), myelosuppression (defined as haemoglobin < 8 g/L or platelets < 80000/μL, or leukocytes < 2000/μL, or lymphocytes < 500/μL, or neutrophils < 1000/μL);
— Karnofsky scale < 60;
— World Health Organisation (WHO)/Eastern Cooperative Oncology Group (ECOG) scale 3 or 4;
— no tracer uptake in SRI [2].

Laboratory evaluation

Venous blood samples were taken fasting between 07:30 and 08:30 AM. They were collected with the BD Vacutainer Tests in the Department of Endocrinology and Radioisotope Therapy and analysed in the Department of Laboratory Diagnostics (both Military Institute of Medicine - National Research Institute, Warsaw, Poland). During Course I and IV, samples were collected on admission (before RLT) and 48 hours after RLT administration. Analyses were performed on an automatic biochemistry analyser Cobas C501 (2016) by Roche Diagnostics, Switzerland. The reference range for fasting glucose was 70–99 mg/dL (3.9–5.5 mmol/L), and for insulin 1–25 mIU/L. Serum glucose was measured a day before and 2 days after radioisotope administration. Insulin and glycated haemoglobin (HbA_{1c}) were measured before RLT infusion.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics package, Version 25.0., Armonk, NY, USA: IBM Corp. (Released 2021). All data are presented as mean values (M) and standard deviation (SD). A p-value of < 0.05 was considered statistically significant. Basic descriptive statistics with the Shapiro–Wilk test and 2-way mixed analysis of variance were used to perform the statistical analyses.

Results

Course I (of RLT)

Results showed a significant increase in glucose concentration ($p = 0.009$) during the first course of treatment. Before RLT administration, fasting glucose was 104.45 ± 21.94 mg/dl, while 48 hours after RLT, it was 109.66±19.93. A higher increase was observed for patients with primary tumour localisation in the pancreas (although results were at a statistical trend level of $p = 0.054$). The change of glycaemia was not dependent on previous diagnosis of diabetes, GFR, or other analysed factors (Tab. 2). Among patients without a diagnosis of diabetes, the increase in glucose concentration was depended on pancreatic localisation of the tumour ($p = 0.02$) and use of tandem therapy; however, in this case, results reached only a statistical trend level ($p = 0.06$). In all patients (both diabetic and non-diabetic combined), no significant difference ($p = 0.174$) was observed between the therapies used ("lutetium" *vs*. "tandem"). However, an increase in the subgroup receiving [^{177}Lu] Lu/[^{90}Y] Y-DOTA-TATE ($n = 11$) was higher than that of the subgroup receiving [^{177}Lu] Lu-DOTA-TATE ($n = 30$), and the results were 10.3 mg/dl and 3.4 mg/dl, respectively.

Course IV

During the fourth RLT administration, fasting glucose was 114.36 ± 21.94 mg/dl. In contrast, 48 hours after the fourth course of RLT, we did not observe significant changes in fasting glucose serum concentration ($p = 0.064$). Before the fourth RLT administration, fasting glucose was 114.36 ± 21.94 mg/dl, while 48 hours after the fourth course of RLT, it was 110.75 ± 24.22 mg/dl.

Course I vs. course IV

Comparing laboratory results between the first and last course of RLT, the data showed a significant increase in serum glucose concentration ($p = 0.021$). Insulin concentration also increased, but not significantly. HbA_{1c} concentration did not change (Tab. 3). The increase of glucose concentration was higher in patients receiving tandem therapy ($p = 0.01$) (Tab. 4) and was not dependent on tumour localisation (Tab. 5) or previous diagnosis of diabetes. The separated subgroup data with complete data are presented in Supplementary File — Table S2.

Table 2. *Glucose concentration change due to analysed factors during Course I of radioligand therapy (RLT)*

	Glucose changes due to demographic and medical factors during Course I		
	Δ	SD	p
Sex			
M (n = 22)	5.63	18.25	0.853
F (n = 19)	4.79	7.16	
Age			
< 60 (n = 19)	6.68	7.67	0.541
> 60 (n = 22)	3.74	17.92	
BMI [kg/m^2]			
< 25 (n = 23)	6.88	10.95	0.333
> 25 (n = 18)	2.36	17.51	
GRF [ml/min/1.73 m^2]			
> 60 (n = 35)	6.31	14.13	0.257
< 60 (n = 6)	-0.67	9.83	
Diabetes			
No (n = 29)	4.00	13.47	0.334
Yes (n = 12)	9.11	14.43	
Hyperlipidaemia			
No (n = 30)	5.24	14.45	0.975
Yes (n = 6)	5.00	3.37	
Hypertension			
No (n = 23)	6.29	14.98	0.425
Yes (n = 18)	2.20	9.05	
NEN localisation			
Pancreas (n = 15)	11.5	11.51	0.054
Other (n = 26)	2.31	13.82	

U — units; Δ — change; SD — standard deviation; Bold values indicate statistical significance; BMI — body mass index; GFR — glomerular filtration rate; NEN — neuroendocrine neoplasms; p — p-value

Course I vs. Follow-up

Most essential results regarding the safety profile and possible RLT adverse events were obtained after analysing differences in glucose serum concentrations before Course I and a year after treatment (follow-up). We noticed a statistically significant increase in fasting glucose concentration ($p = 0.001$); before the first RLT administration, fasting glucose was 106.26 ± 226.04 mg/dL, while during follow-up it was 123.47 ± 31.62 mg/dL. The results were more marked (on statistical trend level) in patients who received "tandem" therapy ($p = 0.072$); $\Delta = 39.0$ mg/dl compared to 13.1mg/dl in the "lutetium' group. This hyperglycaemic tendency was observed more often in male patients ($p = 0.020$) and with primary NEN location in the pancreas ($p = 0.028$). Glucose concentration did

Table 3. *Glucose metabolism parameters before Course I and before Course IV of radioligand therapy (RLT)*

	Before Course I (n)		Before Course IV (n)		
Parameter	**M**	**SD**	**M**	**SD**	**p**
Glucose [mg/dL] (n = 34)	112.15	42.49	115.23	44.48	**0.021**
Insulin [mIU/L] (n = 15)	12.72	13.83	14.73	15.19	0.105
HbA_{1c} (%) (n = 11)	6.00	0.71	6.00	0.59	0.408

HbA_{1c} — glycated haemoglobin; U — units; M — mean value; SD — standard deviation; p — p-value; bold values indicate statistical significance

Table 4. *Glucose metabolism parameters depending on the used radioisotope*

Parameter	[^{177}Lu]Lu-DOTA-TATE (N)		[^{177}Lu]Lu/[^{90}Y]Y -DOTA-TATE (n)		p
	Δ	SD	Δ	SD	
Glucose [mg/dL] (n = 26; n = 8)	0.08	13.77	12.88	10.62	**0.010**
Insulin [mIU/L] (n = 11; n = 4)	–1.27	6.66	11.03	15.86	**0.145**
HbA_{1c} (%) (n = 7; n = 4)	0.20	0.30	–0.35	0.17	**0.011**

HbA_{1c} — glycated haemoglobin; U — units; Δ — change; SD — standard deviation; p — p-value

Table 5. *Glucose metabolism parameters due to primary neuroendocrine neoplasms (NEN) location*

Parameter	Pancreas (N)		Other locations (n)		p
	Δ	SD	Δ	SD	
Glucose [mg/dL] (n = 21; n = 13)	0.71	15.10	6.92	11.76	**0.216**
Insulin [mg/dl] (n = 6; n = 9)	–0.47	9.55	3.66	11.86	**0.491**
HbA_{1c} (%) (n = 6; n = 5)	–0.08	0.27	0.10	0.49	**0.465**

Δ — change; SD — standard deviation; p — p-value; bold values indicate statistical significance

not correlate with age, BMI, previous diabetes diagnosis, and other chronic diseases (Tab. 6). In a subgroup of patients without previous diabetes, we observed an increase in glycaemia from 98.33 ± 16.61 mg/dl to 112.2 ± 24.93 mg/dl (p = 0.023).

Adverse events analysis

Adverse events (AE) were assessed using the National Cancer Institute (NCI) CTCAE version 6.0. Initially, 44.7% of patients presented Grade 1–2 AE regarding glucose concentration. During treatment this number increased to 63.2%, and a year later it increased even more to 68.4%. No G3–G5 adverse events in glucose metabolism were observed. The total number of all assessed AEs in the study group is presented in Table 7.

Discussion

Studies describing complications of glucose metabolism after radioligand therapy still need to be included. Our prospective study was one of the first to analyse this issue by measuring glucose metabolism parameters during treatment and long-term observation.

Our results showed that RLT can affect glucose metabolism, fasting glucose concentrations, and HbA_{1c} values during the RLT and long-term follow-up. The most important factors that affected the results were pancreatic tumour location and the use of tandem therapy.

One could assume that it is due to direct radiation injury of Langerhans islets and impairment of their excretive and regulative function [23]. Higher energy and range of 90Yttrium radiation are also likely rea-

Table 6. *Glucose concentration change due to analysed factors a year after treatment (follow-up)*

	Glucose [mg/dl] change due to other factors during a year after treatment		
	Δ	SD	p
Sex			
F (n = 8)	3.38	13.35	0.020
M (n = 11)	27.27	23.74	
Age			
< 60 (n = 18)	16.00	16.28	0.851
> 60 (n = 11)	18.09	27.66	
BMI [kg/m²]			
< 25 (n = 12)	19.92	28.44	0.416
> 25 (n = 7)	12.57	8.10	
GRF [mL/min/1.73 m²]			
> 60 (n = 15)	21.00	22.82	0.171
< 60 (n = 4)	3.00	20.15	
Diabetes			
No (n = 15)	13.87	20.99	0.230
Yes (n = 4)	29.75	29.23	
Hypertension			
No (n = 12)	24.08	24.52	0.088
Yes (n = 7)	5.43	15.15	
NEN localisation			
Pancreas (n = 7)	35.29	26.38	0.028
Other (n = 12)	6.67	12.55	

U — units; Δ — change; SD — standard deviation; bold values indicate statistical significance; BMI — body mass index; GFR — glomerular filtration rate; p — p-value

sons for higher hyperglycaemia rates in a subgroup of patients receiving tandem therapy. However, no change in insulin concentration was observed during the study. We also did not observe any statistical changes in liver parameters during the study, which suggests a non-hepatic cause of insulin resistance changes (Supplementary File — Table S1). Hence, one more answer — even more possible — is the effect of RLT on peripheral glucose metabolism. During the study, we did not observe a decrease in insulin concentration in any patient; there was only a slight, insignificant increase.

Furthermore, in a group treated with ^{177}Lutetium/^{90}Yttrium, an increase in insulin concentration was much higher, which can also advocate more for peripheral metabolism changes and speak against a decrease in insulin concentration due to direct islet injury. Still, clear evidence of this observation in the available literature must be precise. However, RLT can cause injury in peripheral blood lymphocytes, other cells, and tissues, so it could also change some metabolic pathways, including glucose metabolism [24, 25]. A notable fact is that glucose metabolism impairment remains permanent, and its proper function does not return to the baseline even a year after therapy. Similar results were obtained in the assessment of RLT nephrotoxicity. After RLT, renal filtration decreased progressively, and this decrease remained permanent in up to 10% of initial GFR values in long-term observation [26]. The Bodei et al. study on 807 patients receiving ^{177}Lu only or tandem therapy with ^{177}Lutetium/^{90}Yttrium showed a higher rate of nephrotoxicity and myelotoxicity in the second group [27]. Although some data advocate for similar possible complications when using tandem therapy, with a higher potential for treatment, a greater number of studies and observations is necessary [14]. This situation was different from the one observed in bone marrow adverse events. It was confirmed that bone marrow has some regenerative potential, and despite RLT injury (mainly in leukocyte number), the blood count could increase over time [27, 28].

Our study also showed a relatively high number of mild adverse events in glycaemia concentration (CTCAE v 6.0). Initially, almost half of the patients presented G1/G2 stages of glycaemic disturbances, and this percentage increased to over two-thirds at the end of the observation. None of the patients experienced severe glycaemic complications, and no significant difference in glycated haemoglobin value was observed.

Table 7. *Adverse events (AE) summary*

	Before Course I (n = 38)		After Course I (n = 38)		One year after treatment (n = 19)		
Grade of AE	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G3**
Hyperglycaemia	12 (31.6%)	5 (13.1%)	20 (52.6%)	4 (10.6%)	8 (42.1%)	5 (26.3%)	0 (0%)
Leucocytes	5 (13.1%)	1 (2.6%)	5 (13.1%)	1 (2.6%)	0 (0%)	4 (21.1%)	0 (0%)
Lymphocytes	7 (18.4%)	1 (2.6%)	7 (18.4%)	1 (2.6%)	1 (5.3%)	7 36.8%)	1 (5.3%)
Neutrophiles	1 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)	1 (5.3%)	3 (15.8%)	1 (5.3%)
Kidney function	15 (39.5%)	7 (18.4%)	15 (39.5%)	7 (18.4%)	8 (42.1%)	5 (26.3%)	0 (0%)

There are only a few studies in which the authors observed RLT's impact on metabolic parameters. Teunissen et al., on a group of 79 patients treated with 600 to 800 mCi of ^{177}Lutetium (administrated in 3–4 cycles), performed an analysis of pituitary and peripheral hormones and glycated haemoglobin concentration. Of those patients, 9 had diabetes mellitus diagnosed before treatment, and 5 of them had HbA_{1c} concentrations above 6.5% before therapy. In long-term observation (up to 24 months), they assessed 69 patients and observed an increase in HbA_{1c} values from 5.7% to 6.0% ($p < 0.05$). Only 5 extra patients reached HbA_{1c} concentrations above 6.5% during the observation. Unfortunately, fasting glucose concentrations were not measured during the study [29].

The affinity of radioligands to somatostatin receptors located physiologically in the pancreas could affect the function of Langerhans islets and change insulin secretion [30, 31], but our study did not confirm this.

Some adverse effects on glucose metabolism can also be related to permanent somatostatin analogues (SSA) administration in patients with NENs. However, all patients who qualified for our study had chronically received SSA before RLT started [32–34]. There is also no possibility of comparing those patients to those who do not receive SSA due to NEN treatment protocols, guidelines, and medical ethics. It is worth noticing that Mazziotti et al., on a group of 26 patients with acromegaly, confirmed that an increase in octreotide LAR dose (30 to 60 mg) or frequency (30 mg every 21 days instead of 28) did not impact glucose metabolism in most patients. Similar results were obtained in a group of patients treated with lanreotide. Couture et al., in a group of 42 patients, noticed that in 84% of them, glucose concentration did not change, or patients improved glycaemic control.

Nevertheless, Patel et al. measured the incidence of new diabetes or worsening of glycaemic control for 279 patients with NETs who were treated with SSAs and had a pre-existing diagnosis of diabetes. The retrospective study covered 5 years of observation. Treatment with SSAs for NENs was associated with an increase in HbA_{1c} despite a reduction in BMI and risk of developing type 2 diabetes [35]. Considering all the above, the relatively short time of observation (one year), and the fact that almost all patients with NENs are receiving almost all patients with NENs receive octreotide or lanreotide, we can assume that RLT was the only factor influencing the results obtained in our study.

There is a relative dearth of research describing glycaemia disruption after RLT in available databases, so discussion is limited. Our preliminary study suggests more extensive groups of NEN patients. This influence and potential complications of glucose metabolism should be confirmed in future studies, preferably on groups of NEN patients, and deepening glucose metabolic pathway tests to point out the main pathomechanism of RLT action.

Study limitations

The study was conducted with fewer patients, mainly because of 3 factors. First was a low incidence of neuroendocrine neoplasms in the population; second was the lack of consent among all patients treated in our clinic; and third was the time of the COVID-19 pandemic, which limited the possibility of hospitalisation and patient treatment. Another limitation was the lack of complete glucose metabolism parameters (HbA_{1c}, insulin, or c-peptide) and the calculation of insulin resistance factors (like Homeostatic Model Assessment — Insulin Resistance [HOMA-IR] or Matsuda index) in all patients. However, this was a preliminary study, and further investigations of RLT influence on metabolic parameters have already begun in our centre.

Study strengths

The study was prospective. There is a dearth of studies focusing on glucose metabolism changes among patients treated with RLT. So, our study was one of the first in the available literature to show the glycaemic disturbances in these patients.

Conclusions

In our study, the radioligand therapy caused glucose metabolism disruption with increased fasting glucose concentration. This increase was observed during the first radioisotope administration, and the effect remained permanent even a year after therapy. No increase in insulin concentration was observed. Hence, the possible mechanism could be peripheral glucose metabolism disturbances. Nevertheless, the radioligand therapy is still a safe method of NEN treatment, and even though it may affect glucose metabolism, it probably does not cause adverse severe glycaemic events.

Data availability statement

Data other than that published in the manuscript is partially unavailable due to privacy or ethical restrictions.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Military Institute of Medicine, Protocol Code 52/WIM/2017; date of approval: 20 September 2017.

Author contributions

All authors confirm proportional impact on creating of the manuscript. Conceptualisation: M.S. and B.B.; Formal analysis: M.S., A.D.,

B.B., and A.L.; Funding acquisition: M.S. and B.B.; Investigation: M.S., A.D., B.B., G.R.-G., K.J., and D.B.-K.; Methodology: M.S.; Project administration: M.S. and G.K.; Resources: B.B.; Software: A.L.; Supervision: M.S.; Validation, B.B.; Writing — original draft: A.D.; Writing — review and editing: M.S., A.D., and G.K.

Funding

The research was funded by Ministry of Science and Higher Education via Military Institute of Medicine, Warsaw, Poland (Grant number 491/2017).

Conflict of interest

The authors declare no conflict of interest.

Supplementary File

Table S1 and Table S2.

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