University of South Bohemia in České Budějovice

Fakulty of Science

Ioduria and type 1 diabetes mellitus – relationships to selected clinical markers of diabetes in adults

RNDr.Thesis

Mgr. Michala Vosátková

České Budějovice 2017

Michala Vosátková, Denisa Žďárská Janíčková, Václav Zamrazil, Martina Salátová, Martin Hill, Karel Vondra. Ioduria and type 1 diabetes mellitus – relationships to selected clinical markers of diabetes in adults. Journal of Applied Biomedicine 3 Nov 2016; In press. DOI 10.1016/j.jab.2016.11.002

Article history

Received 15 July 2016

Received in revised form 25 October 2016

Accepted 3 November 2016

Avalilable online

DOI 10.1016/j.jab.2016.11.002

RNDr. Thesis in English. Faculty of Science. University of South Bohemia in České Budějovice, Czech Republlic.

Annotation:

The main aims of this study were to obtain information about iodine saturation in patients with type 1 diabetes, determine to what extent this saturation differs from the non-diabetic population and determine whether iodine levels are related to several clinical and laboratory parameters characteristic of diabetic syndrome, including thyroid status.

Declaration: [in Czech]

Prohlašuji, že svoji rigorózní práci jsem vypracovala samostatně pouze s použitím pramenů a literatury uvedených v seznamu citované literatury.

Prohlašuji, že v souladu s § 47b zákona č. 111/1998 Sb. v platném znění souhlasím se zveřejněním své rigorozní práce, a to v úpravě vzniklé vypuštěním vyznačených částí archivovaných Přírodovědeckou fakultou elektronickou cestou ve veřejně přístupné části databáze STAG provozované Jihočeskou univerzitou v Českých Budějovicích na jejich internetových stránkách, a to se zachováním mého autorského práva k odevzdanému textu této kvalifikační práce. Souhlasím dále s tím, aby toutéž elektronickou cestou byly v souladu s uvedeným ustanovením zákona č. 111/1998 Sb. zveřejněny posudky školitele a oponentů práce i záznam o průběhu a výsledku obhajoby kvalifikační práce. Rovněž souhlasím s porovnáním textu mé kvalifikační práce s databází kvalifikačních prací Theses.cz provozovanou Národním registrem vysokoškolských kvalifikačních prací a systémem na odhalování plagiátů.

České Budějovice 6. 2. 2017 Michala Vosátková

Prohlašuji, jako první a korespondující autor práce, že jsem se významnou měrou podílela na získání výsledků a přípravě rukopisu předložené práce: Michala Vosátková, Denisa Žďárská Janíčková, Václav Zamrazil, Martina Salátová, Martin Hill, Karel Vondra. Ioduria and type 1 diabetes mellitus – relationships to selected clinical markers of diabetes in adults. Journal of Applied Biomedicine 3 Nov 2016; In press. DOI 10.1016/j.jab.2016.11.002

Michala Vosátková

prof. MUDr. Václav Zamrazil, DrSc.

Ing. Martin Hill, DrSc.

prof. MUDr. Karel Vondra, DrSc.

Ioduria and type 1 diabetes mellitus – relationships to selected clinical markers of diabetes in adults.

Michala Vosátková[1], Denisa Žďárská Janíčková[2], Václav Zamrazil[1], Martina Salátová[1], Martin Hill[1], Karel Vondra[1]

[1]Institute of Endocrinology, Prague, Czech Republic

[2]Department of Internal Medicine, 2nd Faculty of Medicine, Charles University in Prague, Czech Republic

denisa.janickova.zdarska@fnmotol.cz

vzamrazil@endo.cz

msalatova@endo.cz

mhill@endo.cz

kvondra@endo.cz

Corresponding author:

Mgr. Michala Vosátková

Institute of Endocrinology

Národní 8

Prague 1

116 94, Czech Republic

Tel.: +420 224 905 244

Email: mvosatkova@endo.cz

www.endo.cz

Abstract:

There is a lack of data on the state of iodine reserves and the possible consequences of iodine deficits in diabetic patients. The main aims of this study were to: a) obtain information about iodine saturation in patients with type 1 diabetes; b) determine to what extent this saturation differs from the non-diabetic population; and c) determine whether iodine levels are related to several clinical and laboratory parameters characteristic of diabetic syndrome, including thyroid status.

Subjects and methods: A total of 54 males and 51 females treated for type 1 diabetes mellitus (DM1) were included in this cross-sectional study. In addition to iodine saturation determined as the concentration of iodine in the first urine sample of the day, we measured clinical, anthropometric, and biochemical parameters in relation to DM1.

Results: Measured iodine levels were: median 152 μg/l, first quartile 117 μg/l, and third quartile 219 μg/l. More than 50% of iodine levels varied within the optimal saturation range of 100-200 μg/l, while about 14% showed incomplete saturation (<100 μg/l), and 34% had increased saturation (>200 μg/l).

Multi-dimensional regression showed significant positive relationships; (an OPLS model explaining 9% of the variability) between ioduria and male sex, body weight and height, and serum creatinine levels, which to date have not yet been published. Relationships to the other analyzed parameters (glycated hemoglobin, insulin dose, DM duration, body mass index, microalbuminuria, glomerular filtration rate, thyroid function and volume, thyroid autoimmune markers) were not significant.

Conclusions: Iodine saturation levels in our study group were within the ICCIDD (WHO) recommendations for optimal/good saturation for the non-diabetic population, and patients with diabetic syndrome did not differ with respect to the chosen normal ioduria concentrations, i.e. 100 or 150 μg/l. The question remains, however, whether past attempts to deal with iodine deficits in the Czech Republic are responsible for this satisfactory iodine status of the type 1 diabetic population, or if there are other factors involved.

Key words: Diabetes mellitus, iodine, ioduria, iodine deficiency, thyroid

Introduction:

According to WHO (Zamrazil et al., 2004), since 2004 the Czech Republic is among those countries that have successfully addressed iodine deficiency. Despite this overall positive situation, however, there exist groups of people in these countries at risk of iodine deficiency and its negative effects, in particular pregnant and breastfeeding women, children, and the elderly (Szybinski Z, 2015, Sullivan et al., 2013, Abalovich et al., 2007, Als et al., 2000). In addition, patients with diabetes mellitus are also at risk (Zamrazil V, 2015), as demonstrated by data on pregnant women with diabetes and diabetic children (Okten et al., 2006). For instance, a recent study by Vítkova et al. found that 60% of pregnant diabetic women in the 2nd trimester had ioduria of < 100 µg/l (Vítková et al., 2015).

The aim of our study was to obtain information on the iodine status of patients with type 1 diabetes, and to determine to what extent this differs from the non-diabetic population. Further, we focused on the question of whether iodine levels in our study group were related to several clinical factors (diabetes duration, diabetic compensation, insulin dose), laboratory parameters characteristic of diabetic syndrome (renal function), and other markers. We also analyzed the volume and function of the thyroid gland, including the presence of thyroid autoimmunity.

Subject:

Our study group consisted of a total of 54 men and 51 women treated for DM1 at the Institute of Endocrinology in Prague and at the Motol Hospital of the 2nd Faculty of Medicine, Charles University in Prague. Medical, clinical, and laboratory parameters of this group are given in Table 1.

This study was approved by the ethical commission of the Institute of Endocrinology, in agreement with the most recent Declaration of Helsinki.

Table 1

Protocol:

This was a cross-sectional study, with data obtained during standard examinations as part of regular check-ups at the diabetic clinic of the Institute of Endocrinology and Motol Hospital, performed in the spring of 2015. None of the studied patients took supplementary iodine or organic medicines containing iodine, and at least for the prior year had no medical history of treatment with iodine-based contrast medium.

Samples of coagulated and non-coagulated blood were taken between 7-9 A.M. after fasting. Basal insulin was given unchanged before sampling, while morning prandial insulin given with food was delayed until after sampling was performed.

Methods:

a) Serum or plasma examinations

Glycated hemoglobin (HbA1c) was measured using an immunoturbidimetric assay (Tina quant, Cobas 6000, Roche, Manheim, SRN).

Creatinine was measured spectrophotometrically, using an enzymatic method with creatinase (Cobas 6000, Roche, Manheim, Germany).

Estimation of glomerular filtration (eGF) according to MDRD (Modification of Diet in Renal Disease) was calculated as: 515.3832 x (serum creatinine)-1.154 x (age)-0.203 x (0.742 for women).

Thyreotropic hormone (TSH), free thyroxine fraction (fT4) and Vitamin D (25OHD total - $25OHD_2$+$25OHD_3$) were measured by immunoanalytic ECLIA methods (Cobas 6000, Roche, Manheim, Germany).

Thyroid auto-antibodies (T-Ab) – antibodies to thyroid peroxidase (anti TPO) and antibodies to thyreoglobulin (anti Tg) were measured using an ELISA method (Aesku.Diagnostics, Wendelsheim, Germany) on an Immunomat BASE (Serion Immunologics, Germany).

b) Urine examinations

Ioduria was analyzed from samples taken from the first morning urine. Patients were instructed on hygienic sampling methods and to take samples from the middle part of

urination. The measurement of ioduria was done spectrophotometrically on a Helios Alfa spectrophotometer (Spectronic Unicam) at 430 nm, using alkaline mineralized melting and the Sandell-Kolthoff reaction (Bílek et al., 2005).

For analyzing microalbuminuria (MAU), albumin was measure from urine sampled during the nighttime, with sampling starting when lying down to sleep and ending before the morning urine sampling. For analyzing the albumin/creatinine ratio (ACR), albumin was measured from the first morning urine, which was sampled in the same way as for ioduria. Measurements were performed using an immunoturbidimetric assay: normal MAU values < 21 μg/min, ACR for men < 2.5 mg/mmol, for women < 3.5 mg/mmol (Cobas 6000, Roche, Manheim, Germany).

Calculations: MAU = (Albumin (mg/l) x urinary volume (ml)) / (time of sampling (min))

ACR = Albumin (mg/l) /Creatinine (mmol/l)

c) Clinical examinations:

Thyroid volume was measured by ultrasonography using a 3D image reconstruction and volume calculations according to Brunnan on a SonoAce X8 (Samsung Medison).

Thyroid volume was calculated for each lobe separately according to the equation:

V (ml) = 0,479 x length x depth x width

Total volume was the sum of both lobes; the volume of the isthmus was not included. For the purposes of this study we used the upper limits for a normal thyroid given by WHO for the European population: 18 ml for women and 22 ml for men. WHO does not give a lower limit for thyroid volume, so we used data from the Czech population (Dvořáková et al., 2006).

d) Anthropometric examinations:

Body weight, body height, body mass index (BMI) calculated as weight (kg)/height (m^2).

Criteria recommended by ICCIDD (WHO) for evaluating ioduria in the non-diabetic population:

Severe iodopenia is classified as ioduria values < 19 μg/l, serious iodopenia 20-49 μg/l, slight iodopenia 50-99 μg/l, optimal saturation 100–199 μg/l, increased saturation 200–299 μg/l, and high saturation 300–499 μg/l, excessive saturation > 500 μg/l (WHO 1999).

Statistical evaluation

Multivariate regression with a reduction in dimensionality (method of orthogonal projections to latent structures, OPLS) (Table 4), ordinary multiple regression (Table 4), and the Mann-Whitney test (Tables 2, 3) were used to analyze the data, using the statistical software Statgraphics Centurion version XIV (Manugistics, USA) and the multi-dimensional statistics software Sitica version XII (Umetrics, Sweden). Statistical methods were used at the significance levels $2\alpha = 0.05$.

Results:

The incidence of measured ioduria in individual categories for evaluating iodine saturation according to the ICCIDD (WHO) for non-diabetics is shown in Figure 1.

Figure 1

55 (52 %) of samples tested for ioduria were within the optimal saturation range, while 14 (13%) had decreased saturation; however, no sample had ioduria < 20 μg/l. Increased/higher saturation was found in 36 (35%) of samples.

Table 2

Table 3

The measured clinical and biochemical parameters tested here characterizing diabetic syndrome were not significantly related to the chosen normal iodine saturation range, with the exception of height (the group with ioduria < 100 vs. > 100) and weight (groups with ioduria < 150 vs. > 150) (Tables 2 and 3).

We further found differences in the incidence of positive thyroid auto-antibodies in men compared to women. The presence of some individual T-Ab or their combination (anti TPO and/or anti TgI) reached almost 40% in women, while positive T-Ab was found in only 24% of men.

Table 4 shows results of the multi-dimensional regression analyzing relationships between ioduria and other laboratory and clinical parameters. Of all analyzed parameters, only sex, body height and weight, and creatinine levels were statistically significant predictors of ioduria. The model predicted 9% of the ioduria-related variability.

Table 4

Discussion:

According to WHO, more than about 2 billion people are at risk of a lack of sufficient iodine, and providing iodine has been the subject of much attention worldwide (Delange et al., 2002). The Czech Republic was among those countries having insufficient iodine levels, and was one of the first countries to address this problem more than 50 years ago (Šilink et al., 1957). Iodine comprises more than 60% of the molecular volume of the thyroid gland hormones – thyroxine and triiodothyronine. Especially during pregnancy, even a slight iodine deficit may lead to many serious fetal defects. Iodine deficits just after birth result in defects in psychosomatic development, while in later years and in adulthood a lack of iodine results most often in goiter (Völzke et al., 2016, Horáček et al., 2013). An overall success in addressing iodine deficits does not mean, however, that there are not certain population groups for whom iodine deficiency does not present a continued risk (Zamrazil V, 2015), in particular for pregnant/breastfeeding women and children (Abalovich et al., 2007, Pearce EN, 2014, Péter et al., 2015).

Another group considered to be at risk includes those suffering from diabetes mellitus (Zamrazil V, 2015). However, there are only sporadic data on the status of iodine reserves and the consequences of iodine deficits and/or increased saturation in those with diabetes. This is surprising considering that diabetes affects about 10% of the population, and

treatment of these patients is associated with an economic burden many times higher than for the non-diabetic population (Doležal et al., 2009, Köster et al., 2014, ADA, 2013).

The main aim of our study was to obtain basic information on the iodine saturation status in patients with type 1 diabetes, and to analyze the relationships between iodine saturation and clinical-laboratory parameters characteristic of diabetic syndrome. We measured iodine saturation as the iodine concentrations in the first morning urine, in line with common epidemiological practice.

Our results from 105 patients with type 1 diabetes showed that 52% had good/optimal iodine saturation, i.e. between 100-199 µg/l. This is in agreement with a recently published study on the adult non-diabetic Czech population, who had median ioduria values between 110-250 µg/l (Dvořáková et al., 2006).

We found ioduria of ≤ 100 µg/l in 14 (13%) of diabetic patients, in the category of a slight deficiency. Serious iodine deficiency levels of < 20 µg/l were not found in any patient. In contrast, about one third (35 %) of our study group had increased/high iodine saturation according to the ICCIDD (WHO) criteria (> 200 µg/l), 2/3 of whom were men. The OPLS model from our data found significant predictors of ioduria to be male sex, body weight and height, and creatinine. These correlations are in agreement with the findings of a group of epidemiological studies on iodine deficiency in the Czech population, which repeatedly found higher iodine levels in men (Dvořáková et al., 2010). The level of creatinine in the blood under physiological conditions and normal kidney function reflect the total muscle mass, or respectively muscle metabolism, and thus tends to be higher in men. The positive correlation of iodine with creatinine levels is logical with respect to male-linked physiological parameters, and also explains the lack of correlation with BMI. Importantly, these relationships have not yet been reported in the literature.

When commenting on iodine values in adult diabetics it must be kept in mind that currently no normal ioduria values have been set and/or published for this population. In order to analyze to what extent the level of iodine saturation influences the clinical-biochemical parameters of our diabetic study group, we chose two levels as normal, the ≤ 150 µg/l

recommended for pregnant women with diabetes, and the ≤ 100 μg/l considered the lower normal level for the general population.

Our statistical analysis found that besides body height and weight, no other parameters characterizing diabetic syndrome – diabetes duration, BMI, diabetic compensation (HbA1c, insulin dose), renal function (creatinine, eFG, MAU, ACR), thyroid function (TSH, fT4) or vitamin D levels – were associated with normal iodine concentrations of either 100 or 150 μg/l (Tables 2, 3).

We also did not find a significant relationship between levels of glycated hemoglobin and ioduria in our patient group. Diabetic compensation evaluated by HbA1c values did not differ between patients with lower iodine saturation (< 100 μg/l) and those with good saturation (> 100 μg/l). It should be noted, however, that HbA1c values in our group reflected very good or good compensation. A study by Steisse et al. indicates that the diabetic compensation status should be taken into account when evaluation ioduria in diabetics (Steiss et al., 1996). Similarly to our results, Okten et al. found no differences between HbA1c values, DM duration, or thyroid hormone levels between child diabetics with iodine deficiency and those with good saturation (Okten et al., 2006).

In agreement with our previous findings (Vondra et al., 2005, Vondra et al., 2004), our results here showed a high percent of positive T-Ab, particulary in women. Irrespective of the presence of T-Ab, we also found lower thyroid volume in diabetic women, with the median of 9.6 ml falling within the 10^{th} to 25^{th} percentile of Czech women with good iodine saturation (Dvořáková et al., 2006). A tendency toward a lower thyroid volume in the male part of the study group was not seen, with volume ranging between the 75^{th} to 90^{th} percentile of Czech men with ioduria > 100 μg/l (Dvořáková et al., 2006).

Conclusions:

Based on our results, iodine saturation in adult DM1 patients met the conditions of ICCIDD (WHO) for optimal/good saturation. Steps taken in the past to address iodine insufficiency in the Czech Republic currently seems to have been adequate. The question remains, however,

whether the satisfactory status of the type 1 diabetic population is also influenced by additional factors. This is a subject for future research.

When discussing normal values of ioduria in an adult diabetic population, results of our analysis on the relationships between clinical-laboratory parameters characteristic for diabetic syndrome are important. No direct significant correlations were found, but multi-dimensional regression found a new, as yet unpublished positive relationship between ioduria and male sex, body weight and height, and creatinine levels.

References:

Abalovich M, Amino N, Barbour LA et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice quideline: J Clin Endocrinol Metab 2007; 92: 1-47.

American Diabetes Association (ADA). Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013; 36: 1033-1046.

Als C, Keller A, Minder C et al. Age- and gender-dependent urinary iodine concentrations in an area-covering population sample from the Bernese region in Switzerland. Eur J Endocrinol 2000; 143: 629-637.

Bílek R, Bednář J, Zamrazil V. Spectrophotometric determinantion of urinary iodine by the Sandell-Kolthoff reaction subsequent to dry alkaline ashing. Results from Czech Republic in the period 1994-2002. Clin Chem Lab Med 2005; 43: 573-580.

Delange F, Bürgi H, Chen ZP et al. World status of monitoring iodine deficiency disorders control programs. Thyroid 2002; 12: 915-924.

Doležal T, Písaříková Z, Zemanová P et al. Costs of type II diabetes in the conditions of the Czech republics medical care systém. Vnitr Lek 2009; 55: 342-344.

Dvořáková M, Bílek R, Čeřovská J et al. The volumes of the thyroid gland in adults aged 18-65 years in the Czech Republic-determination of the normal. Vnitr Lek 2006; 52: 57-63.

Dvořáková M, Hill M, Čeřovská J et al. Influence of iodine saturation on thyreopathy incidence in selected regions of Czech republic. Vnitr Lek 2010; 56: 1262-1270.

Péter F, Podoba J, Muzsnai A. Iodine status of schoolchildren in hungary: Improvement a decade on. Eur Thyroid J 2015; 4: 71-72.

Horáček J, Jiskra J, Límanová Z et al. Doporučení pro diagnostiku a léčbu onemocnění štítné žlázy v těhotenství a pro ženy s poruchou fertility. DMEV 2013; 16: 38-61.

Köster I, Huppertz E, Hauner H et al. Costs of diabetes mellitus (CoDiM) in Germany, direct per-capita costs of managing hyperglycaemia and diabetes complications in 2010 compared to 2001. Exp Clin Endocrinol Diabetes 2014; 122: 510-516.

Okten A, Akcay S, Cakir M, et al. Iodine status, thyroid function, thyroid volume and thyroid autoimmunity in patients with type 1 diabetes mellitus in an iodine-replete area. Diabetes Metab 2006; 32: 323-329.

Pearce EN. Iodine deficiency in children. Endocr Dev 2014; 26: 130-138.

Steiss JO, Otten A, Graef V et al. Thyroid gland ultrasound and urinary iodine excretion in children and adolescents with type I diabetes mellitus. Klin Pediatr 1996; 208: 327-333.

Sullivan KM, Perrine CG, Pearce EN et al. Monitoring the iodine status of pregnant women in the United States. Thyroid 2013; 23: 520-521.

Šilink K, Reisenauer R. Metabolic studies among the populatin of Bohemia and Moravia. 1. Nitrogen metabolism. 2. Relation of nitrogen to iodine in the population of Bohemia and Moravia in 1953. Cas Lek Cesk 1957; 96: 809-812.

Vítková H, Anderlová K, Radiměřská V et al. Jodurie u těhotných žen s gestačním a pregestačním diabetem mellitem. In: Houdek L Sborník abstrakt, 38. Endokrinologické dny, Špindlerův Mlýn. Praha: Galén 2015: 58.

Vondra K, Vrbíková J, Šterzl I et al. Thyroid autoantibodies and their clinical relevance in young adults with type 1 diabetes during the first 12 yr after diabetes onsent. J Endocrinol Invest 2004; 27: 728-732.

Vondra K, Vrbíková J, Bendlová B et al. Differences in type 1 diabetes mellitus of young adults with and without thyroid autoimmunity. Exp Clin Endocrinol Diabetes 2005; 13: 404-408.

Völzke H, Caron P, Dahl L et al. Ensuring effective prevention of iodine deficiency disorders. Thyroid 2016; 26: 189-196.

WHO, UNICEF, ICCIDD: Assessment of iodine deficiency disorders and monitoring their eleimination. A guide for programme managers. Report of Consulation, May 4-6, Geneva, 1999.

Zamrazil V. Saturace jodem v České republice a ve světě – nedostatky a perspektivy. Kardiol Rev Int Med 2015; 17: 167-171.

Zamrazil V, Bílek R, Čeřovská J et al. The elimination of iodine deficiency in the Czech Republic: the steps toward succes. Thyroid 2004; 14: 49-56.

Zamrazil V, Bílek R, Čeřovská J et al. Iodine deficiency in the world and in the Czech republic – current status and perspectives . Vnitr Lek 2010; 56: 1310-1315.

Szybinski Z. Poland remains iodine sufficient after 20 years of IDD prevention, but pregnant women may be at risk. IDD Newsletter; 2015 Aug, Poland.

"Supported by MH CZ - DRO (Institute of Endocrinology - EÚ, 00023761)"

Table 1. Basic parameters of the study group (n=105).

Variable	**Unit**	**Median** (25. a 75. Quartile)
Age	Years	42 (31, 55)
Body weight	kg	78 (66, 91)
Body height	cm	172 (165, 180)
BMI	kg/m^2	25.9 (23.3, 29.7)
Ioduria	µg/l	152 (117, 219)
Diabetes duration	Years	18 (13, 23)
Insulin dose/kg/day	IU/kg/day	0.62 (0.44, 0.75)
Insulin dose/day	IU/day	49 (36, 62)
HbA1c	mmol/mol	61 (51.2, 71.0)
Creatinine	mmol/l	71 (61, 83)
eGF	$ml/s/1.73m^2$	1.63 (1.38, 1.92)
Microalbuminuria	µg/min	4.3 (1.9, 11.8)
Albumin/Creatinine ratio	mg/mol	0.54 (0.23, 2.08)
Vitamin D	nmol/l	58 (39.3, 82.8)
TSH	mIU/l	1.77 (1.12, 2.80)
fT4	pmol/l	15.6 (13.9, 18.2)
Thyroid volume males	ml	18.5 (12.0, 22.1)
Thyroid volume females	ml	9.6 (7.7, 12.6)

BMI (body mass index), HbA1c (glycated hemoglobin), eGF (estimation of glomerular filtration), TSH (thyrotrophic hormone), fT4 (free thyroxine fraction). Data are given as median (25., 75.quartile).

Table 2. Comparison of median for selected parameters characteristic of diabetic syndrome in patients with ioduria ≤150 vs > 150 µg/l.

		Ioduria		
Variable		≤150	>150	signif.
n (%)		49(47%)	56(53%)	
Body weight	kg	75.0	79.5	
Body height	cm	168	175	*
BMI	kg/m^2	25.5	26.0	
Ioduria	µg/l	114	217	***
Diabetes duration	years	19.5	17.0	
Insulin dose/kg/day	IU/kg/day	0.643	0.602	
Insulin dose/day	IU/day	49	49	
HbA1c	mmol/mol	64	60	
Creatinine	mmol/l	67	72	
eGF	$ml/s/1.73m^2$	1.59	1.69	
Microalbuminuria	µg /min	4.3	5.1	
Albumin/Creatinine ratio	mg/mol	0.50	0.75	
Vitamin D	nmol/l	66.8	55.9	
TSH	mIU/l	1.82	1.75	
fT4	pmol/l	16.2	15.1	

BMI (body mass index), HbA1c (glycated hemoglobin), eGF (estimation of glomerular filtration), TSH (thyrotrophic hormone), fT4 (free thyroxine fraction). Mann-Whitney test was used at the significance levels 2α = 0.05, 0.01**, and 0.001***.*

Table 3. Comparison of median for selected parameters characteristic of diabetic syndrome in patients with ioduria ≤100 vs > 100 µg/l.

		Ioduria		
Variable		≤100	>100	signif.
n (%)		15(14%)	90(86%)	
Body weight	kg	65.1	79.5	*
Body height	cm	169	172	
BMI	kg/m^2	24.2	26.6	
Ioduria	µg/l	77	167	***
Diabetes duration	years	18	18	
Insulin dose/kg/day	IU/kg/day	0.643	0.615	
Insulin dose/day	IU/day	44	50	
HbA1c	mmol/mol	64.2	60.8	
Creatinine	mmol/l	65	72	
eGF	$ml/s/1.73m^2$	1.75	1.62	
Microalbuminuria	µg /min	5.1	4.3	
Albumin/Creatinine ratio	mg/mol	0.53	0.55	
Vitamin D	nmol/l	56.9	62.4	
TSH	mIU/l	2.17	1.75	
fT4	pmol/l	15.1	15.9	

BMI (body mass index), HbA1c (glykovaný hemoglobin), eGF (estimation of glomerular filtration), TSH (thyrotrophic hormone), fT4 (free thyroxine fraction). Mann-Whitney test was used at the significance levels 2α = 0.05, 0.01**, and 0.001***.*

Table 4. Relationships between ioduria and various clinical-laboratory parameters evaluated by multivariate regression (method of orthogonal projections to latent structures, OPLS) and ordinary multiple regression.

			OPLS, predictive component				**Ordinary multiple regression**		
		Variable	Component loading	t-statistic	R^{a}		Regression coefficient	t-statistic	
Relevant predictors (**matrix X**)	↑	Male	0.595	15.89	0.888	**	0.147	2.50	*
	↑	Body Weight	0.466	6.94	0.695	**	0.074	5.42	**
	↑	Body Height	0.543	10.53	0.810	**	0.098	2.48	*
	↑	Creatinine	0.424	5.52	0.634	**	0.060	8.50	**
Dependent variable (**matrix Y**)		Ioduria	1.000	1.97	0.299	*			
Variability explained			9% (6.8% after cross-validation)						

[a]R…Component relationship expressed as a correlation coefficient with predictive component. OPLS model and multiple regression models were used at the significance levels 2α = 0.05, and 0.01**.*

Your manuscript JAB_2016_181_R2 has been accepted

Josef Berger (Journal of Applied Biomedicine) <EviseSupport@elsevier.com>

Ref: JAB_2016_181_R2
Title: Ioduria and type 1 diabetes mellitus – relationships to selected clinical markers of diabetes in adults.
Journal: Journal of Applied Biomedicine

Dear Miss. Vosatkova,

I am pleased to inform you that your paper has been accepted for publication. My own comments as well as any reviewer comments are appended to the end of this letter. Now that your manuscript has been accepted for publication it will proceed to copy-editing and production.

Thank you for submitting your work to Journal of Applied Biomedicine. We hope you consider us again for future submissions.

Kind regards,

Josef Berger
Editor-in-Chief
Journal of Applied Biomedicine

Comments from the editors and reviewers:

Have questions or need assistance?
For further assistance, please visit our Customer Support site. Here you can search for solutions on a range of topics, find answers to frequently asked questions, and learn more about EVISE® via interactive tutorials. You can also talk 24/5 to our customer support team by phone and 24/7 by live chat and email.